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Noradrenaline involvement in basic and higher integrated REM sleep processes

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In memoriam of Jean-Michel Gaillard.

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ABSTRACT

There has been an abundance of literature devoted to the involvement of noradrenaline in basic rapid eye movement (REM) sleep processes since the subject was first investigated in 1964. Nowadays, the great majority of studies highlight the need for silence in the locus coeruleus noradrenergic neurons as a condition for the occurrence and maintenance of REM sleep. However, throughout the successive years of work on this topic, few researchers have consistently claimed that some amount of noradrenaline is essential for the appearance of this sleep stage. In the first part of this review, each of the papers published in this field is analyzed. Then, in the discussion, arguments supporting the requirement for a given level of noradrenaline for REM sleep occurrence are presented. This second part also examines, based on waking noradrenergic influences on higher integrated brain processes, the major consequences of noradrenergic neuron silence during REM sleep for mental functioning.

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Abbreviations: AMPT, α-methyl-*para*-tyrosine; CNQX, 6-cyano-7-nitroquinoxaline-2-3-dione; COMT, catechol-*O*-methyl transferase; DMI, desmethylimipramine; DOPA, dihydroxyphenylalanine; DOPS, D,L-thyreo-3,4-dihydroxyphenylserine; DSP-4, *N*-(2-chlorethyl)-*N*-ethyl-2-bromobenzylamine; EEG, electroencephalography; GABA, gamma aminobutyric acid; GAD, glutamic acid decarboxylase; HVA, homovanilic acid; MAO, monoamine oxidase; MHPG, 3-methoxy-4-hydroxy-phenyl-glycol; 6-OHDA, 6-hydroxy-dopamine; NA, noradrenaline; POB, phenoxybenzamine; PPT, pedunculopontine tegmentum; REM sleep, rapid eye movement sleep; TH, tyrosine hydroxylase.

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1. Preamble

We were not exactly friends, but we had a friendly relationship. I invited Jean-Michel Gaillard several times to lecture to my students in Nice, and I often traveled to his annual January sleep seminar in Geneva, where I was always impressed by his ability to acutely and kindly discuss each basic neurobiological or psychophysiological result presented by the participants working on animals or humans. I also taught at Abidjan University (Ivory Coast), and once when a student in my laboratory completed his PhD thesis, I had to fly there to conduct the thesis viva. I invited Jean-Michel Gaillard to be on the board of examiners. So, we traveled together with our wives and had a pleasant stay at each other's place. It was his first trip to Africa and he enjoyed it very much. The last time I hosted him in Nice, just before his resignation from Bel-Air Hospital, he was disillusioned and slightly depressed at not being appointed permanent head of the department that he had directed so well for many years.

This introduction briefly recalls how Jean-Michel Gaillard was an eminent researcher and a precursor in many sleep research fields. He was the first to develop an automatic sleep–waking scoring system for human clinical use (Gaillard et al., 1971) (another team did it the same year for animals; Gottesmann et al., 1971). Between 1971 and 1996, he published 140 papers devoted to human as well as animal research. I want to particularly emphasize here that Jean-Michel Gaillard was the first to be consistently convinced that some amount of noradrenaline (NA) is necessary for rapid eye movement (REM) sleep-generating processes, and that current results strongly support his now old and generally forgotten position.

2. Introduction

2.1. Sleep stages

Waking is followed by sleep. Sleep is first characterized by a progressive increase in slow and high amplitude electroencephalographic (EEG) patterns (slow-wave sleep, stages 1–4). In humans, about 90 min after sleep onset, the REM dreaming sleep stage begins. The first such period is short (lasting a few minutes), with the subsequent three to four REM sleep periods that occur each night gradually increasing in duration; the final period, generally

occurring just prior to awakening, lasts for up to 50 min. The REM sleep stage, which is characterized by rapid, low voltage EEG in animals (Klaue, 1937) and in humans (Aserinsky and Kleitman, 1953; Loomis et al., 1937), resembles active waking EEG, a state involving both rapid eye movement bursts in humans (Aserinsky and Kleitman, 1953) and animals (Dement, 1958) as well as atonia first observed in animals (Jouvet et al., 1959; Klaue, 1937) and then subsequently in humans (Berger, 1961).

2.2. Noradrenaline

Noradrenaline is one of the main brain monoamines (–CH_2–NH_2), involving neurons situated in the pons and medulla oblongata. The most important nucleus containing noradrenergic neurons is the locus coeruleus, or A_6 area (Dahlstrom and Fuxe, 1964) which only comprises about 1000 cellular bodies. These give rise to local axon projections, mainly collaterals, as well as to projections to forebrain structures within the dorsal noradrenergic bundle and mainly innervate the thalamus, hippocampus, and cortex. There are also projections to motoneurons. There is, however, at least one other nucleus (A_5) that functions like the locus coeruleus nucleus during the sleep–waking cycle (Fenik et al., 2002). The other major noradrenergic nuclei, though less studied, are the A_1 and A_2 nuclei, which are located in the medulla oblongata and project to forebrain structures through the ventral noradrenergic bundle. These nuclei principally innervate the hypothalamus and limbic structures, particularly the amygdala and nucleus accumbens. Noradrenaline is a neuromodulator, since in addition to possessing few axon synapses it is essentially released at the varicosity level, inducing a sustained diffuse action because of the absence of immediate reuptake or rapid destruction by monoamine oxidase (MAO). In the brain stem, NA has both facilitatory and inhibitory influences. The inhibitory activity is predominant in the forebrain, particularly in the cortex. At this level, noradrenaline acts on α_2-receptors, causing them to block Ca^{2+} channels or to open K^+ channels. In contrast, α_1-receptor activation decreases K^+ channel conductance, and β_1-receptors are positively coupled to adenylate cyclase (Nicoll et al., 1990).

3. Results

In this review, I will first analyze all of the papers that have addressed the involvement of NA in basic REM sleep processes. All individual papers have been analyzed based on their full text, and abstracts were almost never taken into account alone. Only the data strictly related to the topic are reported. In Section 4, I will outline our present-day knowledge in this field and then analyze the involvement of NA in the higher integrated brain processes of REM sleep. Since the initial bibliographic analysis could be of less interest to some readers, Table 1 shows the basic conclusion of each paper related to the topic. As the large majority of papers underline the necessity of NA silencing for REM sleep, two tables and the figures of the present review emphasize the positive influence of NA on REM sleep.

3.1. 1964–1974

3.1.1. 1964

The first demonstration of the probable involvement of NA in REM sleep-generating processes was made by Matsumoto and Jouvet (1964) in cats (Fig. 1). They showed that 0.25–0.50 mg/kg of reserpine administered intraperitoneally (i.p.) suppressed REM sleep, an effect that was counteracted by the addition of 30 mg/kg of dihydroxyphenylalanine (DOPA), a precursor of dopamine, noradrenaline, and adrenaline. Injection of 30 mg/kg of 5-hydroxytryptamine (5-HTP), a precursor of serotonin, was without effect. Indeed, reserpine blocks the intracellular uptake of monoamines into vesicles, thereby allowing their destruction by monoamine oxidase.

Likewise, Yamaguchi et al. (1964) injected several cholinergic and monoaminergic compounds into different brain structures. Introducing noradrenaline (20–30 μg) into the preoptic area induced central and peripheral arousal. In contrast, when applied to the thalamic centralis medialis nucleus, "alternating periods of high-voltage slow-wave activity and fast-wave sleep patterns (REM sleep) were observed (in 5 out 6 cats)" (p. 16). However, in the same year, Toyoda (1964) showed that the antidepressive compound imipramine (50 mg/kg), which inhibits transmitter reuptake, decreased REM sleep from 23% to 10% in humans. Amitryptyline, desmethylimipramine (DMI) (compounds with similar actions), and the MAO inhibitor nialamide had the same effect.

3.1.2. 1965

Similarly, Jouvet et al. (1965) injected (i.p.) cats with four MAO inhibitors (harmaline: 20 mg/kg; tranylcypromine: 2 mg/kg; iproniazide: 80–100 mg/kg; nialamide: 10 mg/kg) and observed REM sleep suppression. The same results were observed by Hishikawa et al. (1965), who injected cats with the MAO inhibitors imipramine and desmethylimipramine. Four and 2 mg/kg (i.p.) increased the latency of REM sleep occurrence (except the 2 mg/kg dose of DMI). The number of REM sleep phases decreased and the percentage of REM sleep diminished considerably, again with the same exception of DMI. Even in humans, Tissot (1965) found a similar result, showing that 3–4 mg of reserpine increased REM sleep from 22% to 41% ($P < 0.01$), with the mean number of phases increasing from 3 to 4.6 ($P < 0.02$). This increase occurred at the expense of stages 3 and 4.

Jouvet and Delorme (1965) published one of the most spectacular results of Jouvet's team. It concerned the utility of bilateral lesions of various brain stem structures to help pinpoint the area responsible for REM sleep-generating processes. While different structural lesions were without effect, the bilateral lesion of the noradrenergic locus coeruleus was described as suppressing REM sleep. In the first week the cats showed waking and slow-wave sleep. Then, phasic activities increased during slow-wave sleep (paw and vibrissae movements). However, nearly 20 days after the lesion, hallucinatory behavior appeared in three animals. PGO waves were increased in number, the cortical EEG was rapid, the pupils were in myosis, and the nictitating membranes were relaxed. The animals seemed to be taking part in a dream event. Raised up on their paws, they seemed in some cases to fight with an

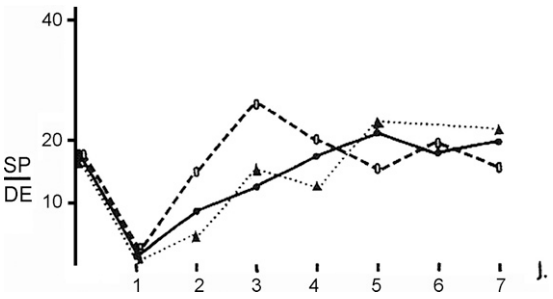

Fig. 1. Using cats, Matsumoto and Jouvet (1964) showed that reserpine (0.5 mg/kg i.p. black line) induced REM sleep rapid suppression followed by a long-lasting decrease. Injection of 30 mg/kg DOPA (dashed line) induced rapid reappearance of REM sleep while 30 mg/kg of 5-HTP (dotted line) had no influence. Ordinate: percentage. Abscissa: days. SP/DE: REM sleep/duration of recording. Reprinted from *Comptes Rendus de la Société de Biologie*, with permission.

Table 1
Main conclusion of noradrenaline influence on REM sleep-generating processes

Matsumoto and Jouvet (1964)	NA +
Yamaguchi et al. (1964)	NA +
Toyoda (1964)	Mo –
Jouvet and Delorme (1965)	Mo –
Hishikawa et al. (1965)	Mo –
Tissot (1965)	Mo –
Jouvet and Delorme (1965)	NA +
Hartmann (1966)	Mo –
Gottesmann (1966)	Mo –
Marantz and Rechtschaffen (1967)	NA –
Matsumoto and Watanabe (1967)	NA +
Marantz et al. (1968)	NA –
Torda (1968)	NA +
Dusan-Peyrethon et al. (1968)	NA +
Weitzman et al. (1969)	NA +
Jouvet (1969)	NA +
Mark et al. (1969)	NA ?
Iskander and Kaelbling (1970)	NA +
Branchey and Kissin (1970)	NA –
Wyatt et al. (1971)	NA – +
King and Jewett (1971)	NA –
Hartmann et al. (1971)	NA –
Jones (1972)	NA – +
Laguzzi et al. (1972)	NA +
Panksepp et al. (1973)	NA –
Hartmann and Schildkraut (1973)	NA –
Sinha et al. (1973)	NA +
Stern and Morgane (1973b)	Mo – +
Stern and Morgane (1973a)	NA –
Satoh and Tanaka (1973)	NA +
Zolovick et al. (1973)	NA +
Matsuyama et al. (1973)	NA +
Chu and Bloom (1974)	NA –
Stein et al. (1974)	NA –
Kleinlogel et al. (1975)	NA +
Oswald et al. (1975)	NA –
Hobson et al. (1975)	NA –
Hartmann and Zwilling (1976)	NA –
Barratt et al. (1976)	NA +
Kafi et al. (1977)	NA +
Jones et al. (1977)	NA –
Autret et al. (1977)	NA +
Putkonen and Leppävuori (1977)	NA +
Hilakivi et al. (1978)	NA +
Gaillard and Kafi (1978)	NA +
Hilakivi et al. (1978)	NA +
Ramm (1979)	NA –
Hilakivi et al. (1980)	NA –+
Kafi and Gaillard (1980)	NA +
Leppävuori and Putkonen (1980)	NA +
Radulovacki et al. (1980)	NA +
Milon and Enslen (1980)	NA +
Spiegel and Devos (1980)	NA +
Sakai (1980)	NA –
Kafi and Gaillard (1981)	NA +
Justafre and Gaillard (1981)	NA ?
Claude et al. (1981)	NA +
Braun and Pivik (1981)	NA +
Radulovacki et al. (1981)	NA +
Aston-Jones and Bloom (1981a)	NA –
Gaillard et al. (1982)	NA +
Masserano and King (1982)	NA –
Cespuglio et al. (1982)	NA –
Gaillard (1983)	NA +
Monti (1983)	NA –
Hilakivi (1983)	NA ?
Foote et al. (1983)	NA –
Hilakivi and Leppävuori (1984)	NA –
Gordon and Lavie (1984)	NA +
Pellejero et al. (1984)	NA –
Gaillard (1985)	NA +
Lanfumey et al. (1985)	NA +
Depoortere (1985)	NA +
Greene and Carpenter (1985)	NA +
Betts and Alford (1985)	NA +
Kanno and Clarenbach (1985)	NA +
Nicholson et al. (1986)	Mo –
Rasmussen et al. (1986)	NA –
Caballero and De Andres (1986)	NA –
Mirmiran (1986)	NA – +
Mäkelä and Hilakivi (1986)	NA –
Monti et al. (1988)	NA –
Gerber et al. (1990)	NA +
Mühlethaler et al. (1990)	NA +
Tulen et al. (1990)	NA +
Tulen et al. (1991)	NA +
Nicholson and Pascoe (1991)	NA +
Cirelli et al. (1992)	NA –
Williams and Reiner (1993)	NA –
Mastrangelo et al. (1994)	NA +
Bier and McCarley (1994)	NA +
Gonzalez et al. (1995)	NA +
Gentili et al. (1996)	NA +
Singh and Mallick (1996)	NA –
Python et al. (1997)	NA –
Kaur et al. (1997)	NA –
Yamuy et al. (1998)	NA –
Crochet and Sakai (1999a)	NA – +
Crochet and Sakai (1999b)	NA –
Maloney et al. (1999)	NA –
Koyama and Sakai (2000)	NA +
Shouse et al. (2000)	NA –
Hou et al. (2002)	NA –
Mallick et al. (2002)	NA –
Hunsley and Palmiter (2003)	NA –
Ouyang et al. (2004)	NA +
Jones (2004)	NA –
Sakai and Crochet (2004)	NA –
Mallick et al. (2005)	NA +
Pal and Mallick (2006)	NA –
Rasch et al. (2007)	NA –
Pal and Mallick (2007)	NA –

NA, noradrenaline; Mo, monoamines; +, essential for REM sleep basic processes; –, unessential or inhibition of REM sleep.

enemy for several minutes. Their behavior evoked rage and the animals appeared to be totally awake, although they did not react to sensory stimulations and their ocular behavior evoked sleep. This beautiful result was anticipated by Jouvet and Mounier (1960), who described such hallucinatory behavior after pontine tegmentum lesions, a result later confirmed and extended by Henley and Morrison (1974). This finding was further developed by Sastre and Jouvet (1979). It was later shown that the area responsible for REM sleep atonia is the locus coeruleus-α (Sakai, 1988).

3.1.3. 1966

Hartmann (1966) also administered a single dose of reserpine to humans (1.5 mg/70 kg), inducing "early release or the longer-lasting depletion of brain serotonin and noradrenaline" (p. 246). His results showed that, "it is clear that REM sleep percent tends to be higher after reserpine, the increase is significant ($P < 0.05$) within the subject in five of six cases. Across subjects, means on reserpine nights exceed corresponding subject means on control nights ($P < 0.01$)" (p. 244).

These results with reserpine were indirectly confirmed by a study published the same year by myself (Gottesmann, 1966). Many doses of reserpine, from 0.5 to 7 mg/kg, were administered i.p. to rats. Even at 2.75–5 mg/kg, doses which suppress central monoamines (Dahlstrom and Fuxe, 1964), REM sleep was not eliminated. At 7 mg/kg, REM sleep was systematically suppressed starting in the second hour of recording. It reappeared in the ninth hour, and 30 h after injection the phases appeared as usual. The effect of these high doses could be, at least in part, related to peripheral influences of the compound. I also noticed that there seemed to be a difference between the optimum level of

neurotransmitters and a reduced level which, nevertheless, still allows normal behavior.

3.1.4. 1967

A new molecule, α-methyl-*para*-tyrosine (AMPT), strongly reaffirmed the apparently negative influence of NA on REM sleep. This agent inhibits tyrosine hydroxylase (TH) and decreases central dopamine and noradrenaline synthesis. Indeed, as Spector et al. (1965) stated, "tissue concentration of noradrenaline failed to rise following MAO inhibition, and decarboxylase inhibitors failed to block the AMPT effect; the conversion of tyrosine-C^{14} to NA was inhibited whereas that from DOPA-H^3 was not" (p. 94).

The first experiment with this compound was performed by Marantz and Rechtschaffen (1967). Since the administration conditions are crucial for this molecule used by several researchers, they need to be somewhat detailed in all experiments. "At 4-day intervals, each rat received a series of three intraperitoneal injections (at 4 a.m., 8 a.m. and noon) of ... 50 mg/kg AMPT ... Clearly, there was no systematic decrement or increment in percentage of REM sleep" (p. 806). "AMPT was effective in lowering brain noradrenaline by about 59%" (p. 807).

Matsumoto and Watanabe (1967) injected cats with both α-adrenergic (phenoxybenzamine (POB) and dibamine) and β-adrenergic (dichloroisoproterenol and nethalide) blocking compounds. At 15 mg/kg (i.p.) of POB, the ratio of REM sleep/total sleep decreased from 23.8% to 14.6%. For dibenamine, the decrease was from 24.0% to 11.7%. In contrast, "the effects of the β-adrenergic blocking agents were not remarkable; the amount of REM sleep decreased (only) a little" (p. 682). The authors concluded that their result, in agreement with the previous findings of Yamaguchi et al. (1964), "confirms the significance of NA in the induction of REM sleep" (p. 682).

3.1.5. 1968

Pujol et al. (1968) showed with tritiated NA that the accumulation of NA is increased during REM sleep deprivation and during the rebound from REM sleep deprivation. Their rats were deprived for 91 h by the small flower pot method, in which the animal stands on a small surface surrounded by water; this method prevents REM sleep because its characteristic atonia would cause the animal to fall into the water. When compared to controls, the rate of noradrenaline synthesis after deprivation was increased only in the telencephalon and the diencephalon. During the REM sleep rebound, the synthesis of noradrenaline increased by 89% in the brain stem and mesencephalon, and by 119% in the telencephalon and diencephalon. After a 5-h recovery of REM sleep, there was a reduction in the specific activity of noradrenaline: "This effect is visible in the two parts of the brain examined and suggests an increase of turnover of noradrenaline, which likely indicates an augmentation of synthesis and utilization of the amine, leading possibly to an increased availability of physiologically active noradrenaline in some central synapses during this period of rebound of REM sleep" (p. 113).

Marantz et al. (1968) studied the effect of AMPT on REM sleep rebound after specific deprivation by the water-pot method, which had just before been shown to induce an increase in NA turnover (Pujol et al., 1968). The rats were REM sleep-deprived for 90 h and received four (i.p.) injections of 75 mg/kg of AMPT at 2-h intervals starting in the 86th hour of deprivation. The animals were recorded after the third injection. There was no difference in REM sleep between the injected animals and uninjected controls in spite of a 77% depletion of brain NA. The authors concluded: "Clearly, the synthesis of brain noradrenaline is not essential for REM sleep in the rat" (p. 163).

Torda (1968) also injected rats with AMPT (80 mg/kg 6 h apart), inducing a gradual but complete depletion of NA by the end of the 18th hour following the first AMPT dose. Behaviorally, this induced a "shortening of both REM sleep and waking... Microinjections of NA into the preoptic area or the reticular activating system temporarily reversed the EEG changes... (which) consisted of shortening of deep sleep and lengthening of both REM sleep and wakefulness" (p. 204). In Section 4, REM sleep changes were not addressed.

Dusan-Peyrethon et al. (1968) administered 100 and 200 mg/kg of α-methyl DOPA *per os* to cats. This compound decreases brain catecholamine levels. The authors observed a selective suppression of REM sleep for 16 ± 6 h, without a rebound effect. Ponto-geniculo-occipital (PGO) waves were suppressed for 12 h. After 3 days of specific REM sleep deprivation and a daily injection of 200 mg/kg, the rebound also decreased. This result suggested the necessary contribution of catecholamines to REM sleep occurrence.

3.1.6. 1969

Weitzman et al. (1969) undertook a study with AMPT on monkeys (Macaca Mulatta). Two doses were administered i.p. or by naso-gastric tube at 2-h intervals prior to an 8-h recording period at night, for two consecutive days. The doses given in their Table 1 are not shown clearly. However, the compound decreased REM sleep (Fig. 2) with an inconsistent small rebound. The same year, Jouvet (1969) wrote a review in which he hypothesized that "the successive intervention of serotonergic, cholinergic, and NA mechanisms in the triggering and effecting of REM sleep is strongly implied by neuropharmacological results" (p. 39).

Mark et al. (1969) studied NA turnover in the whole brain of rats after REM sleep deprivation from 4 to 10 days. The specific radioactivity of the noradrenaline was significantly lower on days 4, 5, 6, and 10 after REM sleep deprivation. However, the weight of the adrenal glands was higher (similar to in a stress control situation without deprivation) and, after an 8-day deprivation period, the level of corticosterone decreased. The authors concluded that "the observed metabolic change was not a consequence of REM sleep deprivation and it seemed possible that stress reactions were occurring" (p. 1092). This result was not in accordance with the findings of Pujol et al. (1968).

3.1.7. 1970

Iskander and Kaelbling (1970) injected cats with AMPT: "80 mg/kg were administered i.p. every six hours to a total of four injections for each animal... The decrease in REM sleep activity that is seen by the end of the 24 h during which the drug was administered is significant when tested by an analysis of variance ($p < 0.01$). The rise in REM sleep activity seen in the subsequent 24 h was also statistically significant to a similar degree" (p. 45). Consequently, there was a strong rebound effect. In Abstract and Section 4, the authors emphasized the increase in REM sleep during the rebound effect, when the catecholamine levels were still low, rather than the decrease in REM sleep during drug administration: "the increase in REM sleep activity above baseline values ceased by the end of the second post-treatment day" (p. 45).

Branchey and Kissin (1970) studied the influence of 200 mg/kg (i.p.) AMPT in rats over a 24-h recording period. Although there was an increase in slow-wave sleep ($P < 0.005$), they did not observe any variations in REM sleep. The authors conclusion emphasized the importance of catecholamines in waking processes.

Karczmar et al. (1970) injected eserine into rats, rabbits, and cats after pretreatment with reserpine. The doses and modes of administration (i.p., intravenous, subcutaneous) varied with the species: "The results prove conclusively that, in reserpinized animals, eserine is capable of inducing EEG and behavioral

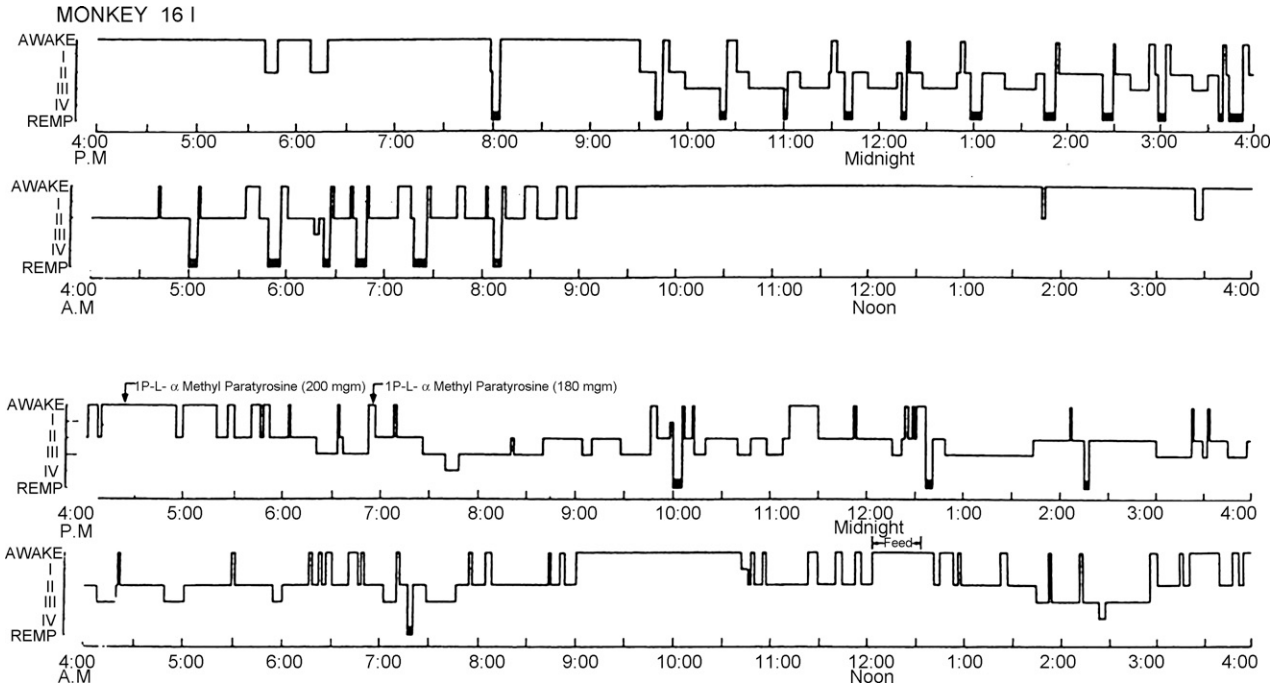

Fig. 2. Weitzman et al. (1969) clearly first showed a decrease of REM sleep (black marks) in monkeys submitted to i.p. injection of AMPT (200 mg followed by 180 mg, 2 1/2 h later. Top: control; bottom: AMPT. Reprinted from *Life Science*, with permission.

syndrome similar to that of REM sleep" (p. 180). "REM sleep was never obtained when eserine or reserpine alone were administered to the intact animal" (p. 181) (although Jouvet and Michel (1960), in the intact cat, and Jouvet (1962), in midbrain transected cats, had induced REM sleep and REM sleep-like behavior, respectively, after eserine administration). Thus, decreasing or eliminating monoamines did not prevent REM sleep from occurring under conditions of choline esterase inhibition.

3.1.8. 1971

Wyatt et al. (1971) had the opportunity to administer AMPT and α-methyl-*p*-phenylalanine (AMPHe), another inhibitor of catecholamine synthesis, to patients for therapeutic purposes (two with essential hypertension, four with pheochromocytoma, one with Huntington's chorea, and one with *dystonia musculorum deformans*). All previous medications were discontinued for at least 10 days before the beginning of the study. Patients received identical capsules, administered four times a day, containing either placebo or AMPT at a maximum dose of 2–3 g/24 h. Sleep recordings were processed every day over five nights. "In all patients, AMPT or AMPHe administration was associated with an elevation in total REM sleep ranging from 3–52% ($P < 0.05$). This increase seemed to be related to an increase in the length of each REM sleep period, because the total number of REM sleep cycles was unaffected. Three patients on AMPT had decreased REM sleep after 5 nights" (p. 64). During the post-drug placebo period, there was a decrease in REM sleep in all patients (from 3% to 77%). Finally, lumbar punctures were performed at the time of maximum AMPT dose, and showed a 59% reduction in homovanilic acid (HVA) levels. This result is in general agreement with the findings of Weitzman et al. (1969).

King and Jewett (1971) administered AMPT i.p. to cats and observed an increase in both REM sleep and total sleep. The doses were 25, 50, and 100 mg/kg. The effect lasted for 16 h with the two higher doses. Noradrenaline concentrations were decreased at 8 h (after i.p. injection) in the medulla oblongata, pons, midbrain, thalamus, and septal area. It was not significantly different in the cortex. The authors concluded: "This does not support the noradrenaline hypothesis of REM sleep" (p. 188).

Dunleavy et al. (1971) administered several compounds with anti-hypertensive properties to humans. One of them, debrisoquine (20 mg the first day, 40 mg the five following days, and 60 mg for four additional l4 days), decreased REM sleep from the second day onward. The maximum decrease, which was followed by a rebound after discontinuance, was observed with 60 mg. A 200 mg overdose suppressed REM sleep. One hundred and twenty milligrams of propanolol, a β-noradrenergic blocking compound, did not change the amount of REM sleep. In Section 4, the authors underlined the similarity between the effect of debrisoquine and that of IMAOs.

Hartmann et al. (1971) injected 6-hydroxy-dopamine (6-OHDA) intracisternally into rats. Two hundred micrograms were injected, followed by a second administration 72 h later (300 μg). One week later, the NA concentration in the brain had decreased to 27% of the control level, and was at 41% of the control level after 21 weeks. Two to 3 weeks after both injections, sleep–waking recordings were processed (8-h duration each). Only REM sleep was modified, increasing from 48.4 to 69.7 min ($P < 0.002$). "6-OHDA seems to increase both number and length of REM sleep periods but there is a much more prominent effect in the latter (1.9 vs 2.4 min, $P < 0.005$), suggesting that the mechanism controlling the length of REM sleep periods may be particularly influenced by catecholamines" (p. 427).

Schildkraut and Hartmann (1971) undertook a 72-h REM sleep deprivation on rats and quantified noradrenaline metabolism. One hundred and sixty micrograms of tritiated NA was injected intracisternally (icv) under light ether anesthesia at the end of the deprivation period. The rate of disappearance of the H^3-noradrenaline in the brain was increased in deprived animals 2 h after injection ($P < 0.001$). After a 2-h rebound, there was a decrease in metabolites and tritiated noradrenaline. In contrast, endogenous NA and serotonin were higher. Five hours after injection, there was a decrease in tritiated noradrenaline and in metabolites, while endogenous noradrenaline was unchanged.

After REM sleep rebound, only endogenous serotonin was higher. "The unchanged levels of endogenous noradrenaline in the brain of deprived animals, in the face of an increase in the rate of disappearance of H^3-noradrenaline from the brain, suggests that the rate of synthesis of endogenous noradrenaline was increased in deprived animals to compensate for the increase of utilization of noradrenaline (as determined by the rate of disappearance of icv administered H^3-noradrenaline from the brain" (pp. 23–24). Taking into account their own research as well as that of Pujol et al. (1968), the authors concluded: "These studies suggest that there is an increase in the synthesis and utilization of noradrenaline during the period of REM sleep deprivation... A high rate of noradrenaline synthesis relative to its utilization would be consistent with the role proposed for REM sleep in the regulation of central catecholaminergic neural system" (pp. 25–26).

3.1.9. 1972

Jones (1972) injected cats i.p. with several compounds that modulate the influence of noradrenaline. Inhibiting catechol-*O*-methyl transferase (COMT) by tropolone (50 mg/kg) induced a rebound of REM sleep after an induced waking period. In combination with DOPA (25 mg/kg), tropolone increased REM sleep. In contrast, desipramine (5 mg/kg), an inhibitor of NA reuptake, suppressed REM sleep for 15 h. Likewise, the short-lasting IMAO (tranylcypromide: 8 mg/kg) suppressed REM sleep for 20 h, while long-lasting inhibitors (phenylprazine: 10 mg/kg; pargyline: 100 mg/kg) suppressed REM sleep for 90 h. The author postulated that cells of "the pontine tegmentum which contains both noradrenaline and MAO may be involved in REM sleep through the release of deaminated metabolites of noradrenaline".

Petitjean et al. (1972) showed in cats that an intraventricular (icv) injection of 2.5 mg of 6-OHDA performed 1 h after the administration of 10 mg/kg clomipramine, followed by a second injection of 2.5 mg 6-OHDA 24 h later, leads to a decrease in cerebral catecholamines, without disturbing serotonin functioning.

The same team (Laguzzi et al., 1972) studied the influence of icv 6-OHDA administration on sleep, again in cats. The authors observed an initial suppression of REM sleep, followed by a lower than normal amount that lasted more than 18 days (Fig. 3). They hypothesized that the intact remaining catecholaminergic neurons were able to generate the remaining REM sleep. The long-lasting strong decrease in REM sleep highlighted the crucial role of noradrenergic neurons in the executive mechanisms of REM sleep. It can be added that PGO waves were not modified during REM sleep.

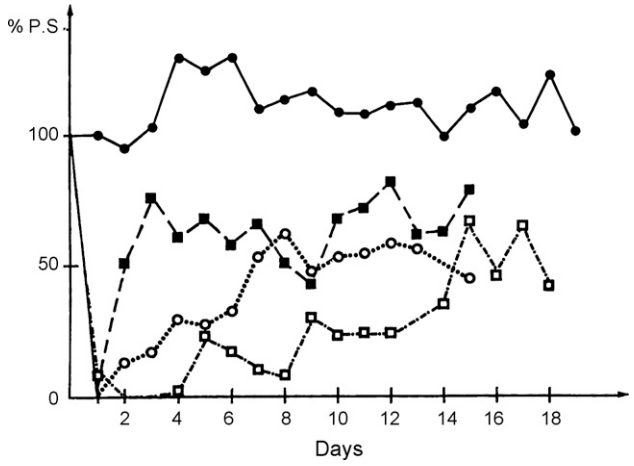

Fig. 3. Laguzzi et al. (1972) demonstrated that injection of 6-OHDA (icv) to cats induced a suppression of REM sleep at first, followed by a partial recovery, the decrease lasting more than 18 days. Ordinate: percentage of REM sleep. Abscissa: days. Filled circles and solid line: control (Ringer). Open squares and dotted line: after 5 mg of 6-OHDA. Open circles and dotted line: after 2.5 mg. Filled squares: after 1.2 mg. Reprinted from *Brain Research*, with permission.

Jouvet (1972) published a major review on monoamines and acetylcholine functions in the sleep–waking cycle. This paper on "wet" neurobiology was associated with another major review by Moruzzi centered on corresponding more classical "dry" processes (Moruzzi, 1972).

3.1.10. 1973

Panksepp et al. (1973) injected 6-OHDA bilaterally into the ventral noradrenergic ascending funiculus of cats at the mesencephalic level. "On subsequent days ... animals exhibited an increase in deep slow wave sleep and REM sleep... It was attributed to a slight increase in duration and the number of REM sleep periods (10.4 to 12.7%)" (p. 238).

In addition, Hartmann and Schildkraut (1973) quantified urine concentrations of 3-methoxy-4-hydroxy-phenyl-glycol (MHPG), the specific metabolite of noradrenaline, in patients with depression and hypomanias. There was "an inverse correlation between REM sleep duration and MHPG excretion (which) is consistent with the inverse relationship between REM sleep time and central catecholaminergic activity suggested by pharmacological studies" (p. 414).

Still the same year, Sinha et al. (1973) quantified tyrosine hydroxylase activity in rats after REM sleep deprivation. "Ninety-six hours of REM sleep deprivation caused a significant increase in tyrosine hydroxylase activity in the whole brain ($P < 0.05$), lower brain stem (pons and medulla: $P < 0.02$) and cerebral cortex ($P < 0.02$)". This result is in agreement with the increased NA turnover observed by Pujol et al. (1968) after a similar deprivation.

Stern and Morgane (1973b) also performed two experiments in which they first injected 0.15 mg/kg of reserpine i.p. into cats. Like Matsumoto and Jouvet (1964), they also observed a suppression of REM sleep, but contrary to these earlier authors, the effect of reserpine was not reversible by DOPA. In contrast, 0.125 mg/kg of reserpine injected daily into the ventricles (icv) increased REM sleep from 14% to 27% of the total recording time on the second day. While noradrenaline levels were decreased in 12 brain structures after i.p. injection, after icv injection the levels were only lower in the cerebellum, mesencephalon, medial hypothalamus, and occipital cortex.

In the second experiment (Stern and Morgane, 1973a), the same authors injected cats with a single dose of AMPT (75 mg/kg) and recorded them for 8 h. AMPT induced a significantly lower concentration of noradrenaline in 10 brain structures, while REM sleep increased ($P < 0.05$). The authors put forward the hypothesis that "the function of REM sleep might be to maintain or restore catecholamine activity in the central nervous system" (p. 305). Fifteen years later, Siegel and Rogawski (1988) proposed a similar hypothesis.

Satoh and Tanaka (1973) published a paper on the influence of fusaric acid (5-butylpicolinic acid), a specific inhibitor of dopamine-β-hydroxylase that was already known to decrease central and peripheral levels of NA. Injection (i.p.) of a single dose of fusaric acid (30–40 mg/kg) or of its calcium salt (50–200 mg/kg) into rats suppressed REM sleep for 5–10 h. Thereafter, there was a rebound, and the normal amount reappeared about 30 h after drug administration. Large doses (over 70 mg/kg of fusaric acid or over 300 mg/kg of the calcium salt) suppressed REM sleep for a longer duration, and the rebound lasted for up to 2 or 3 days (Fig. 4). In some cases, there was no rebound after the large doses. "This might be due to a shift in the level of need for REM sleep to a lower one,

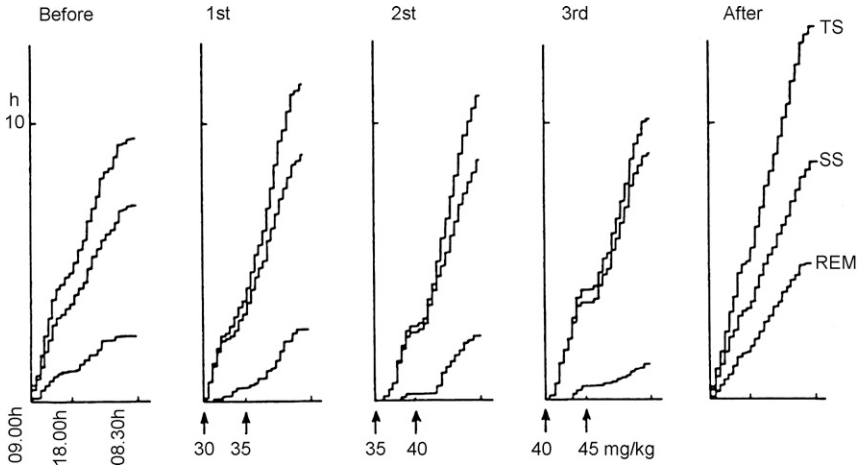

Fig. 4. Satoh and Tanaka (1973) injected (i.p.) two doses of fusaric acid to cats during three consecutive days. REM sleep was first increasingly suppressed by this blocker of dopamine-β-hydroxylase, then decreased. SS: slow-wave sleep; TS: total sleep. Reprinted from *Experientia*, with permission.

the level being determined by many biological parameters, including the concentration of noradrenaline in the body that can be manipulated by the drug" (p. 178).

Unlike Laguzzi et al.'s (1972) icv administration, Zolovick et al. (1973) injected cats bilaterally with 6-OHDA into the dorsolateral pontine tegmentum and observed lower NA concentrations in many structures of the forebrain. The dose was 15 μl of a 40 mg/ml solution. As confirmation, the main lesions concerned the locus coeruleus. REM sleep was decreased for up to 25 days after the lesion, while slow-wave sleep was increased. It should be emphasized that serotonin levels were also lower in corresponding anterior structures.

Matsuyama et al. (1973), in a paper written in French, described the effects of 500 μg of 6-OHDA (icv) administered to rats. In the chronic state, REM sleep first nearly disappeared, then it decreased relative to controls for up to 6 days, and finally it recovered up to 90% by 8 days after injection. A decrease of 10% lasted up to the 51st day (Fig. 5). Descriptions of other behavioral stages were

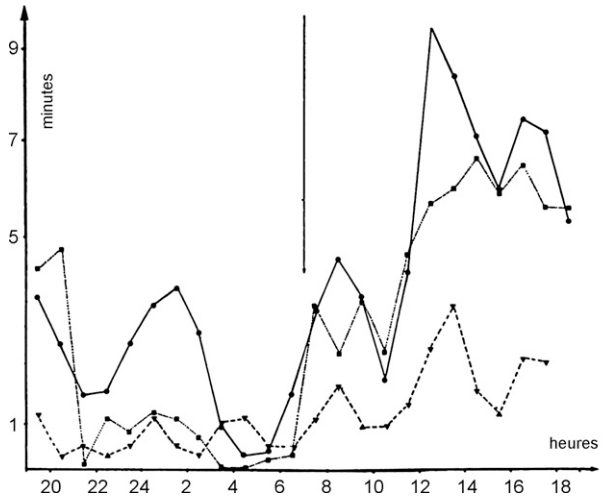

Fig. 5. The injection (icv) of 6-OHDA to rats performed by Matsuyama et al. (1973) first induced nearly suppression of REM sleep (dashed line when compared to control dark line), then a strong decrease up to day 6. The dotted line which represented the mean value of REM sleep from days 46 to 51, showed that there was a nearly recovery at this time. Each point represented the mean value of 128 measures for the control and 72 measures for AMPT. Heures: hours. Ordinate: minutes. Abscissa: hours. Arrow: light on. Reprinted from *Brain Research*, with permission.

difficult because the animals showed cortical slow-wave sleep patterns in spite of arousal.

Chu and Bloom (1973) recorded the noradrenergic neurons of the locus coeruleus in cats. These were first identified by monoamine oxidase inhibitors. Contrary to what is seen in rats, they were diffusely distributed in the locus coeruleus. The neurons fired by bursts during REM sleep.

3.1.11. 1974

Chu and Bloom (1974) published a more complete paper related to their previous preliminary article. The majority of locus coeruleus neurons situated in the medial part of the nucleus fired by bursts during the ponto-geniculo-occipital spikes of REM sleep. Laterally or dorsally located NA neurons fired more slowly and their firing tended to decrease during REM sleep.

Stein et al. (1974) administered (i.p.) a single dose of 200 mg/kg AMPT to cats. Five to 8 h after injection, there was an increase in REM sleep accompanied by a decrease in NA levels in the cortex, striatum, thalamus, hypothalamus, mesencephalon, pons, and cerebellum. As there was an increase in serotonin in the cortex and pons, the authors attributed the behavioral change to these two modifications.

Stern and Morgane (1974), taking into account all of the data available at the time, postulated that the function of REM sleep is to repair catecholamine systems (here also, see later Siegel and Rogawski, 1988). Although such a process may occur during waking and slow wave sleep, it is "most efficient during REM sleep" (p. 23).

Fuxe et al. (1974) administered (i.p.) 5 mg/kg of piperoxane to rats; this compound antagonizes the effects of clonidine (the α_2-nordrenergic agonist) on sedation and blood pressure lowering. However, it was also known to increase cortical NA turnover. It did not affect REM sleep.

By histochemical analysis, Jones and Moore (1974) found no subdivisions of NA neurons in the locus coeruleus of cats.

Conclusion. At the beginning of this first period of research into the influence of noradrenaline, the first molecules to be studied were those acting globally on monoamines, the central increase of which inhibited REM sleep. Other results showed both positive and negative influences of this neuromodulator. However, the initial findings with AMPT (Weitzman et al., 1969; Wyatt et al., 1971), α-methyl-DOPA (Dusan-Peyrethon et al., 1968), 6-OHDA (Laguzzi et al., 1972; Zolovick et al., 1973), and inhibitors of dopamine-β-hydroxylase (Satoh and Tanaka, 1973) already supported the

Table 2
Kleinlogel et al. (1975) administered clonidine to rats *per os*, an α_2-agonist

Dosage (mg/kg p.o.)	Awake	Dozing	SWS	PS (min)	*n*
Clonidine[a]					
0.2					
Control	217	116	121	26	4
Drug	109	313	58	0	
% of control	50*	270*	48	0	
1.0					
Control	184	142	131	24	
Drug	74	290	116	0	
% of control	40*	204*	89	0	

It inhibited REM sleep. SWS: slow-wave sleep; PS: REM sleep. Reprinted from *European Journal of Pharmacology*, with permission. *$P < 0.05$.
[a] Drugs.

hypothesis that NA plays a positive role in REM sleep-generating processes.

3.2. 1975–1984

3.2.1. 1975

Kleinlogel et al. (1975) administered clonidine (0.2 and 1 mg/kg *per os*) to rats. REM sleep was suppressed (Table 2).

Using electrophysiological methods, Hobson et al. (1975) deepened Chu and Bloom's (1974) findings by showing that the neurons of the locus coeruleus fire maximally during waking and become nearly silent during REM sleep. This result gave rise to the reciprocal model of discharges of the noradrenergic and pontine tegmentum cholinoceptive neurons.

Oswald et al. (1975) intravenously injected young adults with 150 mg of thymoxamine, an α_1-adrenergic blocking agent. The compound was administered in five successive injections made every 20 min. It increased REM sleep from 10.5% to 17.6% in 2–4 h.

3.2.2. 1976

Hartmann and Zwilling (1976) administered rats i.p. with different doses of propranolol, a β-noradrenergic blocking agent, and observed no effect on REM sleep. In contrast, only 40 mg/kg (among five other lower and higher doses administered) of phenoxybenzamine, an α_1-noradrenergic blocker, increased the REM sleep percentage by 128.3% compared to placebo-treated controls; the number of REM sleep periods increased by 132.1%. The authors concluded that REM sleep: "helps in restoring the noradrenergic system" (p. 138) (see Siegel and Rogawski, 1988; Stern and Morgane, 1973a, 1974).

Barratt et al. (1976) administered to squirrel monkeys 50 units/kg of phenylalanine ammonia-lyase (PAL), an enzyme which specifically deaminates both phenylalanine and tyrosine to form inactive products. Two hours after i.p. injection, the amount of REM sleep (recorded from 6 p.m. to 6 a.m.) had decreased from 11.4% to 2.6%. The concentration of both amino acids was only quantified after 100 units/kg. It was significantly lower 4 h after injection.

3.2.3. 1977

The team of Jean-Michel Gaillard (Kafi et al., 1977) published their initial research on this topic. Rats received (i.p.) AMPT in a complex, well-organized investigation. First, animals were injected with different doses and were killed for histochemical analysis. Then, 30 rats received 75 mg/kg at 4 h intervals: 3 series of 10 animals each received from 1 to 10 doses of the molecule, with the pH being adjusted. Some rats were injected at 7 a.m., others at 7 p.m. Hypothermia was carefully prevented by maintaining the animals at a temperature of 27 °C in the room.

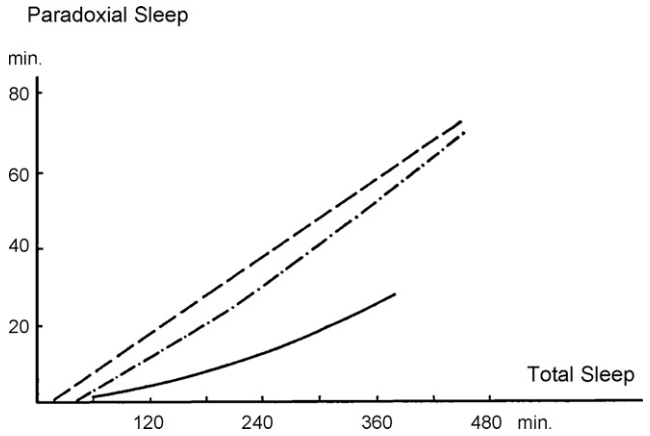

Fig. 6. Following the i.p. injection of AMPT to rats performed by Kafi et al. (1977), REM sleep was significantly decreased after 7× 75 mg/kg (—) ($P < 0.005$), whereas it was nearly unchanged after 1× 150 mg/kg (– · – · –) when compared to control: 7× solvent (– – –). Reprinted from *Brain Research*, with permission.

"Three–four injections were sufficient to completely deplete the substantia nigra (dopaminergic A_9 area), whereas 6–7 injections were necessary to do so for the locus coeruleus noradrenaline. On one hand, the fluorescence of cell bodies decreased faster than the fluorescence of nerve terminals... Curiously, after the fifth, sixth or seventh injections, the animals presented more fluorescence in the noradrenergic perikarya than after the fourth or eighth injections. It could indicate a transient and light refilling of catecholamine store, possibly a consequence of a regulatory mechanism, adapting the output of the transmitter from the cell to the limited catecholamine synthesis" (p. 127).

Behavioral results showed that "when AMPT is given at a dosage inducing an almost complete disappearance of green fluorescence of catecholaminergic neurons in the brain, REM sleep was clearly depressed (Fig. 6). The slope of the general trend of REM sleep shows a clear dose–effect relationship... It is likely that the decrease of REM sleep observed here is related to the decrease of catecholamine stores as shown by histochemistry. This lowering of catecholamine stores, especially in nerve terminals, leads to a disturbance of synaptic transmission in catecholaminergic synapses" (p. 132). "When AMPT is given at low dose, the evolution of REM sleep is different. There is a curvature with a tendency to increase the occurrence of REM sleep after 2–3 h. After such doses, the depletion of brain catecholamines is only minimal and the remaining catecholamines, especially in terminals, are likely to be sufficient to ensure a nearly normal synaptic transmission. After two injections of 75 mg/kg, we observed an enhancement of the number of REM sleep phases. In other words, the total REM sleep is slightly greater than in controls, principally due to a more frequent appearance of this stage... Thus, when catecholamine stores are only minimally diminished, the synaptic transmission in catecholaminergic synapses is only lightly impaired. The amount of REM sleep can be enhanced due to the increase of activity of a primer mechanism, leading to more frequent appearance of this stage. When catecholaminergic stores are further emptied by inhibition of catecholamine synthesis, REM sleep is markedly diminished in a dose-related manner. Thus, our experiment supports the view that an intact synaptic transmission in catecholaminergic neurons is necessary for the realization of REM sleep" (p. 132).

This remarkable study, neurochemically enlarged to encompass dopamine and NA, did not take into account the near silence of noradrenergic neurons during REM sleep that had been described just previously (Chu and Bloom, 1974; Hobson et al., 1975).

Table 3
In humans, Autret et al. (1977) studied the influence of clonidine (300 μg orally)

Stage of sleep	Control nights[a] ($n = 20$)	Clonidine nights[a] ($n = 20$)
Duration of paradoxical sleep (min)	80 ± 22	$7 \pm 1^{***}$
Duration of paradoxical sleep with rapid eye movements (REM) (min)	57 ± 21	$4 \pm 7^{***}$
Duration of stages 1 + 2 sleep (min)	295 ± 57	$401 \pm 55^{***}$
Total duration of sleep (min)	433 ± 60	$466 \pm 49^{*}$

It induced a suppression of REM sleep. Reprinted from *Eur. J. Clin. Pharmacol.*, with permission. $^{*}P < 0.05$, $^{***}P < 0.001$.
[a] Mean ± S.E.M.

Jones et al. (1977) bilaterally destroyed the locus coeruleus of cats. Noradrenaline was reduced by 85% in the cortex and by 60% in the thalamus and midbrain. REM sleep reappeared within 48 h and returned to normal amounts by the second week post-lesion, while PGO waves occurred during all sleep–waking stages but were reduced by 50% during REM sleep. The authors concluded that the neurons of the locus coeruleus "are not necessary to the occurrence of REM sleep although they may be involved in the modulation of its phasic activity" (PGO waves) (p. 493).

Also in 1977, Autret et al. (1977) administered clonidine (300 μg *per os*) to 10 volunteers. This compound, already described here as an α_2-noradrenergic pre-synaptic activating compound which thus reduces noradrenaline release (Rochette et al., 1974), decreased REM sleep from 80 to 7 min, with the specific periods involving rapid eye movements being decreased from 57 to 4 min. While yohimbine (10 mg), a pre-synaptic α_2-noradrenergic blocking compound, did not modify the amount of REM sleep by itself, when associated with clonidine (300 μg) it attenuated the decrease in REM sleep: it dropped from 85% to 20%, vs. to 1.3% with clonidine alone (Table 3).

Putkonen et al. (1977) injected (i.p.) 5–20 μg/kg of clonidine into cats and induced a dose-dependent decrease in REM sleep that lasted from 4 to 12 h (Fig. 7). The additive administration of yohimbine (2 mg/kg) partially reversed the effect of clonidine. This finding, like the previous one, is in agreement with the result of Gaillard's team.

Finally, Putkonen and Leppävuori (1977) injected (i.p.) cats with 20 mg/kg of phentolamine, which is considered to be an α_1–α_2-noradrenergic blocking compound. It increased REM sleep from 14.0% to 22.7% for the whole 16-h recording period. The authors stated that the results were not conclusive because the effects depended on the balance of pre- and post-synaptic receptors.

3.2.4. 1978

Gaillard and Kafi (1978) administered chlorpromazine and clonidine to humans. Here we will only detail the results obtained with clonidine, whose function, described in this paper for the first time, is "to stimulate pre-synaptic alpha-receptors, thus disrupting the feedback mechanism normally activated by NA which controls the release of the transmitter in the synaptic cleft" (pp. 90–91). Six normal subjects received four consecutive doses of 0.2, 0.4, 0.8, and 1.8 μg/kg. To avoid possible confusion with a rebound effect, a second group of six subjects was given only the 0.4 and 1.6 μg/kg doses, separated by one placebo night. "The two small doses of 0.2 and 0.4 μm/kg remained without effect; the general trend of REM sleep was dose-dependently depressed by the two other doses...

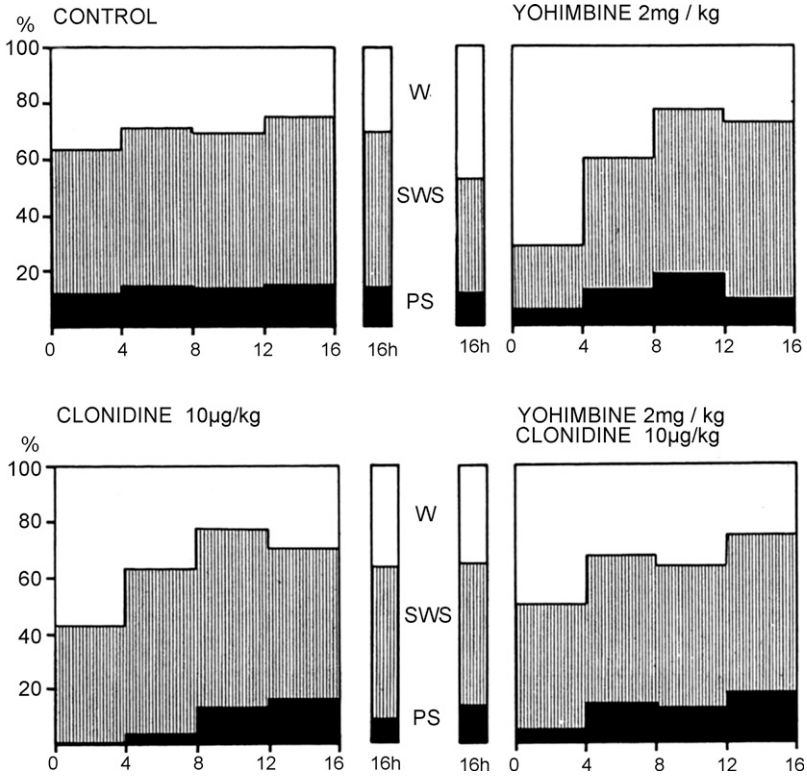

Fig. 7. Putkonen et al. (1977) observed a decrease of REM sleep in cats after clonidine i.p. injection, particularly in the first 8 h. Yohimbine in combination with clonidine practically reversed this effect. Reprinted from *Life Science*, with permission.

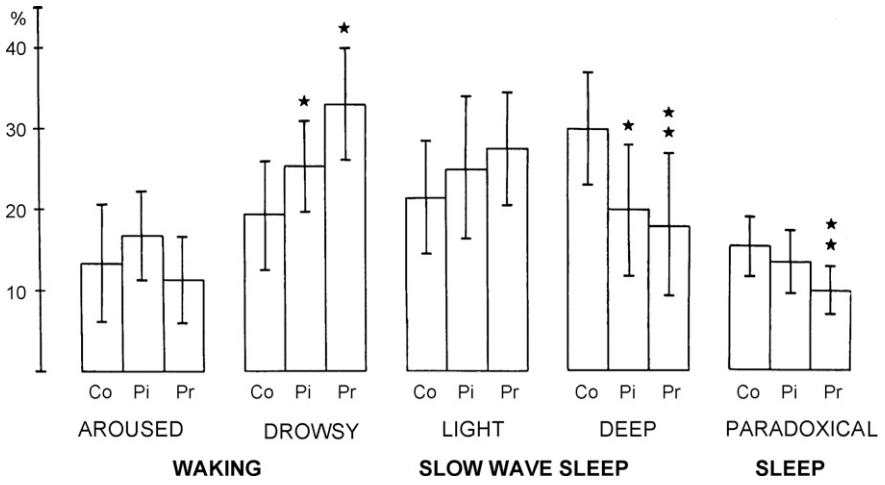

Fig. 8. Hilakivi et al. (1978) showed that after injection of 0.5 mg/kg (i.p.) of pindolol and 5 mg/kg of propranolol in rats, only the latter induced a significant ($P < 0.01$) decrease of REM sleep, when taking into account the 16 h of recording. Co, control; Pi, pindolol; Pr, propranolol. $^{*}P < 0.05$; $^{**}P < 0.01$. Reprinted from *Medical Biology*, with permission.

This stage was almost absent in about the first quarter of the night, and its production thereafter progressively returned to normal" (p. 91).

"Parallel experiments with clonidine in the rat showed that for doses from 5 to 200 μg/kg the effect was identical to the effect on man... Doses higher than 200 g/kg completely suppressed REM sleep in the period of observation (that is from 8 a.m. to 7 p.m.)" (p. 92).

Thus, this third study showed more precisely that in both rats and humans a decrease of available noradrenaline depresses REM sleep, and hence that a given level of this transmitter is necessary for the occurrence of this sleep stage. The silence or near silence of locus coeruleus noradrenergic neurons during REM sleep (Chu and Bloom, 1974; Hobson et al., 1975) was still not considered in these three studies.

Hilakivi et al. (1978) injected rats i.p. with either 5 mg/kg of propranolol or 0.1 or 0.5 mg/kg of pindolol, two β-noradrenergic receptor blockers. Only propranolol had an effect, decreasing the amount of REM sleep from 15.5% to 9.7% ($P < 0.01$) over the 16 h of recording (Fig. 8).

3.2.5. 1979

Gaillard and Kafi (1979) wrote a specific paper presenting the results obtained with clonidine which had already been described in their 1978 review.

Also in 1979, Ramm (1979) published an extensive review on REM sleep, examining all the available pharmacological and electrophysiological data related to the influence of locus coeruleus noradrenergic neurons. It provides a good overview of the results and conclusions available at the time. "1/ Lesion of the locus coeruleus and/or disruption of most of its projections exert only minor effects upon REM sleep. 2/ Pharmacological incapacitation of catecholaminergic neurons is followed by inconsistent effects upon REM sleep. 3/ Electrophysiological data do not specifically implicate the locus coeruleus in generation of REM sleep. 4/ If REM sleep participates in neuronal protein synthesis, it is a general rather than a catecholaminergic specific participation. It is improbable, therefore, that REM sleep is essential to or an important factor in the maintenance of catecholamine homeostasis. It is also unlikely that catecholaminergic neurons are REM sleep-executive, or that catecholaminergic neurons mediate REM sleep occurrence. Catecholaminergic influences on REM sleep may reflect a general neuromodulatory function of locus coeruleus neurons" (p. 415).

3.2.6. 1980

Hilakivi et al. (1980) i.p. administered prazosin, an α_1-noradrenergic receptor antagonist to cats. The doses were 0.5, 1.0, and 10 mg/kg. During the 16 h of recording, only the 1 mg/kg dose increased the amount of REM sleep from 15.6% to 26.4% ($P < 0.01$), while the latency of REM sleep occurrence decreased from 40.4 to 19 min with 0.5 mg/kg and to 11 min with 1 mg/kg (in both cases $P < 0.01$). With 10 mg/kg, REM sleep was initially suppressed but returned to control levels within 16 h.

Kafi and Gaillard (1980) injected rats i.p. with the α_2 pre-synaptic receptor blocking compound yohimbine. The doses were 10, 30, 100, 300, 1000, and 3000 μg/kg. Induced hypothermia was prevented by keeping the animals at an environmental temperature of 27 °C. "The three low doses ... induced a progressive increase in the production of REM sleep, already evident after as little as 10 μg/kg. The three higher doses also induced some enhancement of REM sleep after the initial depression, but less consistently so than the lower doses" (p. 135).

Leppävuori and Putkonen (1980) wrote an important paper that took into account both previously published and new results. The α_2-noradrenergic pre-synaptic agonists clonidine (see above), xylazine (0.5, 1, and 2 mg/kg), and α-methyl-DOPA (0.5 and 1 mg/kg) dose-dependently decreased REM sleep when injected i.p. In contrast, the α-antagonists phentolamine (10 and 20 mg/kg) and thymoxamine (5 mg/kg) strongly and transiently increased REM sleep, respectively. As already mentioned, "pretreatment with phentolamine (5 mg/kg) clearly antagonized the REM sleep suppressing effect of clonidine, whereas after 10 and 20 mg/kg phentolamine, the 16 hour REM sleep percentage significantly exceeded the control levels with little difference between the two doses" (p. 103). The authors drew the following conclusions: 1/ The present results suggest that REM sleep suppression is a general and specific characteristic of the α_2-agonists, which can be opposed by α_2-antagonists but not by blockade of α_1- nor β-adrenergic receptors...; and 2/ while the contribution of noradrenergic transmission is likely to be essential to the elaboration of REM sleep, the optimal range of noradrenergic activity with REM sleep may be considerably below that for active waking" (p. 111).

Radulovacki et al. (1980) administered to rats phentolamine (5 mg/kg i.p.) and phenoxybenzamine (10 mg/kg i.p.), another α-receptor blocker, to determine whether these α_1- and α_2-adrenergic antagonists suppress the rebound of REM sleep after a 24-h specific deprivation by the flower pot method. During the first 6 h under phentolamine, there was a significant decrease in

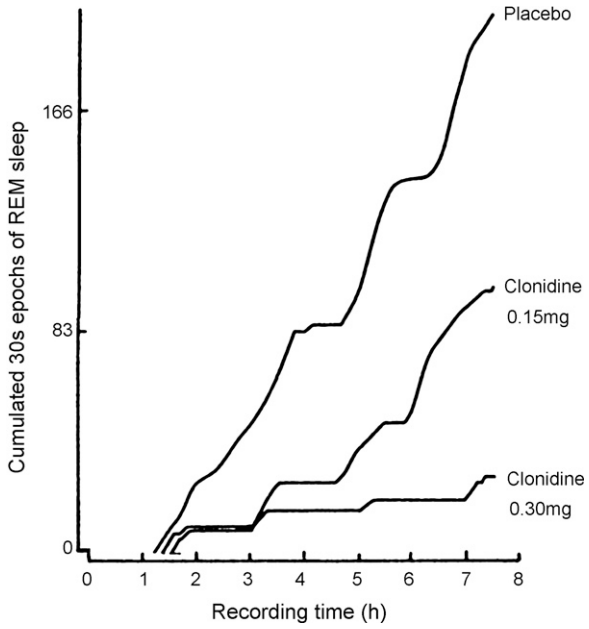

Fig. 9. Spiegel and Devos (1980) administered clonidine to healthy subjects. It induced a decrease of REM sleep. The start of recording began 30 min after drug administration. Reprinted from *British Journal of Clinical Pharmacology*, with permission.

REM sleep as compared to the deprived control ($P < 0.005$). With phenoxybenzamine, the decrease was significant for 18 h following the recovery. To verify that these strong decreases in the rebound were consecutive to a noradrenergic deficit, the concentration of MHPG was quantified in total brains with or without probenecid, which prevents its elimination from the brain. The concentration was significantly increased in both cases under the influence of the two antagonists, "indicating effective drug action on α-adrenoreceptors" (p. 54).

Milon and Enslen (1980) injected female rats with either two or five doses of 75 mg/kg AMPT. In both cases, the NA content of the locus coeruleus fell by 75%, while the dopamine content only dropped by 5 mg/kg. REM sleep decreased by about 50% after five injections, while slow-wave sleep increased.

In a double-blind study, Spiegel and Devos (1980) orally administered clonidine (0.15 and 0.30 mg) and a second compound considered to be anti-hypertensive, guanfacine (1.0 and 2.0 mg *per os*), to healthy subjects. During waking, clonidine reduced systolic blood pressure at the higher dose only ($P < 0.01$) and caused dryness of the mouth even at the lower dose. For the sleep study, the molecules were administered 30 min before the lights were turned out. REM sleep decreased by 50% following the administration of 0.15 mg of clonidine and by 80% with 0.30 mg (Fig. 9). Stage 2 increased while stages 3 and 4 showed no change. Only the higher dose of guanfacine led to a decrease in REM sleep. The REM sleep effect appeared with a shorter latency under clonidine.

Mogilnicka et al. (1980) performed REM sleep deprivation in rats for up to 72 h and investigated its effect on β-adrenergic receptor desensitization through the binding of ^{3}H-imipramine and ^{3}H-dihydroalprenolol, a β_2-antagonist. The results showed a reduction in their high affinity binding sites. The authors concluded that REM sleep deprivation is a good model of chemical treatment of depression.

Sakai (1980) carried out an electrophysiological unit recording study and wrote about PS-on and PS-off neurons, the latter being considered, in those days, as being mainly located in the locus coeruleus and the locus coeruleus-α. Pharmacological characteristics were not considered in this paper.

3.2.7. 1981

The following year, Kafi and Gaillard (1981) further studied the mechanism of clonidine influence on REM sleep in rats. Indeed, this molecule "decreases the release of noradrenaline, decreases the synthesis of NA and inhibits the spontaneous firing of noradrenergic cells in the locus coeruleus" (p. 13). A dose of 20 μg/kg decreased REM sleep, while 2.5 μg/kg increased it. Doses under 2.5 μg/kg induced a short-lasting inhibition that was followed by a facilitation which more than compensated for the initial decrease. In a subsequent experiment, AMPT (150 mg/kg) was administered 30 min prior to clonidine, but did not alter the slightly increased amount of REM sleep. Finally, 2.5 or 10 μg/kg of clonidine were injected 15 h after the administration of 2 mg/kg of reserpine. Both doses decreased REM sleep. In Section 4, the half-life of clonidine (90 min) is noted, as it could explain the dose-dependent inhibition of REM sleep. The authors again stated: "the clonidine inhibition of REM sleep in the rat is a further argument supporting the idea of a positive correlation between catecholaminergic activity and the production of REM sleep" (p. 15). Indeed, the authors recalled that clonidine decreases the output of NA at the nerve endings in the brain.

Gaillard's team (1981) also studied the influence of DMI alone (and combined with AMPT) in rats, as this reuptake-blocking compound acts specifically on noradrenaline. The authors observed a dose-dependent decrease in REM sleep at 2 and 4 mg/kg. Its co-administration (4 mg/kg) with 150 mg/kg AMPT slightly attenuated the lowering of the REM sleep when compared to DMI alone. "The results show that the inhibition of noradrenaline synthesis by AMPT is not quantitatively sufficient to induce the observed effects. It appears more probable that this decrease in REM sleep results from a collateral inhibition, with the possible participation of an anticholinergic effect" (p. 228).

Claude et al. (1981) bilaterally destroyed the locus coeruleus area in rabbits and induced a decrease in REM sleep for up to 30 days post-lesion, in addition to the already classical motor disturbances (Henley and Morrison, 1974; Jouvet and Delorme, 1965; Jouvet and Mounier, 1960; Mouret and Delorme, 1967; Sanford et al., 2001a; Sastre and Jouvet, 1979) which somewhat resemble oneiric behavior. The authors described them as "hallucinatory-like movements" (p. 145).

Braun and Pivik (1981) destroyed the locus coeruleus area in rabbits. The animals were recorded at 5- and 14-day intervals following the lesioning. The authors confirmed that atonia was not complete during REM sleep prior to the lesion. After the bilateral lesion, they observed bizarre motor activities in some cases that could suggest hallucinatory-like behavior observed in cats (Jouvet and Delorme, 1965; Sastre and Jouvet, 1979) and rats (Mirmiran, 1983; Sanford et al., 2001a). "The post-lesion occurrence of PS was inversely related to the degree of LC destruction and, accordingly, to the presence of episodes of phasic motor activation".

Radulovacki et al. (1981) published a new paper on phenoxybenzamine, the α_1-receptor antagonist which suppressed the REM sleep rebound after specific deprivation by the flower pot method (in which the animal stays on a small surface surrounded by water to prevent REM sleep because its atonia would provoke falling into the water). Here, the authors administered the molecule (10 mg/kg i.p.) 30 h before the end of a 36-h REM sleep deprivation period. This suppressed the rebound and even prevented REM sleep during the first hours of recovery. The same protocol was applied with bromocriptine, a dopamine agonist (5 mg/kg, four injections at 6-h intervals). There was nearly no rebound. "This suggests that administration of the two pharma-

cological agents prevented the generation of REM sleep pressure by fulfilling the need for REM sleep" (p. 371).

Aston-Jones and Bloom (1981a) recorded locus coeruleus neurons during the sleep–waking cycle in rats. They observed that the low frequency firing of noradrenergic neurons is highest during waking, decreases during slow-wave sleep, and is silent during REM sleep, and also that the noradrenergic neurons begin to discharge again in the few seconds preceding behavioral arousal. Thus, the target neurons of noradrenergic terminals are already in the waking state when behavioral arousal occurs—an important result for later discussions regarding dream forgetting.

The same authors also observed (Aston-Jones and Bloom, 1981b) that locus coeruleus neurons discharge by bursts during salient sensory stimulations and that NA increases the signal-to-noise ratio of neuron functioning. This observation confirmed older equivalent findings showing that noradrenaline enhances neuron efficiency (Foote et al., 1975) (see later discussion).

3.2.8. 1982

Gaillard et al. (1982) continued their research into the impact of noradrenaline on REM sleep. They first recalled the influence of the α_2-receptor agonist clonidine, which "exerts two different effects: a dose-related increase in REM sleep latency, followed by a secondary facilitation, not dose-dependent" (p. 418). Then, phenoxybenzamine (5 and 10 mg/kg) was shown to decrease REM sleep, although it was increased at 20 mg/kg. Ten milligrams per kilogram of this compound given simultaneously with clonidine (0.02 mg/kg) potentiated the REM sleep inhibition. Yohimbine, an α_2-antagonist, maximally enhanced REM sleep at 0.03 mg/kg. Simultaneously administered yohimbine and clonidine reduced REM sleep. AMPT (150 mg/kg), which had no effect on REM sleep by itself, counteracted the increase in REM sleep that was induced by yohimbine alone (0.03 mg/kg) when the two compounds were co-administered. Piperoxane (0.05–20 mg/kg), another (α_2) antagonist, inhibited REM sleep at low doses and facilitated it at higher doses. "In combination with AMPT, 1 mg/kg of piperoxane yielded a production of REM sleep identical to controls, thus suppressing the decrease seen after piperoxane alone" (p. 422). Finally, the authors administered demethylimipramine, which decreases REM sleep (Justafre and Gaillard, 1981), 30 min after AMPT. The suppressing effect of demethylimipramine on REM sleep was attenuated. "In conclusion, the present data indicate that brain catecholaminergic systems, and probably mainly the coerulean noradrenergic system, are involved in REM sleep. A facilitation of noradrenergic transmission results in an enhancement, whereas a disruption of noradrenergic transmission decreases the production of REM sleep" (p. 428).

Radulovacki and Micovic (1982) compared the effects of a 7-day REM sleep deprivation (flower pot method) with those of desipramine administration (daily 10 mg/kg i.p.) on β-adrenergic binding in the cortex in rats. Indeed, like electroconvulsive therapy, both strategies improve depression. The results showed that only desipramine (which acts on NA), significantly reduced β-receptor density, specifically by 26% ($P < 0.01$).

Masserano and King (1982) infused phentolamine (an α_1- and α_2-antagonist; 3 μg) and epinephrine (60 μg) bilaterally into the locus coeruleus of cats. During the 4-h control recording, there were 43 min of REM sleep. There were 82 min of REM sleep after the administration of phentolamine (an increase), and 9 min with epinephrine; the REM sleep interval decreased under phentolamine and increased with epinephrine.

Cespuglio et al. (1982) induced cooling of the locus coeruleus area. Both bilateral and unilateral cooling (10 °C) of the anterior and dorsal parts of the nucleus rapidly induced (latency 30–60 s) slow-wave sleep, which was associated with PGO waves and REM sleep in 40–50% of cases. If repetitive cooling was performed, there was a 17-min minimum refractory period.

3.2.9. 1983

Gaillard et al. (1983) gave the minute dose of 0.4 μg of clonidine to normal human subjects. When the total sample (16 subjects) was considered, a slight decrease in REM sleep was observed. However, in 12 of them, this sleep stage did not vary during the administration night, while there was an increase in REM sleep during the placebo of recovery night (first placebo 21.3%, clonidine 21.9%, second placebo 24.6%, $P < 0.005$). The authors called this effect "REM sleep rebound without debt". Since the half-life of the compound is 8 h, the authors concluded that it could not be inducing a direct effect after 24 h and must be changing the sensitivity of the α_2-receptors instead decreasing the efficacy of collateral inhibition. In contrast, four of the subjects showed a decreased amount of REM sleep under clonidine ($P < 0.01$) without a significant increase during the recovery night.

Gaillard (1983) published a major review on the present topic, taking into account all the biochemical and pharmacological aspects of REM sleep. With respect to the involvement of NA in this sleep stage mechanism, he first described the functioning of all pre- and post-synaptic receptors, with the former acting as both auto- and heteroreceptors. He also recalled the process of down- and up-regulation of receptors, which is consecutive to an excess or deficit of available neurotransmitters, respectively. The review's strict approach to the involvement of NA in REM sleep began with an examination of results involving lesions of the locus coeruleus. These were not very conclusive, particularly in cats, since the neurons are not tightly packed but are rather interspersed with other neurons, including cholinergic ones. The pharmacological studies were detailed first, starting with the contrasting results obtained with low and high doses of AMPT, with the former increasing, and the latter decreasing REM sleep. The decrease in REM sleep produced by clonidine was also recalled, along with the occasional secondary increase suggesting a rebound effect possibly linked to noradrenergic α_2-receptor up-regulation. In humans, the specific increase in REM sleep observed during the placebo recovery night after small doses of clonidine, without an effect during the night of administration, was again underlined. It could be related to the desensitization of α_2-receptors, which decreases the effect of collateral inhibition. The antagonist yohimbine facilitated REM sleep at low doses by blocking α_2-receptors, and decreased REM sleep at higher doses by acting on α_1-receptors. A specific paragraph was devoted to collateral inhibition and its impact on REM sleep by the induced silence of locus coeruleus noradrenergic neurons. In Section 4, J.M. Gaillard analyzed for the first time the apparent discrepancy between the electrophysiological and pharmacological results. Indeed, "electrophysiological recordings of unit activity in the locus coeruleus indicate that noradrenergic cells become silent during REM sleep, which seems to rule out their active participation in the executive mechanism of this sleep stage. In contrast, the results of pharmacological experiments suggest that when noradrenergic synaptic transmission is impaired, the production of REM sleep is hindered, whereas when this transmission is facilitated, the production of REM sleep is enhanced" (p. 219S). In addition, he insisted on the fact that collateral inhibition probably occurs more easily in the locus coeruleus, principally in rats, than in other noradrenergic areas where the neurons are more dispersed. He concluded, premonitorily: "REM sleep preparation would be positively linked to noradrenergic cell activity, but actual REM sleep realization would be negatively related to this activity" (p. 221S).

Monti (1983) wrote a detailed review on catecholaminergic mechanisms of REM sleep in which he analyzed the effects of

lesions as well as the pharmacological results available at that time. He concluded, "The data we have reviewed indicate that noradrenaline or dopaminergic neurons are not necessary for the initiation and maintenance of REM sleep... Changes in REM sleep after drug treatments could be associated not merely with the decrease or increase of a neuromodulator, but also with the disruption of a critical balance among multiple neuromodulator systems. Present evidence indicates that functional interactions of noradrenaline, serotonin, dopamine, histamine and acetylcholine systems occur during physiological sleep... (Moreover) the functional significance of the coexistence of peptides and amines in neurons involved in sleep modulation is at present unclear" (p. 1409). To my knowledge, this was the first time that the possible function of peptides in REM sleep was alluded to in relation to noradrenergic processes.

Hilakivi (1983) injected cats i.p. with different compounds that interact with adrenoceptors. Prenalterol (20 and 40 mg/kg), a β_1-agonist, increased REM sleep in a dose-related manner. Salbutamol (40 mg/kg), a β_2-agonist, decreased REM sleep over the first 4 h. Metoprolol (10 and 50 mg/kg), a β_1-antagonist, did not significantly modify REM sleep despite inducing an increased drowsy state at high dose. The increase in REM sleep induced by 1 mg/kg of prazosin (α_1-antagonist) was nearly suppressed by metoprolol (10 mg/kg). The increase in REM sleep induced by 10 mg/kg of phentolamine (α_1- and α_2-antagonist) was suppressed by 5 mg/kg of propranolol (β-antagonist). The decrease in REM sleep (and deep slow-wave sleep) induced by 0.01 mg/kg clonidine was potentiated by metoprolol (10 and 50 mg/kg) and propranolol (5 mg/kg), while the drowsy state was increased. Taking into account all the available data, the author concluded: "The results ... support the view that central β_1- and α_1-adrenoceptors have opposite functions in the modulation of REM sleep. REM sleep can be increased at least by two β-adrenoceptor stimulants and by three α_1-adrenoceptors blocking drugs. Conversely, REM sleep may be decreased by three β-adrenoceptor blocking drugs and one α_1-adrenoceptor stimulant" (p. 116).

Vogel (1983) compared the effects of at least 3 weeks of REM sleep deprivation and imipramine administration in humans as determined by other authors. The results showed that both treatments have similar clinical efficacy. Moreover, antidepressive compounds act by decreasing REM sleep, and patients who were not improved by REM sleep deprivation were also not improved by imipramine. Both behavioral and pharmacological REM sleep deprivations were followed by a rebound. Finally, in animals, REM sleep deprivation increased motor, aggressive, pleasure-seeking, and feeding activities, which are the reverse of the behavioral changes seen in human endogenous depression.

Foote et al. (1983) wrote a major review on the locus coeruleus (512 references!). They first insisted on the fact that the rat locus coeruleus, with its homogenous noradrenergic neurons, is a better model than the cat locus coeruleus, which is composed of noradrenergic neurons interspersed with other kinds of neurons. This difference can explain the dual results first observed in cats (Chu and Bloom, 1973, 1974). They recalled the silence of its noradrenergic neurons during REM sleep, accounting for the "permissive" function of this transmitter for this sleep stage. They also confirmed the notion of the enhancement of the signal/noise ratio of neuron functioning by this transmitter (see previously (Aston-Jones and Bloom, 1981b; Foote et al., 1975): "the locus coeruleus-noradrenergic system acts at many target sites to somehow enhance the reliability and efficiency of feature extraction from sensory input" (p. 899). The data on locus coeruleus neuron functioning were later confirmed and extended by further studies (Jacobs, 1986; Mallick et al., 1990, 2004; Thankachan et al., 2001).

3.2.10. 1984

The following year, Hilakivi and Leppävuori (1984) continued their research by adding the α_1-agonist methoxamine (0.5–3 mg/kg) to their previous injections into cats of prazosin (the α_1-antagonist), which increased REM sleep. When given alone, methoxamine increased REM sleep latency (from 52 to 342 min at 3 mg/kg) and decreased the number of phases at both 4 and 16 h. When prazosin was given simultaneously with clonidine (the α_2-agonist), the decrease in REM sleep was potentiated only at the highest dose of prazosin (10 mg/kg). The authors concluded that, "moderate inhibition of central α_1-adrenergic transmission, without concurrent blockade of α_2-adrenoceptors, is sufficient to promote REM sleep in the cat" (p. 370).

Gordon and Lavie (1984) first administered tablets of propranolol to dogs, without significant results. Then, they subcutaneously administered the α pre- and post-synaptic antagonist phentolamine alone (1 mg/kg $\times$ 6 times, one dose a day), finding that it significantly decreased the number of REM sleep episodes ($P < 0.025$) but had no effect on their length.

Pellejero et al. (1984) injected i.p. into rats the α_1-noradrenergic agonist methoxamine. At 4 mg/kg, it decreased REM sleep (11 min vs. 19 min in controls) and increased its latency of appearance (135 min vs. 73 min), without affecting slow-wave sleep. At 8 mg/kg, REM sleep was altered in the same way, but the amount of slow-wave sleep decreased and the latency of occurrence increased. The α_1-receptor antagonist prazosin was given at four doses ranging from 0.125 to 1.0 mg/kg. All decreased REM sleep (one table and one figure are not in agreement). The authors then gave methoxamine (8 mg/kg) together with prazosin, which at 0.5 mg/kg suppressed each other's effects. At 1.0 mg/kg of prazosin, there was a decrease in the amount of REM sleep compared to controls rats, while slow-wave sleep was unchanged. Finally, while yohimbine (3 mg/kg), the α_2-antagonist, decreased both slow-wave sleep and REM sleep, when it was given together with methoxamine (4 mg/kg) there was a stronger decrease in REM sleep accompanied by a decrease in slow-wave sleep. "Thus, previous blockade of α_2-adrenoceptors increases the α_1-receptor activation effects on waking and sleep" (p. 372).

Conclusion. In this second decade of results, both positive and negative influences of NA on REM sleep continued to be found. However, convergent arguments supported the need for REM sleep occurrence. Among other findings, new AMPT results (Kafi et al., 1977; Milon and Enslen, 1980), the introduction of the α_2-agonist clonidine in research on animals (Kleinlogel et al., 1975; Putkonen et al., 1977) and humans (Autret et al., 1977; Spiegel and Devos, 1980), the use of different α- and β-agonists (Hilakivi, 1983; Hilakivi et al., 1978, 1980), and, finally, the deamination of phenylalanine and tyrosine (Barratt et al., 1976), all confirmed its positive influence. Excellent summaries can be found in Leppävuori and Putkonen (1980) and Gaillard (1983).

3.3. 1985–1994

3.3.1. 1985

Gaillard (1985) wrote a short article on the action of clonidine on REM sleep mechanisms. In rats, this α_2-receptor agonist had no influence on REM sleep under 2.5 μg/kg. At this ongoing dose, REM sleep was delayed. However, with doses up to 320 mg/kg, although REM sleep was suppressed in the first hour, there was a rebound effect. When AMPT was given prior to clonidine, the increase in REM sleep was not prevented. The author postulated that the increase in REM sleep "may be related to a decrease of sensitivity of the α_2-adrenoceptors, as a consequence of their transient stimulation by the agonist, whereas the increase of REM sleep latency is probably due to direct stimulation of α_2-adrenoceptors" (p. 24).

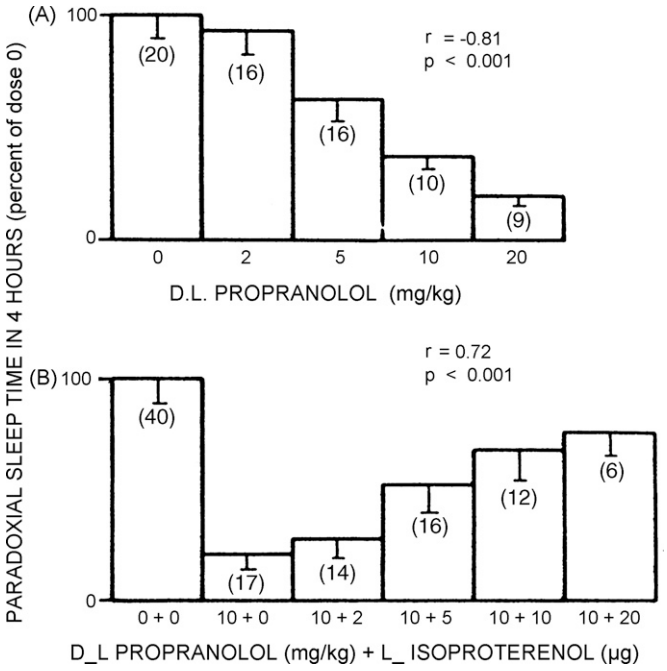

Fig. 10. Lanfumey et al. (1985) showed in rats that propranolol decreased REM sleep and that addition of isoproterenol reversed this effect. In parentheses, the number of tests for a given dose (abscissa). Reprinted from *Brain Research*, with permission.

Lanfumey et al. (1985) studied the involvement of β_1- and β_2-receptors on REM sleep-generating processes. Rats were injected intravenously or icv. D,L-Propranolol and L-propranolol (β_1, β_2 blockers), at 10 mg/kg, reduced REM sleep in the first 4 h of recording by decreasing REM sleep episodes. Acebutolol (β_1-blocker) nearly suppressed REM sleep at 10 mg/kg. L-Isoproterenol (β_1 and β_2-agonist), at 10 mg/kg, had no effect. Prenalterol (β_1-agonist), at 20 mg/kg, had no effect, and neither did clenbuterol, a β_2-agonist. The authors were then able to dose-dependently compensate for the D,L-propranolol-induced decrease in REM sleep with the β_1- and β_2-agonist L-isoproterenol (Fig. 10). Prenalterol, the β_1-agonist, also suppressed the REM sleep depression by D,L-propranolol. The β_2-agonist clenbuterol was without effect on the D,L-propranolol-induced REM sleep insomnia, and at high doses increased the REM sleep deficit. There is "some evidence (that) only the β_1 adrenoceptors are primarily involved in the regulation of REM sleep" (p. 565).

Depoortere (1985) confirmed the decrease in REM sleep induced by α_2-receptor agonists in rats. Moreover, he showed, again in rats, that clonidine (0.1 mg/kg i.p. or 0.5 mg/kg *per os*), and other α_2-agonists induced hippocampal theta activity and high amplitude cortical spindles, and thus the intermediate stage (Depoortere and Loew, 1973; Gottesmann, 1964, 1967, 1972; Weiss and Adey, 1965), for reference see Gottesmann (1996).

Greene and Carpenter (1985) recorded neurons from the caudal third of the nucleus reticularis pontis caudalis to the abducens nucleus in anesthetized cats. Although these neurons were identified by antidromic stimulation of the reticulospinal tract, it is of interest that, among several transmitters studied, five neurons were stimulated by noradrenaline while four were inhibited. In Section 4, the authors emphasized the agreement of their results with the reciprocal interaction model of Hobson et al. (1975). The possible activating influences of NA on pontine neurons was later underlined (Gerber et al., 1990; Mühlethaler et al., 1990).

Sakai (1985) wrote a new review devoted to REM sleep mechanisms. With respect to noradrenergic processes, he first insisted on the influence of the lateral and ventromedial medulla oblongata areas, which are surrounded by noradrenergic neurons (A_1–A_5 areas), with some neurons of the nucleus reticularis magnocellularis firing specifically during REM sleep (REM sleep-on neurons) and others becoming silent (REM sleep-off neurons). Then, in a model, he highlighted the relationship between the pontine area underlying the locus coeruleus, the locus coeruleus-α, and the medulla oblongata. Further, the silence of noradrenergic neurons during REM sleep created a disfacilitation of spinal motoneurons, thus contributing to REM sleep atonia. Finally, he emphasized that NA seemed to have no clear-cut influence on EEG, since similar cortical activity occurred during waking and REM sleep in spite of the silence of noradrenergic neurons in the latter stage.

Betts and Alford (1985) administered four β-blockers: atenolol, propranolol, metropolol and pindolol to 10 female volunteers in a placebo-controlled trial. The night recordings showed that REM sleep was decreased by all compounds while waking was increased.

Kanno and Clarenbach (1985) studied the influence of clonidine (225 µg) and yohimbine (15 mg) *per os* in healthy subjects. The time of medication was 10:00 p.m. and the lights were switched off at 11:00 p.m. The latency of REM sleep was increased by 118.6% ($P < 0.001$) by clonidine, and its percentage dropped from 18.1% to 7.5% ($P < 0.001$); its latency increased from 78.3 to 196.9 min, while stages 2–4 increased. Under yohimbine, slow-wave sleep stages decreased while REM sleep increased, from 18.1% to 20.1% ($P < 0.05$). When both compounds were administered simultaneously, REM sleep decreased from 18.1% to only 11.2% ($P < 0.001$), and its latency of occurrence increased to 153.1 min ($P < 0.05$), while it was reduced when clonidine was given alone. Clonidine decreased blood pressure measured at 1:00 a.m. The authors concluded that the results were in agreement with Jouvet's (1972) theory of NA involvement in REM sleep-generating processes.

3.3.2. 1986

Nicholson et al. (1986) administered two antidepressive compounds to healthy male subjects between 17 and 33 years old. "Nomifensine (50 and 100 mg) and mianserin (20 and 40 mg) reduced the duration of REM sleep and the REM/non-REM ratio ($P < 0.01$). The larger dose of mianserin (40 mg) delayed the appearance of REM sleep ($P < 0.01$) and the larger dose of each drug reduced the number of REM sleep periods ($P < 0.05$)" (p. 272).

Rasmussen et al. (1986) recorded the locus coeruleus of cats with microelectrodes. This paper extended previous findings (Chu and Bloom, 1974; Hobson et al., 1975) by showing a complete silence of noradrenergic neurons during REM sleep. This result also confirmed data obtained in rats (Aston-Jones and Bloom, 1981a).

Caballero and De Andres (1986) performed unilateral lesions in brain stem areas involving the locus coeruleus in cats. The authors observed a significant increase of REM sleep only in the four cats which showed a specific lesion of the locus coeruleus (taken from the abstract). These results were in accordance with those of Cespuglio et al. (1982), but not with those obtained after bilateral lesion carried out by Jouvet and Delorme (1965) in cats and by Claude et al. (1981) in rabbits. Jones et al. (1977) also observed a decrease in REM sleep in cats that lasted for at least 1 week following the partial bilateral lesion of the locus coeruleus; the lesion only induced a 60% decrease in the NA concentration in the thalamus and midbrain.

Our understanding of locus coeruleus functioning was also enriched by Aston-Jones et al. (1986), who determined the different afferents of this nucleus by retrograde tracer. While minor inputs came from the dorsal cap of the hypothalamic paraventricular nucleus (and spinal intermediate grey), major inputs came from the medulla oblongata paragigantocellular and prepositus hypoglossi nuclei.

The same year, Ennis and Aston-Jones (1986) showed strong excitatory responses and low inhibitory influences arising from the paragigantocellular nucleus and innervating locus coeruleus. The monosynaptic response (latency 11.7 ms) was blocked by kynurenic acid, an excitatory amino acid antagonist. The inhibitory responses had a latency of 22.8 ms. These data suggested that the excitatory and inhibitory responses resulted from two different neuron populations. "However, it is also possible that the inhibitory responses were mediated by a collateral feedback mechanism among locus coeruleus neurons" (p. 303).

Mirmiran (1983) had previously carried out research on sleep in neonate rats. Here, he first studied (Mirmiran, 1986), again in pups, the effects of subcutaneous injections of clomipramine, which blocks the reuptake of noradrenaline and serotonin, and clonidine. Clomipramine (15 mg/kg) was given twice a day (9:00 a.m. and 6:30 p.m.) on days 8–21; clonidine (50 mg/kg) was administered at 9:00 a.m. and 1:30 p.m., with a third injection of 100 mg/kg at 6:30 p.m. Both compounds induced "a clear cut reduction of more than 50% in the amount of REM sleep time throughout the 2-week treatment period" (p. 384). In adulthood, these rats, which had been treated after birth, revealed: (1) a much higher incidence of myoclonic jerks during REM sleep; (2) an increased mean REM sleep time; (3) shorter REM sleep latency. In relation to humans, the author mentioned one publication describing increased myoclonic jerks during REM sleep in a boy whose mother received α-methyl-DOPA during pregnancy. Finally, the author suggested that the silence of noradrenergic neurons during REM sleep "might modify the sensitivity of the noradrenergic receptors ... REM sleep might provide the neuronal activity necessary for brain maturation and plasticity during development at a time when attentive wakefulness is poorly developed" (pp. 385–386).

Mäkelä and Hilakivi (1986) injected rats i.p. with yohimbine (1 mg/kg), an α_2-antagonist, phentolamine (10 mg/kg), a potent α_1- and α_2-antagonist, and prazosin (0.5 and 1 mg/kg), an α_1-antagonist. Yohimbine did not change the amount of REM sleep. In contrast, phentolamine increased REM sleep, as did prazosin (at both doses) on the global 12-h recording. This increase was only obtained at the cost of drowsy waking. Since the increase in REM sleep occurred after an initial decrease in this sleep stage, it is possible that the increase resulted from a continuous increase of α-receptors and a progressive decrease of the α-receptor blocker.

Mogilnicka et al. (1986) showed that a 72-h REM sleep deprivation in rats decreases β-adrenoceptors in the cortex, while α_1-adrenoceptor binding was not changed.

3.3.3. 1988

Monti et al. (1988) studied the influence of DSP-4 (*N*-(2-chlorethyl)-*N*-ethyl-2-bromobenzylamine), an NA neurotoxin. Fifty milligrams per kilogram were injected i.p. into rats. The recording lasted 10 h over the 6 days following injection. The amount of REM sleep decreased from 39 to 7 min on days 1–2; there was a return to the control level on days 3–4, and an increase to 52 min on days 5–6; there was thus a late rebound effect. These results were obtained with a relatively low but significant decrease in the concentration of noradrenaline (221 pg/mg vs. 363 pg/mg) in the mesencephalon, with much stronger decreases in the cortex (41 pg/mg vs. 320 pg/mg) and the hippocampus (41 pg/mg vs. 374 pg/mg). The authors observed that the already known decrease in REM sleep under clonidine (3.1–12.5 μg/kg) was not modified by DSP-4. The same was true after co-administration of yohimbine (3 mg/kg) and the α_1-agonist methoxamine (2.0–8.0 mg/kg). Finally, clenbuterol (12.5, 25.0 and 50.0 μg/kg), a β_2-agonist, significantly decreased REM sleep only when associated with DSP-4. The authors concluded that their results indicated a permissive function of NA in REM sleep-generating processes. It is notable that later results (Fritschy and Grzanna, 1991) showed that the affinity of DSP-4 to NA terminals varies according to the structures, suggesting that NA uptake is pharmacologically distinct in the locus coeruleus and in other central structures.

Sakai (1988) continued to explore the mechanisms of REM sleep-generating processes. He showed that muscarinic influences "exert an inhibitory or disfacilitatory influence on (noradrenergic) REM sleep-off cells, supporting the mutual inhibitory interaction hypothesis (Hobson et al., 1975), ... the tonic excitation of REM-on cells (being) more critical for the initiation and maintenance of REM sleep" (pp. 255–256).

Ennis and Aston-Jones (1988) stimulated neurons of the medulla oblongata paragigantocellular nucleus and found that 73% of the locus coeruleus neurons were activated while 16% were inhibited. After blocking excitatory amino acid (EAA) transmission by icv-administered kynurenic acid and γ-D-glutamylglycine, the stimulation of neurons only induced the inhibitory response in the locus coeruleus neurons. This inhibitory response could have resulted from adrenergic neuron activation (Cederbaum and Aghajanian, 1976) of the C_3 nucleus (Pierpibone et al., 1988), or "activation of collaterals of other locus coeruleus neurons which are excited by the paragigantocellular nucleus" (p. 3651). The excitatory response was not prevented by *N*-methyl-D-aspartate (NMDA), nor by quisqualate antagonists. Consequently, the EAAs could act at the kainate receptor level. Neither anti-muscarinic agents nor anti-nicotinic compounds modified the excitatory responses. Thus, acetylcholine was not involved.

Siegel and Rogawski (1988) wrote a detailed review hypothesizing that "REM sleep serves to up-regulate and/or prevent down-regulation of brain NA receptors" (p. 227). Indeed, (1) locus coeruleus neurons become silent during REM sleep; (2) NA itself or its agonists down-regulate noradrenergic receptors; (3) The effects of REM sleep deprivation are similar to those of noradrenergic receptor down-regulation. Accordingly, the function of REM sleep would be to recover noradrenergic receptor sensitivity at an optimal level, which is in near concordance with the concept of Stern and Morgane (1974), Hartmann and Zwilling (1976), and Mirmiran (1986).

3.3.4. 1989

Ennis and Aston-Jones wrote two papers related to inhibitory influences of the medulla oblongata on the locus coeruleus. In the first, antidromic stimulation of the locus coeruleus (Ennis and Aston-Jones, 1989b) activated the prepositus hypoglossi nucleus of the medulla oblongata, the orthodromic stimulation of which inhibited the locus coeruleus neurons (52 out of 63). Only 3 out of 22 were weakly activated. The authors hypothesized that the inhibitory responses were related to adrenergic C_3 influences of the prepositus hypoglossi nucleus, although the α_2-antagonist idazoxan did not alter the evoked inhibition. In the second paper (Ennis and Aston-Jones, 1989a), the authors showed that the inhibition "was substantially reduced by systemic picrotoxin, an antagonist of gamma aminobutyric acid (GABA). The $GABA_A$-receptor antagonist, bicuculine methiodide, blocked the inhibition from the prepositus hypoglossi nucleus, whether applied by local microinfusion or by electrophoresis into the locus coeruleus" (p. 2973). The authors concluded that there is a $GABA_A$-receptor-mediated inhibition in the locus coeruleus. However, they recalled that there are also inhibitory influences originating from the paragigantocellular nucleus that seem to be adrenergic in nature.

3.3.5. 1990

In 1990, Gerber et al. (1990) recorded the neurons of the medial pontine reticular formation in 8–12-day-old rats. Among the 22 *in vitro* intracellularly studied neurons, 9 were depolarized by NA,

with an increase in input resistance also being observed with phenylephrine. This activation was related to an influence on α_1-receptors. However, in two neurons, noradrenaline caused hyperpolarization which could be mimicked by clonidine, indicating an involvement of α_2-receptors. This was the second description of the pontine-activating influences of NA, after Greene and Carpenter's (1985).

The same year, Mühlethaler et al. (1990) came to a similar conclusion in a study mainly involving slices from guinea-pig brain stems. In the intracellularly recorded pedunculopontine neurons, "NA induced a reversible depolarization (6/11) accompanied by an increase in firing rate that also persisted in the presence of TTX (tetrodotoxine) which blocks sodium channels. However, there were also inhibitory effects (2/11) or no effect at all (3/11). The depolarizing effect was not accompanied by a sizable change in membrane resistance" (p. 371). It can be mentioned that serotonin only had inhibitory effects. These three research studies carried out at the neuron level supported a possible positive influence of noradrenaline on REM sleep-on structures.

Tulen et al. (1990) recorded patients (2 females aged 21 and 31 years) with β-hydroxylase (DBH) deficiency. There was a strong decrease of REM sleep (only an amount of 18% and 21% per night, respectively). After treatment with D,L-thyreo-3,4-dihydroxyphenylserine (DOPS), which restored normal levels of noradrenaline, the amount of REM sleep increased to 27%. The authors stressed noradrenaline's "facilitatory role in the generation of REM sleep" (p. 32).

3.3.6. 1991

Tononi et al. (1991b) bilaterally injected cats with the α_2-agonist clonidine (4 μg), the β-agonist isoproterenol (4 μg), and another β-antagonist, propranolol (4 μg), into the dorsal pons, in an area overlapping the locus coeruleus-α and the paralemniscal tegmental field. Clonidine "dramatically decreased REM sleep which dropped from 18.2% of the total recording time in the controls to 2.0%... Following ... injection ... of isoproterenol, REM sleep decreased on the average from 21.2% ... in the controls to 3.0%... After propranolol (β_1–β_2-antagonist) REM sleep was significantly enhanced ... from 21.2 to 34.5%" (pp. 548–549). "The results reported here (with clonidine) indicate that REM sleep, rather than being enhanced as predicted by the reciprocal interaction model, was instead strongly reduced" (p. 550) (Fig. 11). The result with clonidine is in accordance with findings obtained by Gaillard's (Gaillard et al., 1983; Gaillard and Kafi, 1978, 1979; Gaillard, 1979) and Putkonen's (Leppävuori and Putkonen, 1980; Putkonen et al., 1977) laboratories by i.p. administration. The results obtained with β-acting compounds were in contradiction with those obtained by systemic administration (Hilakivi, 1983; Lanfumey et al., 1985).

Jones (1991) wrote an important anatomical review on REM sleep-generating processes and, in relation to noradrenaline, underlined that there is an interaction with cholinergic processes: "there is reason to believe that if not a direct interaction, an interplay of some sort between the cholinergic and monoaminergic systems may underlie the fundamental properties and generation of this state" (p. 649). She addressed for the first time the important notion of varicosities (which means diffuse release outside synapses) for both kinds of related neurons (see later discussion). The presence of GABAergic neurons in the locus coeruleus intermingled with both types of neurons was underlined.

The same year, Nicholson and Pascoe (1991) carried out a study of compounds that interact with α_2-receptors in humans. The agonist "clonidine (0.10 mg) increased the duration of stage 2 sleep ($P < 0.01$). The mean latency to REM sleep was lengthened and the duration of REM sleep and the ratio of REM to slow-wave sleep was reduced ($P < 0.01$)" (p. 369). Idazoxan, an antagonist, decreased total slow-wave sleep at 40 mg, and at 20 and 40 mg, "the mean latency to REM sleep was increased ($P < 0.01$), there was less REM sleep and the ratio of REM to slow-wave sleep was reduced ($P < 0.01$)" (p. 369). Finally, after administration of maprotiline (150 mg), a reuptake inhibitor, "there were fewer periods of REM sleep ($P < 0.05$) and the duration of REM sleep and the ratio of REM to non-REM sleep was reduced ($P < 0.001$ and $P < 0.01$, respectively)" (p. 368). The effects of all three compounds were quantified in the first 200 min after sleep onset.

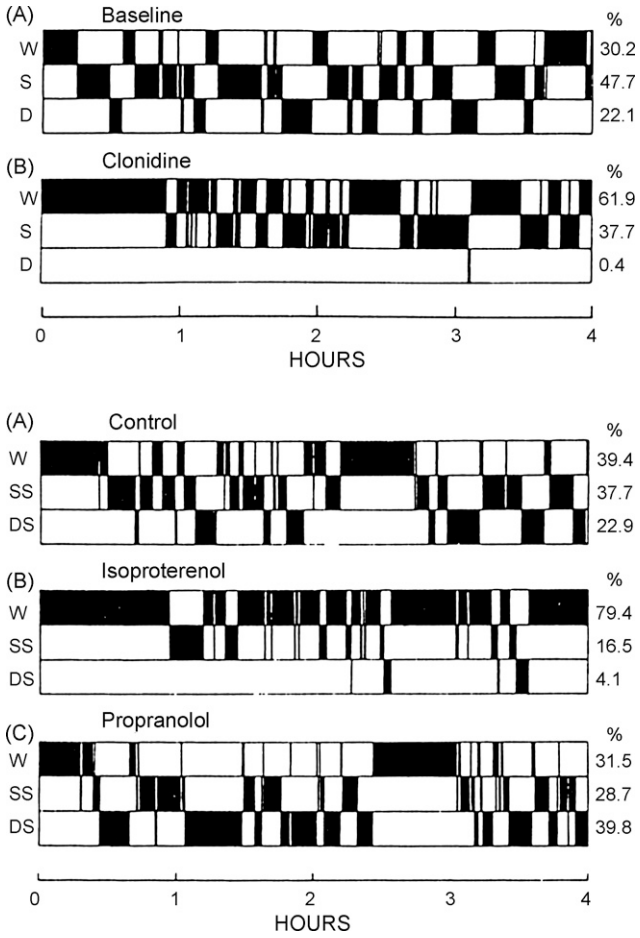

Fig. 11. Tononi et al. (1991b) showed (top) that microinjection of 4 μg clonidine in the dorsal pontine tegmentum induced nearly suppression of REM sleep during the first 4 h of recording (DS). Bottom: isoproterenol (4 μg) also strongly reduced REM sleep whereas propranolol (4 μg) increased REM sleep. Reprinted from *Progress in Brain Research* with permission.

Also in 1991, Sakai (1991) injected unconjugated cholera toxin (CT) into the locus coeruleus and adjacent dorsal pontine tegmental structures of cats in order to identify the retrogradely labeled neurons and show the different afferents of the locus coeruleus. "Tyrosine hydroxylase and dopamine-β-hydroxylase (DβH)-positive, but phenylethanolamine *N*-methyltransferase (PNMT)-negative noradrenergic cell bodies sending axons to the cat locus coeruleus were found both in the pontine (A_4, A_5, A_6 and A_7) and bulbar (A_1 and A_2) catecholaminergic cell groups. These noradrenergic afferent projections were mostly ipsilateral and found mainly when the tracer was injected into the noradrenergic (not the cholinergic) regions of the locus coeruleus... CT-positive and PNMT-immunoreactive double-labeled neurons were observed in the lateral medulla (C_1 cell group) particularly after

CT injections in the noradrenergic regions of the locus coeruleus" (p. 41). It needs to be mentioned that, in contrast to the peri-locus coeruleus-α, the locus coeruleus did not show important afferents from the nucleus prepositus hypoglossi, in spite of inhibitory afferent influences (Ennis and Aston-Jones, 1989b).

3.3.7. 1992

Cirelli et al. (1992) injected methoxamine (α_1-agonist, 4 μg) into the pons of cats, with the histology showing an area covering the peri-locus coeruleus-α, which is critically involved in REM sleep-generating processes (Sakai, 1988). The 4-h recording showed a decrease in REM sleep. Prazosin injections (from 0.0025 to 0.0125 μg) had no clear-cut effect. Finally, "prazosin was consistently able to prevent the effect of methoxamine when injected before the α_1-agonist" (p. 278).

3.3.8. 1993

Using patch-clamp recordings in slices, Williams and Reiner (1993) showed that noradrenaline hyperpolarizes cholinergic neurons of the mesopontine tegmentum of rats. Taking into account the reciprocal interaction model (Hobson et al., 1975), they concluded that their results strongly suggest that the silence of noradrenergic neurons at REM sleep onset disinhibits the cholinergic neurons that are responsible for REM sleep-inducing processes, leading to a release of transmitter in the medial pontine reticular formation.

Thakkar and Mallick (1993) studied the influence of REM sleep deprivation on MAO-A and MAO-B activity in the whole brain, cerebellum, and brain stem of rats. MAO-A activity "is primarily responsible for the breakdown of NA (while MAO-B) is a non-specific enzyme for the breakdown of amines in general" (p. 677). "After one day REM sleep deprivation, the MAO-A activity increased in the medulla ($P < 0.001$) whereas it did not change significantly in the pons or midbrain. Two day deprivation significantly increased MAO-A activity in the medulla compared to the control animals. However, the activity was significantly reduced compared to the one day REM sleep deprived rats" (p. 680). The activity did not change in the pons or midbrain. After 4 days of deprivation, there was a global decrease in MAO-A activity in the whole brain stem. The authors observed that the changes in MAO-A activity underlined the influence of the medulla oblongata in REM sleep-generating processes, particularly REM sleep-on mechanisms (Sakai, 1988). Since noradrenaline is involved in REM sleep-off processes, the increased MAO-A activity observed after short deprivation may constitute an initial attempt to reduce noradrenaline to normal levels, before brain-regulating processes become exceeded by longer deprivation.

The same team, Gulyani and Mallick (1993), showed that REM sleep deprivation, by its continuous increase of NA activity, is probably responsible for the increase in Na–K-ATPase activity that is observed in the medulla oblongata; this is consistent with the previous result about the brain stem level in REM sleep-controlling mechanisms. In contrast, there was no modification in the medulla oblongata in the level of chloride-sensitive Mg-ATPase, which affects neuronal transmembrane potential (Mallick and Gulyani, 1993), although there was an increase in the globally tested whole brain stem.

Wang and McCormick (1993) showed that noradrenaline is able to transform the functioning of corticofugal neurons from a burst mode to single spike tonic activity, as is the case during waking. This is also of interest for understanding higher brain functioning during sleep (see Section 4).

Tsai et al. (1993) wanted to test the hypothesis of Siegel and Rogawski (1988) that the silence of noradrenergic neurons during REM sleep would allow a recovery of desensitization and a down-regulation of noradrenergic receptors induced by waking activation processes (see above). Rats were totally sleep-deprived for 10 days by a disk which was automatically rotated, forcing the animals to walk in a direction opposite to that of disk rotation to avoid being carried into the water (Bergmann et al., 1989). Eleven brain regions were studied to detect α_1-, α_2-, and β-receptor binding to ^{3}H-prazosin, ^{3}H-rawolscine, and ^{125}I-iodocyanopindolol, three respective antagonists. Both total sleep and REM sleep were significantly reduced during deprivation. Although the authors found several significant variations of physiological criteria during sleep deprivation (food intake, weight, etc.), they found no differences in binding, except for an increased level of α_2-receptors in the cerebellum. Consequently, the hypothesis of Siegel and Rogawski (1988) was not clearly verified.

3.3.9. 1994

To my knowledge, the last paper by Gaillard's team to address the relationship between NA and REM sleep was published in 1994

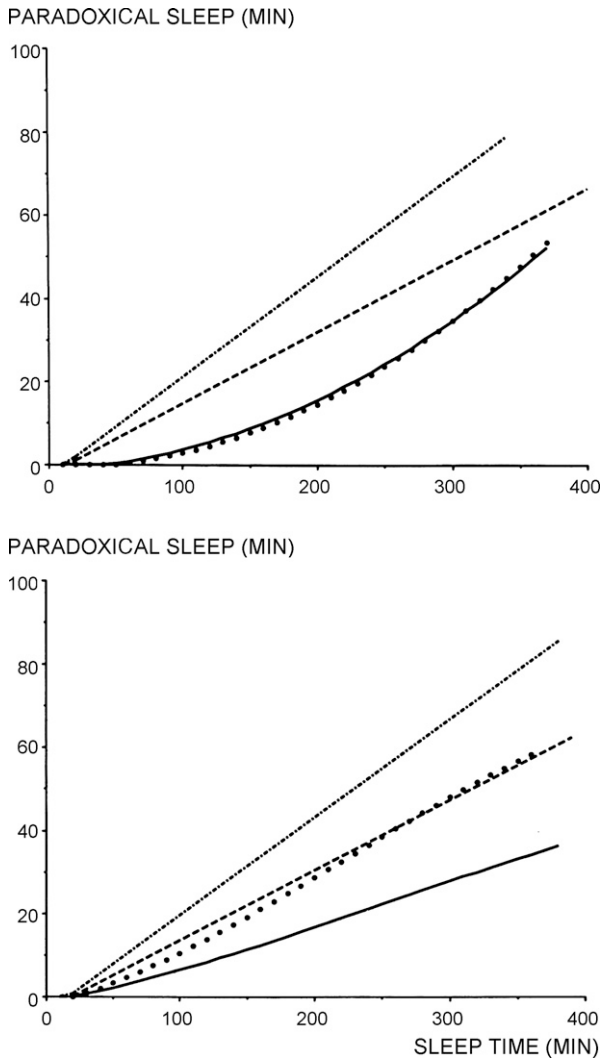

Fig. 12. Top: Mastrangelo et al. (1994) showed in rats that REM sleep was increased after pontine injection of 1 μg carbachol (– · – · –) vs. control (- - -). Five micrograms of clonidine (· · ·) decreased REM sleep, and clonidine + carbachol (—) suppressed the effect of carbachol. Bottom: Influence of AMPT pretreatment on carbachol injection. Control (- - -); 1 μg carbachol alone (– · – · –). One hundred and fifty micrograms per kilogram AMPT i.p. (· · ·) had no effect on REM sleep. AMPT + carbachol (—) induced a long-lasting depression of REM sleep. For top and bottom the abscissa showed total sleep time. Reprinted from *Pharmacology, Biochemistry and Behavior*, with permission.

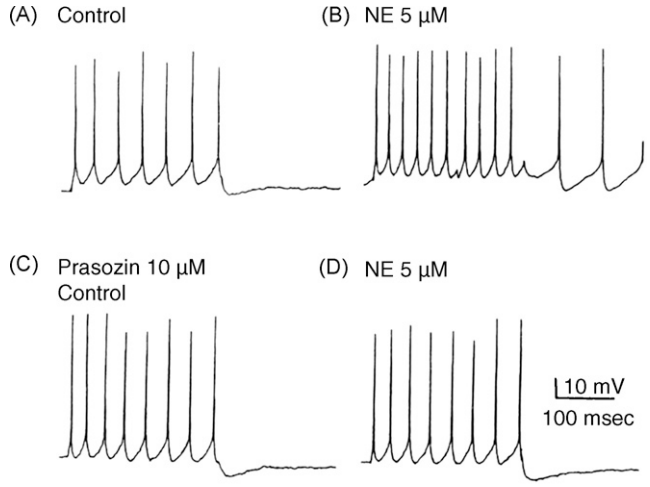

Fig. 13. Stevens et al. (1994) showed in rats that noradrenaline excited pontine neurons and that this activation was suppressed by the α_1-receptor antagonist prazosin. Reprinted from the *Journal of Neuroscience*, with permission.

(Mastrangelo et al., 1994). It was devoted to the already well-known connection between cholinergic and noradrenergic processes that are responsible for REM sleep-generating and sustaining mechanisms. The authors first unilaterally injected 1 μg/0.5 μl of carbachol into rats at the limit between the oral and caudal pontine reticular nuclei. The recordings lasted for 3 h (8–11 a.m.) and showed a 17–23% increase in REM sleep. They then injected clonidine alone (5 μg i.p.) and confirmed the decrease in REM sleep (12% vs. 17%). Finally, they administered the two compounds together. The percentage was also 12% (all results were significant at $P < 0.005$). Thus, clonidine suppressed the effect of carbachol. The authors carried out the same protocol with AMPT. At 150 mg/kg, AMPT added to carbachol suppressed the effect of carbachol (control: 16%; carbachol: 23%; AMPT + carbachol: 9%; $P < 0.005$) (Fig. 12). "Thus, a certain noradrenergic activity would be essential for the expression of cholinergic activation. Pharmacological evidence was used to suggest that a controlled or restricted enhancement of the central noradrenergic activity promotes the emergence of REM sleep, whereas a more pronounced enhancement would support waking" (p. 98).

Stevens et al. (1994) showed on rat slices that "noradrenaline or the α_1-agonist phenylephrine depolarized 83% of medial pontine reticular formation tested neurons" (p. 6482) (Fig. 13). This result was primarily related to a reduction of calcium-dependent potassium conductance.

Bier and McCarley (1994) unilaterally infused idazoxan (α_2-antagonist, 13.2 μg) into the medial pontine reticular formation of cats. REM sleep "was increased by 70% across 5 h, with a significant increase of 1000% in the first hour of recording" (p. 336). The latency of REM sleep occurrence decreased and the duration of episodes increased (Fig. 14). This α_2-receptor antagonist produced similar effects following carbachol infusion. These two last papers are the main data at the origin of Jones's later theory (Hou et al., 2002; Jones, 2004).

Conclusion. This decade gave rise to more positive than negative results regarding NA involvement. The main confirmation came from experiments performed with clonidine in animal pups (Depoortere, 1985; Mirmiran, 1986), in adult animals (Mastrangelo et al., 1994; Tononi et al., 1991a,b), and in humans (Kanno and Clarenbach, 1985; Nicholson and Pascoe, 1991). Complementary arguments came from receptor blocker studies in animals (Bier and McCarley, 1994; Cirelli et al., 1992; Lanfumey et al., 1985) and in humans (Betts and Alford, 1985). Finally, research on humans involving inhibitors of dopamine-β-hydroxylase (Tulen et al., 1991) also confirmed the positive influence of NA on REM sleep-inducing processes.

3.4. 1995–2006

3.4.1. 1995

Luppi et al. (1995) studied locus coeruleus afferents by performing anterograde and retrograde tracing experiments in rats. The authors confirmed that medulla oblongata substantial afferents issued from lateral and dorsal paragigantocellular nuclei and the prepositus hypoglossi nucleus. They also found substantial afferents coming from the preoptic area dorsal to the supraoptic nucleus, areas of the posterior hypothalamus, the Kolliger-Fuse nucleus, and the mesencephalic reticular formation. "Fewer labeled cells were also observed in other regions including the hypothalamic paraventricular nucleus dorsal raphe nucleus, medial raphe nucleus, dorsal part of the periaqueducal grey, the area of the noradrenergic A_5 group, the lateral parabrachial nucleus and the caudoventrolateral reticular nucleus" (p. 119). These results confirmed the previous findings of Aston-Jones's group (Ennis and Aston-Jones, 1986, 1987, 1988, 1989b). Moreover, it could already be indicated that the afferents of the noradrenergic

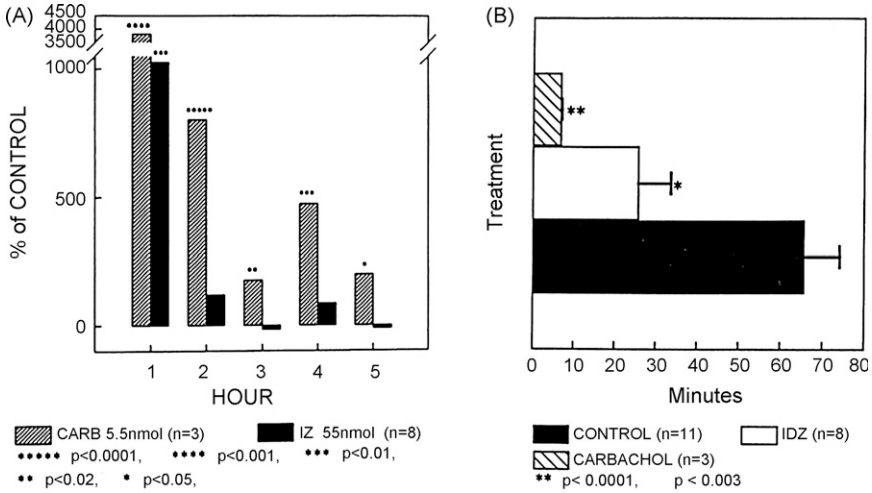

Fig. 14. In cats, Bier and McCarley (1994) massively increased REM sleep amount (left) and significantly reduced its latency of occurrence (right) after pontine reticular infusion of the α_2-receptor antagonist idezoxan. Carbachol infusion was even more efficient. Reprinted from *Brain Research*, with permission.

A_5 nucleus may be involved in locus coeruleus functioning during REM sleep (Fenik et al., 2002).

Porkka-Heiskanen et al. (1995) induced REM sleep deprivation in rats by the small platform method (8, 24, and 72 h). Recovery of deprivation (rebound) was studied for 8 and 24 h. The authors quantified tyrosine hydroxylase gene expression in the locus coeruleus, as well as NA concentrations in the frontal cortex, hippocampus, and anterior and posterior hypothalamus. Twenty-four hours of REM sleep deprivation led to an increase in TH mRNA, which returned to normal levels after 24 h of REM sleep recovery. Noradrenaline concentrations decreased in the prefrontal cortex after 8 and 24 h of deprivation, and increased after 24 h of recovery. Interestingly, there were differences in other structures. In the hippocampus, the noradrenaline level only rose after a 24-h REM sleep rebound. While in the anterior hypothalamus there was no difference during deprivation and recovery, in the posterior hypothalamus the NA concentration decreased after 24 h and increased after 72 h of deprivation. This study confirmed the increased noradrenaline turnover induced by REM sleep deprivation, and showed that noradrenaline release varies after noradrenergic innervation (locus coeruleus for cortex and hippocampus and medulla oblongata A_1 and A_2 nuclei for the hypothalamus). Finally, the authors showed that these results were independent of any stress reactions, as evidenced by corticosterone quantification.

Gulyani and Mallick (1995) sought to elucidate the mechanism by which REM sleep deprivation increases Na–K-ATPase activity (Gulyani and Mallick, 1993). Using their usual small platform method, the rats were deprived for 4 days. Their *in vitro* study showed that the increase in enzyme activity was prevented in the cerebellum, cerebrum, and brain stem by prazosin administered i.p. (1, 2 or 4 mg/kg) to the animals prior to the preparation of the brain homogenate. This was not the case with clonidine and propranolol (β_1–β_2-antagonist). The level of enzyme activity on the large platform, which was used as a control to test for the absence of stress influence, nearly matched that of the second set of control animals without the platform. Thus, during REM sleep deprivation, the increase in enzyme activity was consecutive to the action of NA on α_1-receptors. These data were confirmed by GABA receptor blockade in the same laboratory (Kaur et al., 2004).

Gonzalez et al. (1995) studied the effects of the NA neurotoxin DSP-4. This molecule, which destroys the noradrenergic neuron terminals of the locus coeruleus, decreased the REM sleep rebound after specific REM sleep deprivation. It was further used after stress induced by a 1-h immobilization, which itself increases REM sleep (Dewasmes et al., 2004; Gonzalez et al., 1995). After DSP-4, the rebound of REM sleep duration decreased by 52%.

3.4.2. 1996

In a double-blind, randomized investigation, Gentili et al. (1996) studied the effects of clonidine (0.1 mg) and yohimbine (5.4 mg) capsules on sleep in healthy men. The only significant result was a decrease of REM sleep by clonidine, from 17% to 6% ($P < 0.012$).

Singh and Mallick (1996) bilaterally stimulated the locus coeruleus of rats for 8 h, with low frequency (2 Hz) 300 μs pulses at 200 μA intensity. The animals were recorded for an additional 4 h after cessation of stimulation. During stimulation, REM sleep decreased from 6.81% to 2.32% ($P < 0.001$), while only active waking increased, from 24.62% to 37.18% ($P < 0.01$). The reduction of REM sleep was due to a smaller number of episodes, as their duration remained unchanged. There was a rebound during the recovery period from the second hour, while slow-wave sleep decreased. This result is in parallel with findings obtained for REM sleep deprivation or continuous firing of the locus coeruleus (Mallick et al., 1990). It also confirmed the REM sleep-off processes related to the activation of this nucleus.

3.4.3. 1997

Python et al. (1997) studied the influence of different doses of nisoxetine, a specific blocker of noradrenaline uptake, in rats. The i.p. doses of 0.1, 0.25, and 1 mg/kg increased the latency of occurrence of REM sleep, while there was no difference in slow-wave sleep time. At the first and third dose, the amount of REM sleep decreased.

Kaur et al. (1997) bilaterally injected the $GABA_A$-receptor antagonist picrotoxin (250 ng in 250 nl) into the noradrenergic locus coeruleus of rats. During the 8 h of recording, REM sleep decreased significantly, essentially due to a strong reduction of episode duration. Thus, GABA, by an action on $GABA_A$ receptors, promotes REM sleep maintenance through an inhibitory action on noradrenergic neurons.

3.4.4. 1998

Basheer et al. (1998) quantified tyrosine and NA transporter mRNA levels in the locus coeruleus following REM sleep deprivation. The rats were placed on small platforms for 1, 3, or 5 days. Tyrosine mRNA increased by 32% after 3 days of deprivation, and by 55% after 5 days of deprivation. The noradrenaline transporter mRNA increased by 20.8% after 3 days of deprivation, and by 17.9% after 5 days of deprivation. The authors were able to show that neither increase was related to a stress reaction.

Yamuy et al. (1998) studied tyrosine/c-Fos (TH+) immunostaining of mesopontine cat neurons during carbachol-induced REM sleep-like behavior. TH+ cells were concentrated in the locus coeruleus and the dorso-medial portions of the lateral reticular formation. The noradrenergic neurons were more loosely distributed in more ventral and lateral areas of the lateral pontine reticular formation and the parabrachialis area. The mean number per section of TH+ neurons was similar in the dorsolateral pons of control and REM sleep-carbachol cats. "The lack of increased c-Fos expression in catecholaminergic neurons during active sleep-carbachol confirms and extends previous data that indicate that these cells are silent during REM sleep-carbachol and naturally occurring REM sleep".

3.4.5. 1999

Crochet and Sakai (1999a) unilaterally infused NA (1 and 5 mM) and noradrenaline (5 mM) into the peri-locus coeruleus-α of cats. Both neuromodulators specifically decreased REM sleep by reducing both the number and duration of episodes and by increasing their latency. Further, the episodes that occurred were without atonia. Clonidine (0.2 and 1 mM), the α_2-agonist, decreased REM sleep dose-dependently and induced REM sleep without atonia at 1 mM. In contrast, neither the α_1-agonist methoxamine (1 mM) nor the β-agonist isoproterenol (1 mM) had any effect. The inhibition of REM sleep by NA was prevented by rauwolscine (1 and 5 mM), an α_2-antagonist, with the amount of REM sleep even matching the control level at 5 mM. "The REM sleep effect of NA, however, was not antagonized by either 5 mM benoxathian, an α_1-selective adrenoceptor antagonist, or by 5 mM atenolol, a β_1-selective adrenoceptor antagonist" (p. 2201). The atonia during REM sleep reappeared after rauwolscine administration. Finally, "clonidine also completely blocks the potent REM sleep-inducing effect of carbachol when co-applied to the caudal peri locus-α" (p. 2204).

Crochet and Sakai (1999b) published a second important paper describing results obtained by microdialysis infusion of noradrenaline, adrenaline, and other neuromodulators. Noradrenaline and

adrenaline were first applied to the caudal peri-locus coeruleus-α, which contains non-cholinergic REM sleep-on neurons activated by acetylcholine and glutamate, as well as to non-cholinergic and non-monoaminergic descending neurons. Noradrenaline and adrenaline infused for 2 h decreased REM sleep from 21% to 5.5% and 2.8%, respectively. For both neuromodulators, the effect lasted for less than 1 h after the end of administration. Finally, the REM sleep episodes that continued to appear showed maintenance of some muscular activity (REM sleep without atonia). In the rostral part, the nucleus contained cholinergic ascending neurons as well as both cholinergic and non-cholinergic REM sleep-on neurons. Carbachol induced REM sleep at this level, while kainate induced waking and inhibited REM sleep. In this experiment, NA and adrenaline strongly inhibited REM sleep. In the X area, just anterior to the peri-locus coeruleus-α, which also contains cholinergic neurons and sends ascending axons to the thalamus and hypothalamus, the results with NA and adrenaline infusion were similar to those observed in the anterior part of the peri-locus coeruleus-α: REM sleep was inhibited while waking increased. PGO waves decreased in amplitude, as was the case in the peri-locus coeruleus-α. Finally, these two neuromodulators had no significant influence on the nucleus reticularis pontis oralis, which contains neither cholinergic nor noradrenergic neurons. This last result is of particular importance, since it indicates that this nucleus does not receive REM-off influences. However, it conflicts with previous studies showing the efficacy of noradrenaline in activating and/or inhibiting neurons in this area (Gerber et al., 1990; Greene and Carpenter, 1985; Mühlethaler et al., 1990).

Maloney et al. (1999) quantified mesopontine neuron function in rats by c-Fos immunostaining after about 50 h of REM sleep deprivation. After a 3-h recovery, the number of TH+/c-Fos+ cells in the locus coeruleus area was significantly lower in the recovery condition than in the deprivation condition. Moreover, TH+/c-Fos+ cells were significantly greater in the deprivation condition than in the control condition. "Across conditions, the number of TH+/c-Fos+ within the locus coeruleus was significantly negatively correlated with the percent time spent in REM sleep during the final 3 hour recording period" (p. 3066). Since the authors also quantified cholinergic, serotonergic, and GABAergic neurons, they concluded, "The present results demonstrate that during REM sleep rebound, the number of c-Fos-expressing cholinergic cells is increased, whereas the number of c-Fos-expressing monoaminergic neurons are decreased, suggesting a reciprocal change in the activity of these cell groups. Moreover, the number of GABAergic cells expressing c-Fos during rebound is increased, suggesting that they may also be active during REM sleep and involved in suppressing the activity of surrounding monoaminergic cells" (p. 3068). It can also be mentioned that "Across deprivation days, there was a progressive increase in (EEG) gamma activity during waking that was significant for the deprivation condition ($P < 0.05$)... (During rebound) gamma and theta activities were not quantitatively different from those in baseline REM sleep" (p. 3060).

Mallick et al. (1999a) wrote a detailed review on the impact of NA on REM sleep by describing the various REM sleep deprivation results. The authors recalled that REM sleep deprivation induces continuous firing of locus coeruleus neurons and decreases MAO-A activity. The direct and indirect effect of this deprivation is an increase of central noradrenaline functioning. This increase, in turn, reduces synaptosomal Ca^{2+} levels. The authors also showed that the increase of noradrenaline, together with the Ca^{2+} decrease, leads to an increase of Na–K-ATPase, in the former case by acting on α_1-adrenoceptors (Mallick and Adya, 1999). The increase of this enzyme activity as well as the decrease of Ca^{2+} disturb neuronal excitability, altering the neuronal response and, consequently, behavior.

In a paper not principally related to REM sleep, Thankachan et al. (1999) modulated the EEG of cats with different compounds acting on α_1-, α_2-, β-adrenergic and cholinergic muscarinic receptors. The authors concluded that the same cortical activation observed during waking and REM sleep can be explained during the silence of noradrenergic neurons in the latter stage by an increase of cholinergic functioning, although the authors stressed the less well-known function of glutamate and GABA. While an increase in cholinergic functioning during REM sleep has indeed been confirmed in the nucleus basalis when compared to waking (Vasquez and Baghdoyan, 2001), its release at the cortical level is lower than during active waking, reaching only the level of quiet waking (Marrosu et al., 1995). In addition, it needs to be highlighted that the function of GABA in REM sleep-generating and sustaining processes was beautifully and more elaborately described by Mallick et al. (1999b).

3.4.6. 2000

Koyama and Sakai (2000) infused noradrenaline (0.1–0.2 M) and adrenaline (0.2 M) into cats at the mesopontine level, which was presumed to contain cholinergic neurons. They principally distinguished I–S neurons discharging by single tonic firing at a mean rate of 4 Hz. These neurons, which spontaneously fired at their highest frequency during waking and REM sleep, were excited (and never inhibited) by both transmitters with a slow onset and long duration effect (up to several minutes). In contrast, identified PGO-on neurons fired at 21 Hz, either by single spikes during waking or by bursts during REM sleep PGOs. Noradrenaline and adrenaline excited these neurons (none were inhibited) with the same onset and duration effect as the I–S neurons, and tonic firing was promoted by both transmitters. These results globally confirmed previous findings (Gerber et al., 1990; Greene and Carpenter, 1985; Mühlethaler et al., 1990).

Shouse et al. (2000) used microdialysis to study the concentration of noradrenaline in the locus coeruleus complex and amygdala of cats. In the amygdala the released amount decreased from alert waking to REM sleep (1.53 pg/μl vs. 0.23 pg/μl, $P < 0.05$), a drop of 85%. In the locus coeruleus, it fell from 2.12 to 0.50 pg/μl ($P < 0.05$), a decrease of 76%. The higher concentration in the locus coeruleus was hypothesized to be related to somatodendritic extrusion.

Gulyani et al. (2000) wrote a detailed review on REM sleep, but mainly focused on REM sleep deprivation, the group's main field. In relation to NA function, the authors recalled the results already described in their 1999 book chapter review (Mallick et al., 1999a). With respect to NA function in REM sleep processes, Mallick's team published two papers analyzing Na–K-ATPase activity during REM sleep deprivation. The observed increase in enzyme activity (V_{max} and K_m) suggested a non-competitive stimulation of the enzyme. The increased V_{max} was attributed to noradrenaline increase induced by REM sleep deprivation, while the increase in K_m was shown to be independent of calcium (Adya and Mallick, 2000). In the second paper (Mallick et al., 2000), the authors showed that the increase of Na–K-ATPase activity induced by noradrenaline is the consequence of the activation of the α_{1A}-receptor, which induces the dephosphorylation of the enzyme.

3.4.7. 2001

Charifi et al. (2001) induced a bilateral noradrenaline denervation of the medial prefrontal cortex and dentate gyrus in rats by injecting DSP-4 (20 μg) into both sites, and tested sleep–waking stages after 10 h of REM sleep deprivation by the pedestal method (surrounded by water). DSP-4, which destroyed noradrenergic terminals in both structures, had no effect on the recovery of REM sleep after deprivation. The authors concluded that NA is not involved in REM sleep regulation in either structure.

3.4.8. 2002

Hou et al. (2002) performed immunostaining in rats for α_{2A}- and α_{1A}-receptors in the mesopontine structures comprising the cholinergic laterodorsal tegmental (LTD) and the lateral pedunculopontine (PPT) nuclei. The authors also immunostained cholinergic (Ach-T) and tyrosine hydroxylase neurons (TH+) in the mesopontine and locus coeruleus, respectively. Their Fig. 1 elegantly shows the localization of dense cholinergic and noradrenergic neurons in the two neighboring areas. The double staining showed that cholinergic neurons were labeled for α_{1A}-receptors (about 25% in LTD and 35% in the PPT area), while others (about 45% in LTD and 50% in the PPT area) were labeled for α_{2A}-receptors. "We presume that the cholinergic cells bearing α_{1A} receptors are different from those bearing α_{2A} receptors and that these different cells would accordingly have different activity profiles and roles in sleep–wake states" (p. 519). The authors hypothesized that NA acting on α_{1A}-receptors could be responsible for the induction and maintenance of waking, while its action on α_{2A}-receptors could inhibit cholinergic neurons involved in REM sleep-generating mechanisms as well as contribute to the ascending (thalamus) desynchronizing cholinergic influences of REM sleep.

Mallick et al. (2002) wrote a review devoted to the function of NA in the generation and maintenance of REM sleep. It took into account all the available data in the literature and emphasized the opposition between waking and REM sleep-supporting mechanisms, i.e. waking processes inhibiting REM sleep-on processes and activating noradrenergic REM sleep-off ones. The basic mechanisms studied using their model of REM sleep deprivation showed that the increase in noradrenergic activity is associated with (1) an increase in Na–K-ATPase activity; (2) a decrease in membrane fluidity; (3) a central deficit of lipid peroxidation, with "the causal relation between these changes (being still) unknown" (p. 568).

3.4.9. 2003

Datta et al. (2003) unilaterally infused NA (0.5, 1.5, and 3.0 nmol) into the pedunculopontine tegmentum of rats. "None of these 3 different doses of noradrenaline microinjections into the PPT caused any changes in the total percentage of REM sleep, latency to the first episode of REM sleep, total number of REM sleep episodes and mean duration of REM sleep episodes during the 3 h of recordings" (p. 516). In addition, the authors observed that acetylcholine of PPT origin, which is heavily involved in REM sleep-generating processes, was released at a similar level in the thalamus during waking and REM sleep, when noradrenergic neurons are active and silent, respectively.

Sakai and Crochet (2003) infused clonidine into the locus coeruleus of cats, and the expected decrease in noradrenergic neuron firing was associated with an increase in slow-wave sleep but no changes in REM sleep. Moreover, when the authors infused bicuculine, a $GABA_A$-receptor blocking compound, it did not modify the usual firing modalities of locus coeruleus neurons during sleep–waking stages. In contrast, the glutamate antagonist 6-cyano-7-nitroquinoxaline-2-3-dione (CNQX) did have an effect, decreasing noradrenergic neuron firing. The authors hypothesized that the silence of locus coeruleus neurons during REM sleep results from a local glutamate disfacilitation process, rather than from neuronal inhibition. Indeed, locally applying bicuculine to the locus coeruleus increased waking but did not affect REM sleep, while its application in the peri-locus coeruleus-α, which is involved in REM sleep-generating processes, increased REM sleep. It must be underlined that some researchers, like Mallick (personal communication), believe that there is scant histological confirmation of the distinction between the locus coeruleus, locus coeruleus-α, and peri-locus coeruleus-α.

Hunsley and Palmiter (2003) studied mice deficient in dopamine-β-hydroxylase, the enzyme needed to convert dopamine into NA and adrenaline. Compared to control animals, adult knock-out mice did not show any differences in the amount of REM sleep, either during the daytime or at night, while sleep latency was reduced. Even amphetamine (0.25–1 mg/kg), which dose-dependently increased sleep latency in controls, did not change the latency of sleep onset or the occurrence of REM sleep in the experimental animals. Among other hypotheses to explain the absence of REM sleep disturbances, the authors suggested a compensatory role for serotonin.

Majumdar and Mallick (2003) quantified the concentrations of tyrosine hydroxylase and glutamic acid decarboxylase (GAD) in the locus coeruleus of rats after 6 days of REM sleep deprivation. TH color intensity was increased by 153.9% vs. control animals, and GAD by 133.3%. In contrast, neither choline acetyltransferase (ChAT) nor GAD was affected in the neurons located in the dorsolateral tegmental nucleus, pedunculopontine nucleus or medial preoptic nucleus.

The same team (Majumbar et al., 2003) sought to test whether Na–K-ATPase activity, which is increased after REM sleep deprivation, shows an increased turnover as a result of this deprivation. The rats were deprived for 4 days, and the densitometric analysis of the enzyme showed a significant increase in enzyme molecules in the locus coeruleus of up to 129.2% vs. controls, and in the laterodorsal and pedunculopontine tegmentum of up to 148.9%. Western blot analysis showed a significant increase in the enzyme concentration after deprivation. Moreover, the specific activity of the enzyme increased to 122.4% vs. controls. "Thus, . . . it may be said that the REM sleep deprivation-induced increase of Na–K-ATPase activity was due to increased enzyme synthesis, increased turnover, and to allosteric positive modulation of the enzyme" (p. 873). This phenomenon was mediated by noradrenaline.

3.4.10. 2004

Jones (2004) published a long review devoted to REM sleep mechanisms. Regarding the influence of NA, she described how this neuromodulator, by activating mesopontine α_1-receptors, mainly favors mechanisms involved in the induction and maintenance of waking, while preventing the occurrence of REM sleep by locally inhibiting α_2-receptors. "Bearing α_1 receptors, cholinergic cells, which likely project to the forebrain, are excited by NA and active during both waking and REM sleep (W-REM sleep-on), when they promote cortical activation. Bearing α_2-adrenergic receptors, other cholinergic cells, which likely project to the brain stem, are inhibited by noradrenaline and thus active selectively during REM sleep, where they promote muscle atonia" (p. 390). Jones's conclusion regarding the function of mesopontine α_2-receptors is strengthened by previous findings (Bier and McCarley, 1994; Stevens et al., 1994).

Sakai and Crochet (2004) infused clonidine (50–200 μM) into the locus coeruleus noradrenergic area (locus coeruleus proper and locus coeruleus-α). Noradrenergic neuron firing disappeared within 5–10 min after the start of drug application and lasted for 30–60 min. This unilateral application did not affect REM sleep. However, the lowest dose decreased waking and increased deep slow-wave sleep when applied in the locus coeruleus proper. A complementary application of RX821002 (0.5 mM), a selective α_2-adrenoceptor antagonist, did not suppress REM sleep and induced, with a latency of approximately 10 min, the reappearance of noradrenergic neuron firing. "Our present findings support the postulate that noradrenergic locus coeruleus neurons play an important role in the control of waking and slow wave sleep, but do not support the theory that locus coeruleus noradrenergic activity

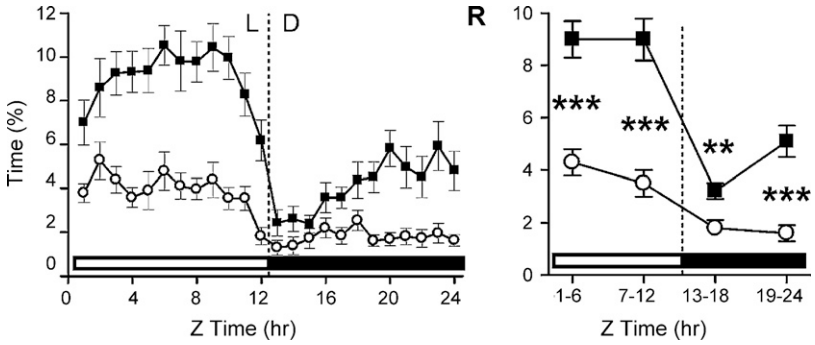

Fig. 15. Ouyang et al. (2004) showed that mutant mice without dopamine-β-hydroxylase show a decrease of REM sleep (R). Black square: $Dbh^{+/-}$ (control); open circle: $Dbh^{-/-}$. L, light; D, dark. $^{**}P < 0.01$, $^{***}P < 0.001$. Reprinted from *Journal of Neurophysiology*, with permission.

inhibits paradoxical sleep-executive neurons located in the pons and that inactivation of noradrenergic locus coeruleus neurons plays a critical role in the initiation and maintenance of paradoxical sleep" (p. 426).

Ouyang et al. (2004) studied sleep–waking stages in mice subjected to the "disruption" of the gene for dopamine-β-hydroxylase ($Dbh^{-/-}$), which is required for the production of both NA and adrenaline (see Satoh and Tanaka, 1973). REM sleep in the recording sessions decreased from 14.3% in controls to 5.2% in the mutants (Fig. 15). This decrease was due to a reduction of bout duration, since the number of episodes was unchanged ($P < 0.10$). Moreover, slow-wave sleep patterns appeared during REM sleep, as the delta wave power increased ($P < 0.01$) and the theta rhythm frequency decreased, from 7.2 counts/s in controls to 6.1 counts/s in mutants. In Section 4, the authors postulated that "extracellular NA/adrenaline levels must be within a critical low (but nonzero) window and that levels above or below this window inhibit REM sleep" (p. 2076). Differences with a previous study involving the same methodology (Hunsley and Palmiter, 2003) were underlined by the authors. They supposed that "technical and possibly genetic factors may be relevant."

Mallick et al. (2004) stimulated the anterior hypothalamic and sleep-inducing areas of the caudal brain stem in cats and recorded their respective influences on neurons located in the pontine REM sleep-inducing area. The caudal brain stem neurons were more effective at activating the REM sleep-on neurons.

3.4.11. 2005

Mallick et al. (2005) published a powerful paper on the noradrenergic processes involved in REM sleep generation. They combined mild bilateral electrical stimulation (2 Hz, 200 μA, 300 μs) of the locus coeruleus and i.p. injection of α_1-, α_2-, and β-antagonists, viz. prazosin, yohimbine and propranolol, respectively, and of the α_2-agonist clonidine. Prazosin (3 mg/kg) decreased REM sleep by reducing episode duration. Under locus coeruleus stimulation plus prazosin, the frequency of REM sleep occurrence also decreased. Yohimbine (0.03 mg/kg) only decreased the frequency of occurrence of REM sleep. Associated with stimulation, the frequency remained lower, while the duration of the episodes was unchanged. Propranolol (10 mg/kg) only decreased the frequency of occurrence of REM sleep. Associated with stimulation, REM sleep was restored. Clonidine (0.1 mg/kg) decreased both the frequency and episode duration of REM sleep. Stimulation plus clonidine enhanced the reduction of REM sleep, essentially by reducing its frequency of occurrence. In Section 4, the authors proposed a neurobiological model: during waking, the noradrenergic REM sleep-off neurons are kept active by waking-inducing structures which maintain a constant release of noradrenaline. Noradrenaline keeps the REM sleep-on neurons inhibited, either via β-adrenoceptors or indirectly through GABA. These β-adrenoceptors are localized in areas rich in REM sleep-on neurons, which are known to be hyperpolarized by NA. The increased noradrenaline during waking could activate GABAergic neurons, which would in turn inhibit REM sleep-on neurons. "As long as locus coeruleus REM sleep-off neurons are active, there will be enough NA to keep the REM sleep-on neurons inhibited and there will be no REM sleep. Thus, pending confirmation, we propose that β-adrenoceptors are present on the REM sleep-on neurons" (p. 19). When noradrenaline reaches a significant level, there is thought to be auto-inhibition of noradrenergic neurons, disinhibition of REM sleep-on neurons, and direct activation of REM sleep-on neurons by lower brain stem neurons, promoting REM sleep. As long as the REM sleep-off neurons are inhibited, REM sleep can be maintained. The GABAergic neurons regulating REM sleep could possess α_1-noradrenergic receptors. One of the main conclusions of the paper is that "a critical level of noradrenaline in the system was required for the generation of REM sleep. However, a higher level may be inhibitory" (p. 9). This paper admirably shows the mechanisms involved in REM sleep-generating processes, although those regulating REM sleep termination remain open to discussion.

Pal et al. (2005), also from Mallick's group, wrote a review which, regarding NA, confirmed that locus coeruleus neurons must be silent for REM sleep to occur. Unlike the previous paper, this article did not stress the need for some amount of noradrenaline, as was also demonstrated by Ouyang et al. (2004).

3.4.12. 2006

Pal and Mallick (2006) bilaterally injected prazosin (0.24 mM), clonidine (3.75 mM), and propanolol (3.38 mM) into the pedunculopontine tegmentum of rats. The animals were injected between 10:00 and 10:30 a.m. and were recorded for 8 h. Prazosin increased REM sleep ($P < 0.001$) by raising the number of REM sleep episodes ($P < 0.05$), while episode duration was unchanged. Clonidine increased REM sleep by lengthening the duration of REM sleep episodes ($P < 0.001$), whereas their number was unchanged. Propanolol increased REM sleep by enhancing the number of episodes ($P < 0.001$), while their duration was unchanged. When 0.83 mM of picrotoxin ($GABA_A$ antagonist) and clonidine were simultaneously injected, overall REM sleep decreased ($P < 0.01$) because the frequency of occurrence decreased ($P < 0.01$), although the duration of episodes increased ($P < 0.01$). The authors emphasized that the influence of propanolol is open to discussion, since it also inhibits serotonergic neurons which, together with locus coeruleus neurons, become silent during REM sleep. Regarding NA, the authors suggested that whereas activating α_1-receptors are situated on pontine neurons which are responsible for waking (as claimed by Jones, 2004), β-receptors, which

inhibit pontine neurons, are situated on REM sleep-inducing neurons (whereas Jones, 2004 thinks that α_2-receptors are concerned). The picrotoxin-mediated blockade of pontine GABA heteroreceptors situated at noradrenergic neuron terminals prevents the inhibition of noradrenergic influences on pontine cholinergic REM sleep-on neurons, an inhibition mediated by these same β-receptors.

3.4.13. 2007

Rasch et al. (2007) studied the blood concentration of NA during the sleep–waking cycle in humans. It was minimal during REM sleep.

Pal and Mallick (2007) wrote an extended review (supported by numerous older as well as more recent references) on noradrenergic REM sleep-off processes. However, here also, and contrary to their earlier paper (Mallick et al., 2005), the function of NA in REM sleep-on processes was not taken into account in spite of citing Jouvet (1972), who supported a positive influence for NA.

Conclusion. This last extended period gave rise to numerous negative results, with research being directed more towards the *a priori* more evident necessity of a decrease in NA for the generation and maintenance of REM sleep. However, the results with neurotoxic DSP-4 (Gonzalez et al., 1995), the animal (Mallick et al., 2005) and human (Gentili et al., 1996) results with clonidine, and finally the knock-out approach in mice (Ouyang et al., 2004), reinforced the hypothesis that some NA is required for REM sleep to occur.

4. Discussion

4.1. Noradrenaline involvement in basic REM sleep mechanisms (Table 4)

The most generally accepted idea concerning the relationship between NA and REM sleep is that the locus coeruleus must be silent for this sleep stage to occur. Hence, this neuromodulator must be absent. The most recent model, proposed by Mallick et al. (2005), postulates that during waking REM sleep-off neurons are activated by waking-inducing structures (Mallick et al., 1998; Thankachan et al., 2001) that trigger NA release. The REM sleep-on neurons of the laterodorsal/pedunculopontine tegmental nuclei should be inhibited by β-adrenoceptors (in contrast, according to Bier and McCarley (1994) and Jones (2004), α_2-receptors are responsible) or indirectly through GABA. Indeed, the induction of REM sleep probably occurs through the inhibition of locus coeruleus noradrenergic neurons by GABA interneurons (Kaur et al., 2004) as well as by medulla afferent neurons (Ennis and Aston-Jones, 1989a,b) (mainly issued from the dorsal paragigantocellular reticular nucleus, Verret et al., 2006; but also from the prepositus hypoglossi nucleus, Kaur et al., 2001), thereby inhibiting REM sleep-off structures and indirectly disinhibiting REM sleep-on ones. A decrease in noradrenergic REM sleep-off auto-inhibition through collateral inputs (Aghajanian et al., 1977) bearing α_2-receptors could also participate indirectly in the progressive deactivation of the noradrenergic waking-supporting structure and disinhibit REM sleep-on structures. Indeed, the infusion of clonidine into the locus coeruleus decreases NA release, although the α_2-receptor antagonist idazoxan does not change it (Kawahara et al., 1999). In addition, the adrenergic medulla oblongata C_1 neurons also innervate the locus coeruleus and act by inhibitory influences (Aston-Jones et al., 1991). Finally, Sakai (Sakai and Crochet, 2003, 2004) has identified the glutamate-induced disfacilitation of the locus coeruleus as being responsible for REM sleep generation.

Nevertheless, in the history of REM sleep studies, several findings have repeatedly underscored the need for noradrenaline for REM sleep to occur. The first, rather crude premonitory research was carried out by Jouvet's team (Matsumoto and Jouvet, 1964), who showed that REM sleep disappearance in reserpinized cats can be reversed by the administration of DOPA. Shortly afterwards, nearly all studies used molecules acting on noradrenergic release or on noradrenergic receptors. The first such compound was AMPT, which inhibits tyrosine hydroxylase and thus leads to a decrease of dopamine and noradrenaline synthesis. Several studies showed that it decreases REM sleep in rats (Gaillard et al., 1982; Kafi et al., 1977; Mastrangelo et al., 1994; Milon and Enslen, 1980; Torda, 1968), cats (Iskander and Kaelbling, 1970), monkeys (Weitzman et al., 1969), and even in humans when used for therapeutic purposes (Wyatt et al., 1971). The second most frequently used molecule was clonidine, a pre-synaptic α_2-agonist, which was also shown to decrease REM sleep in rats (Gaillard, 1985; Gaillard et al., 1982; Kafi and Gaillard, 1981; Kleinlogel et al., 1975; Mastrangelo et al., 1994), cats (Leppävuori and Putkonen, 1980; Putkonen et al., 1977; Tononi et al., 1991a), and humans (Autret et al., 1977; Gaillard, 1985; Gaillard and Kafi, 1978; Gentili et al., 1996; Kanno and Clarenbach, 1985), while antagonists increase REM sleep (Bier and McCarley, 1994). Noradrenergic α_1-antagonist (Matsumoto and Watanabe, 1967; Radulovacki et al., 1980) and β-antagonist (Betts and Alford, 1985; Hilakivi et al., 1978; Lanfumey et al., 1985; Matsumoto and Watanabe, 1967) induced the same decrease in REM sleep. Other molecules that suppress NA synthesis, such as α-methyl-DOPA (Dusan-Peyrethon et al., 1968; Leppävuori and Putkonen, 1980), or noradrenergic neuron lesion by 6-OH-DA (Laguzzi et al., 1972; Matsuyama et al., 1973; Zolovick et al., 1973), also decreased REM sleep. Even the direct lesion of the locus coeruleus in rabbits (Braun and Pivik, 1981; Claude et al., 1981) and in cats (Jones et al., 1977; Jouvet and Delorme, 1965), decreased REM sleep. Finally, modern knock-out mice lacking dopamine-β-hydroxylase provide the best demonstration that NA is a prerequisite for REM sleep occurrence (Ouyang et al., 2004), as

Table 4
Influence of the main drugs encountered in the review.

Monoamine depletion—Reserpine: *Following experiments, REM sleep decrease, increase,* or *no clear-cut effect*
Monoamine oxidase inhibitors (IMAO)—Harmaline, iproniazide, nialamide, tranylcypromine: *REM sleep decrease*
Uptake inhibitors—Clomipramine, desmethylimipramine, imipramine, maprotiline, nisoxetine: *REM sleep decrease*
Catechol-*O*-methyl transferase (COMT) blockade—Tropolone: *REM sleep increase*
Tyrosine hydroxylase blockade—α-methyl-*para*-tyrosine (AMPT): *REM sleep decrease*
Dopamine-β-hydroxylase blockade—Fusaric acid: *REM sleep decrease*
Noradrenaline synthesis blockade—α-methyl-DOPA: *REM sleep decrease*
Deamination of phenylalanine and tyrosine—Phenylalanine ammonia-lyase: *REM sleep decrease*
Noradrenaline neurotoxin—*N*-(2-Chlorethyl)-*N*-ethyl-2-bromobenzylamine (DSP-4): *REM sleep decrease*
Destruction of noradrenergic neurons and terminals—6-Hydroxy-dopamine (6-OHDA): *Mainly REM sleep decrease*
α_1-, α_2-Receptor antagonist—Phentolamine: *REM sleep increase*
α_1-Receptor antagonists—Benoxathian, dibamine, phenoxybenzamine, prazosin, thymoxamine: *Various findings*
α_1-Agonists—Methoxamine, phenylephrine: *Mainly REM sleep decrease*
α_2-Antagonists—Idazoxan, piperoxane, rawolscine, yohimbine: *Mainly REM sleep increase*
α_2-Agonists—Clonidine, guanfacine, xylazine: *Mainly REM sleep decrease*
β_1-, β_2-antagonists—Dichloroisoproterenol, nethalide, pindolol, propranolol: *Mainly REM sleep decrease, except increase after injection in the pons*
β_1-, β_2-Agonist—Isoproterenol: *REM sleep increase, except decrease after injection in the pons*
β_1-Antagonists—Acebutolol, atenolol, metropolol, stenolol: *Mainly REM sleep decrease*
β_1-Agonist—Prenalterol: *Mainly REM sleep increase*
β_2-Antagonist—Iodocyanopindolol: *In one case, REM sleep decrease*
β_2-Agonists—Clenbuterol, salbutamol: *REM sleep decrease*

had already been shown by clinical deficiency (Tulen et al., 1990, 1991). Another complementary argument for NA's positive influence on REM sleep-generating processes was the fact that it activates pontine neurons involved in REM occurrence (Gerber et al., 1990; Greene and Carpenter, 1985; Koyama and Sakai, 2000; Mühlethaler et al., 1990; Stevens et al., 1994); Jones's team (Hou et al., 2002; Jones, 2004), however, has postulated that pontine reticular cholinergic neurons bearing α_1-receptors promote waking when stimulated by NA, while other cholinergic neurons bearing α_2-receptors are inhibited by NA and are responsible for disinhibiting REM sleep-on neurons by NA silence during REM sleep. This last conclusion was also reached by Bier and McCarley (1994).

Consequently, in the ongoing history of the relationship between NA and REM sleep, it is important to recall various authors who clearly claimed NA to be a prerequisite for REM sleep. First, already in 1977, in work from Gaillard's laboratory: "Thus, our experiments support the view that an intact synaptic transmission in catecholaminergic neurons is necessary for the realization of REM sleep" (p. 132) (Kafi et al., 1977). Then, Putkonen's laboratory (Leppävuori and Putkonen, 1980), another early (but less dogged) defender of noradrenaline involvement stated: "While the contribution of noradrenergic transmission is likely to be essential to the elaboration of REM sleep, the optimal range of noradrenergic activity with REM sleep may be considerably below that for active waking" (p. 111). Finally, although a recent result does not support the involvement of NA in REM sleep-generating processes (Sakai and Crochet, 2004), both Ouyang et al. (2004) and Mallick's team (Mallick et al., 2005) have definitively accepted the need for some amount of NA to trigger REM sleep occurrence.

4.1.1. How can one account for NA as an essential contributor to REM sleep occurrence when a silent locus coeruleus is also an indispensable factor?

To begin with, it should be borne in mind that several studies on locus coeruleus firing were the first to demonstrate the silence of noradrenergic neurons during REM sleep (Aston-Jones and Bloom, 1981a; Hobson et al., 1975; Rasmussen et al., 1986). However, while the resumption of discharges at the end of the REM sleep period, occurring a few seconds prior to behavioral arousal, has been well described (Aston-Jones and Bloom, 1981a), the precise timing of the silent state occurring at the onset of REM sleep has been less thoroughly studied; the two best figures from rats (Aston-Jones and Bloom, 1981a) demonstrate some firing just prior to and/or at the onset of REM sleep. This means that the low level of noradrenaline that is required for the generation of REM sleep could be provided by the final spikes of noradrenergic neurons prior to their disappearance during REM sleep. The second major response is that NA, like other monoamines, is mainly released at the varicosity level. This kind of volume transmission (slow and less reliable than synaptic release), which reaches a large number of targets (Zoli et al., 1998), was first shown at the cortical level (Descarries et al., 1977; Fuxe et al., 1968; Levit and Moore, 1978; Seguela et al., 1990). It involves diffuse transmitter release without rapid reuptake by transporters in the pre-synaptic neuron and with an absence of rapid destruction at the synaptic level by COMT. These varicosities have been confirmed in the brain stem in several species (Masuko et al., 1986; Mons et al., 1995; Smeets and Steinbusch, 1989). Furthermore, the importance of this same phenomenon has been identified in the brain stem in relation to sleep–waking processes (Jones, 1991).

The low remaining level of NA necessary for REM sleep occurrence could be gradually metabolized and the steady degradation of diffuse residual NA could promote the end of each REM sleep episode by the progressive disappearance of the auto-inhibition of the locus coeruleus (Aghajanian et al., 1977), as has been hypothesized (Hobson et al., 1975, 2000). However, up until the present, particularly with the recent work of Mallick et al. (2005), the mechanisms underlying REM sleep entrance and maintenance have been better understood than those governing the termination of the REM sleep stage.

To conclude, as stated by numerous early (Autret et al., 1977; Kafi et al., 1977; Kleinlogel et al., 1975; Laguzzi et al., 1972; Lanfumey et al., 1985; Matsuyama et al., 1973; Putkonen et al., 1977; Satoh and Tanaka, 1973; Spiegel and Devos, 1980; Weitzman et al., 1969) and more recent (Bier and McCarley, 1994; Gentili et al., 1996; Mallick et al., 2005; Mastrangelo et al., 1994; Ouyang et al., 2004; Tononi et al., 1991a,b) researchers, a low brain stem level of NA is necessary for the occurrence of REM sleep, while the noradrenergic neurons have to become silent to avoid a level of NA which would be high enough to inhibit REM sleep, as shown by the numerous papers devoted to NA-related REM sleep-off processes. Both NA pre-synaptic receptors at other neuron terminals acting at post-synaptic level (heteroreceptors), and NA post-synaptic receptors situated on target neurons, are involved in the regulation of REM sleep.

Although numerous studies have implicated NA in the basic processes of REM sleep generation and maintenance (although the specific influence of medullary noradrenergic afferents on mesopontine REM sleep has not been elucidated), it must be emphasized that several recent results strongly suggest another, at least complementary, mechanism involving other neurotransmitters, such as dopamine, GABA, and glutamate (Crochet et al., 2006; Hunsley and Palmiter, 2003; Lu et al., 2006; Luppi et al., 2006; Vanini et al., 2007).

4.2. Noradrenaline involvement in higher integrated processes of REM sleep

Still more than for the basic mechanisms REM sleep, it is illusory to claim that a single neurotransmitter or neuromodulator could support the most elaborate feature of the brain, namely consciousness. However, despite the obvious plurifactorial influences in consciousness, the functions of noradrenaline in the forebrain need to be highlighted, in association with those of acetylcholine, glutamate, GABA, and serotonin, also bearing in mind the numerous peptides and trace amines that intervene alone and otherwise modulate transmitters and neuromodulators.

4.2.1. Cortex and thalamus

4.2.1.1. General functioning. In the forebrain, the cortex is mainly involved in cognitive processes. The prefrontal cortex, the phylogenetically most recent structure, is involved in anticipatory processes, attentive behavior to irrelevant stimuli and working memory. Noradrenergic neurons, which innervate the cortex, originate exclusively from the locus coeruleus with between 10,000 and 15,000 neurons in primates, with the highest density of cortical innervation being in layers III (external pyramidal cells) and IV (internal granular layer) (Berridge and Waterhouse, 2003). Cortical release is dependent on two modes of functioning of the locus coeruleus (Aston-Jones and Cohen, 2005). First, there is a basic tonic mode that increases with vigilance level. Once again, these pontine neurons fire maximally albeit at low frequency during waking, and the discharges slow down during slow-wave sleep and become silent during REM sleep (Aston-Jones and Bloom, 1981a; Hobson et al., 1975; Rasmussen et al., 1986). Consequently, the pontine (Shouse et al., 2000) and prefrontal (Léna et al., 2005) release of NA is highest during waking and is strongly decreased

during REM sleep. The second is a phasic mode of discharge which is associated with sensory target detections and which is most efficient on a sufficient tonic background. This mode of functioning is sensitive to afferent novelty changes rather than to intrinsic stimulus characteristics, and the discharges generally precede behavioral changes during a task (Bouret and Sara, 2005). The tonic locus coeruleus firing which occurs during increased vigilance could enhance responses of the sensory neurons to threshold and above threshold stimuli, whereas phasic discharges could amplify the detection of sub-threshold stimuli (Berridge and Waterhouse, 2003). Recently, Johnson (2003) postulated that "the tonic noradrenergic activity provides ongoing global attenuation of other neural activity. It promotes vigilance by preventing unimportant events from disrupting this state of anticipation. By comparison, phasic noradrenergic activity serves to interrupt ongoing neural processes when a significant new event is experienced" (p. 689). Because of colocalization, this second kind of activation is usually associated with cortical peptide release, particularly that of galanin, the gene expression of which is more generally increased after REM sleep deprivation (Toppila et al., 1995), which enhances noradrenaline release.

Both kinds of discharge recruit all locus coeruleus neurons (mass discharges) and are responsible for waking EEG processes (Berridge and Foote, 1991). This kind of global functioning could be sustained by electrical coupling processes, as already shown in the subcoeruleus (Heister et al., 2008), because of nearly situated neurons, at least in rats. However, this waking firing is under the control of locus coeruleus α_2-autoreceptors situated on the collaterals, since agonists like clonidine infused into the nucleus inhibit waking EEG and induce cortical slow waves in rats that can be reversed by the α_2-antagonist yohimbine (De Sarro et al., 1987). Besides, α_2-agonists are used in humans because clonidine decreases the required dose of anesthetic (Berridge et al., 1993; Bloor and Flacke, 1982). What is most interesting is the difference between the optimal and minimal functional levels of transmitter (Abercrombie and Zigmond, 1989). Similarly, while about 30% of dopaminergic substantia nigra neurons are sufficient to prevent the appearance of Parkinson's symptoms, 10% of locus coeruleus discharges are sufficient to maintain forebrain activation (Berridge et al., 1993). This phenomenon can be explained by well-known noradrenergic neuron compensatory processes (Chiodo et al., 1983).

Noradrenaline acts on cortical neurons through α_1-, α_2- and β-receptors. Alpha$_1$ receptor activation decreases resting K^+ conductance (Nicoll et al., 1990), and agonists impair cognitive processes in rats (Arnsten, 1997; Arnsten et al., 1999) and monkeys (Arnsten and Jentsch, 1997; Mao et al., 1999), while antagonists improve them (Arnsten et al., 1999). Noradrenaline facilitates glutamate-induced activation only at medium doses, in an inverted U-curve. It is possible that this increased facilitation of glutamatergic processes is at least partly responsible for the debilitating influence of α_1-receptor agonists on cognitive performance, since they induce excessive cortical excitation within a narrow optimum stimulation window. However, the cognitive facilitatory influences of systemically administered α_2-autoreceptor antagonists can be blocked in the prefrontal cortex by the local infusion of α_1-antagonists (Lapiz and Morilak, 2006), suggesting that NA α_1-receptors possess some cognition-enhancing properties.

In contrast, β-receptors increase the inhibitory influences of GABA, and co-administration of α_1- and β-antagonists induces slow-wave sleep patterns (Berridge and Espana, 2000). The global involvement of β-receptors produces few changes in performance. Indeed, a joint β_1 and β_2 blockade has no impact on working memory in rats or in monkeys. In contrast, β_1-antagonists infused into the prefrontal cortex of rats or systemically administered to monkeys improve working memory. Thus, β_1-agonists acting in the prefrontal cortex could impair cognitive functions (Ramos et al., 2005).

However, a large number of older, well-established results have shown that NA mainly inhibits cortical neurons (Foote et al., 1975; Frederickson et al., 1971; Krnjevic and Phillis, 1963; Manunta and Edeline, 1999; Nelson et al., 1973; Reader et al., 1979) by opening K^+ channels or by activating inhibitory interneurons. The receptors involved are mainly post-synaptic α_2 ones. Although NA has mostly inhibitory properties on the cortex, this neuromodulator increases the ratio of signal-to-noise to significant stimuli, thus increasing neuron efficiency (Aston-Jones and Bloom, 1981b; Berlucchi, 1997; Foote et al., 1975; Warren and Dykes, 1996; Waterhouse et al., 1990). While acetylcholine enhances the signal relative to unchanged noise, NA reduces the noise relative to an unchanged signal (Berlucchi, 1997; Berridge and Waterhouse, 2003).

The dorsolateral prefrontal cortex is organized asymmetrically, and right-side lesions increase distractibility as shown by event-related potential studies (Knight et al., 1981; Woods and Knight, 1986). Noradrenaline is involved in these processes. For example, prefrontal neurotoxic inhibition of dopamine-β-hydroxylase impairs attentional processes (Milstein et al., 2007). Post-synaptic α_2 receptor activation favors cognitive processes (Arnsten, 1997; Mao et al., 1999; Milstein et al., 2007; Steere and Arnsten, 1997), and α_{2A}-receptors are particularly responsible for the improvement in performance since their affinity for NA is higher than it is for α_1-receptors (Renouard et al., 1994) (quoted by Berridge and Waterhouse, 2003). Their optimal activation for behavioral performances is restricted to the precise limits (Arnsten and Li, 2005) of an inverted U-curve (Arnsten and Dudley, 2005). Another argument is that in monkeys the P300-like component involved in cognitive and memory processes is decreased by locus coeruleus lesions (Pineda et al., 1989), and clonidine specifically decreases the cortical area of the P300-like component and increases its latency (Swick et al., 1994). Finally, once again, the amount of cortical NA release is controlled by α_2 pre-synaptic autoreceptors located on noradrenergic terminals, which modulate noradrenaline release when locus coeruleus firing becomes too intense.

From a general standpoint, NA, by means of α_1-receptor activation as well as through phasic locus coeruleus stimulation (Holdefer and Jacobs, 1994), shifts the cortical and thalamic mode of neuron discharge from a burst mode to a single-spike mode; the single-spike mode favors sensory transmission, while burst discharges induce thalamic neuron hyperpolarization by increased K^+ currents (McCormick, 1992; McCormick et al., 1993). Noradrenaline favors sensory encoding processes in the ventro-posteromedial nucleus of the thalamus by activating α_1-receptors, whereas post-synaptic α_2- and β-receptors mediate inhibition. This facilitation related to NA release follows an inverted U-curve (Devilbiss et al., 2006). The thalamic activation by noradrenaline should be underlined, since beyond its involvement in sensory transmission which is decreased in schizophrenia, favoring hallucinations (Behrendt and Young, 2005), "it is the dialogue between the thalamus and the cortex which is crucial for consciousness" (p. 532) (Llinas and Paré, 1991). In this respect, the tonic discharge mode of cortical neurons by noradrenaline recalls the first conclusion of Evarts (1964), who postulated that the regular tonic spike discharges of pyramidal neurons during waking result from a frequency-limiting mechanism that involves inhibitory processes and that disappears during REM sleep.

It should be emphasized that there are reciprocal interactions between the locus coeruleus and prefrontal cortex which exert strong facilitatory influences on the noradrenergic nucleus by stimulating the dendrites of locus coeruleus neurons. Single

prefrontal pulses activated 81% (and trains of pulses activated 92%) of the locus coeruleus cells. Prefrontal lidocaine infusion inhibited 62% of locus coeruleus neurons, reflecting strong facilitatory descending tonic influences (Jodo et al., 1998) which should activate locus coeruleus REM sleep-off processes.

Finally, recent studies have revealed the importance of noradrenaline in cortical neuroplasticity. "If cortical noradrenergic innervation is destroyed, the expression of cAMP-triggered phosphorylation of cAMP response element binding protein (P-CREB), activity-regulated cytoskeleton-associated protein (arc) and brain-derived neurotrophic factor (BDNF) in the cerebral cortex is significantly reduced, despite the presence of a normal waking EEG" (p. 9188) (Cirelli and Tononi, 2000). This was demonstrated by i.p. injection of DSP-4, the neurotoxin that depletes noradrenaline in neuron terminals issued from the locus coeruleus but not from medulla oblongata A_1 and A_2 neurons. The serotonergic neurons were protected by fluoxetine. The expression of several waking-activated transcripts related to synaptic plasticity and the cellular response to stress was decreased. The expression of these genes, among other processes, is involved in long-term potentiation (supporting long-term memory) and are mainly mediated by β_1-receptor activation (Cirelli and Tononi, 2004). The impairment of performance by lesions of the noradrenergic dorsal bundle (Leconte and Hennevin, 1981; Tait et al., 2007) is probably the consequence of the dysfunction of the same transcripts.

4.2.1.2. REM sleep. During REM sleep, the silence of locus coeruleus neurons strongly lowers NA levels in the cortex. In our research on the medial prefrontal cortex, the concentration dropped from 20.9×10^{-10} M during waking to 9.98×10^{-10} M ($P < 0.01$) (Léna et al., 2005). Here again, it should be noted that some amount of noradrenaline is maintained, certainly because of its diffusion at the varicosity level without immediate pre-synaptic reuptake or synaptic destruction. However, in view of its crucial role in cognitive functioning, noradrenaline is certainly outside its positive inverted U-curve level. By virtue of its quasi-absence, particularly on post-synaptic α_2 receptors, it induces considerable disinhibition, which could explain why REM sleep reverts from regulated single spike discharges to the more anarchic burst discharge (Evarts, 1964). Also, the more rapid recovery cycle of evoked potentials in animals (Allison, 1968; Demetrescu et al., 1966; Rossi et al., 1965) (for reference see Gottesmann, 2005, 2006a) and the disappearance of prepulse inhibition of the N_{100} component in humans (Kisley et al., 2003) confirm this cortical disinhibition during REM sleep. This physiological abnormality could also explain the dysfunction observed in the occurrence of the EEG gamma rhythm. Indeed, during waking, this now classic synchronized high frequency activity, which is mainly centered around 40 counts/s and appears in animals (Bouyer et al., 1981; Ferster, 1988; Llinas et al., 1991; Murphy and Fetz, 1992; Steriade et al., 1991, 1996a,b) as well as in humans (Ribary et al., 1991), is synchronized over cortical areas (Cantero et al., 2004; Massimini et al., 2005; Perez-Garci et al., 2001). In contrast, specifically during REM sleep, the same gamma rhythm that has also long been observed in animals (Franken et al., 1994; Maloney et al., 1997) and humans (Llinas and Ribary, 1993) loses its coherence in the cortical areas (Cantero et al., 2004; Massimini et al., 2005; Perez-Garci et al., 2001). Although the relationship between the gamma rhythm and consciousness is open to discussion (Vanderwolf, 2000), the loss of gamma rhythm coherence during REM sleep is an indication of functional connectivity disturbances between brain structures, a process strongly hypothesized for schizophrenia (Meyer-Lindenberg et al., 2001, 2005; Peled et al., 2000; Spencer et al., 2003; Tononi and Edelman, 2000; Yeragani et al., 2006; Young et al., 1998). The noradrenergic deficit could, directly at the cortical level or indirectly by subcortical afferents (Cape and Jones, 1998), disturb such connectivity.

All of these above-described data indicating a cortical loss of control processes could explain the irrational mentation of dreams that was highlighted long ago (Gottesmann, 1967, 1970, 1971). Noradrenergic disinhibition could be also responsible for frequently recurrent dreams, particularly in post-traumatic syndromes. Indeed, by analogy with the discharge of an overloaded capacitor, a high load of the corresponding specific memory "trace", or possible holographic representation (Bokkon, 2005), could cause eruptions in the conscious field because of a lowered threshold of evocation (Gottesmann, 1999). We previously hypothesized a kind of lowered physiological censorship (Gottesmann, 2006b) in the cortex due to this noradrenergic deficit, rather than the obligatory loss of psychological censorship postulated by Freud (1900).

Dreaming, with its hallucinations and delusions, shows strange similarities with phenomena encountered in schizophrenia. Indeed, just as we showed a strong decrease of noradrenaline concentrations in the cortex during REM sleep (Léna et al., 2005), there is also a deficit of noradrenaline in this psychosis, and several new neuroleptics associate the dopamine receptor blocking component with a noradrenaline transporter inhibiting function (Friedman et al., 1999; Linner et al., 2002). The argument in favor of cortical disinhibition during REM sleep is supported by the classic observation that, as in schizophrenia during waking, there is nearly no EEG alpha rhythm during this sleep stage, which is characteristic of a decrease or loss of habituation processes. However, as already noted (Gottesmann, 1999; Hobson and Pace-Schott, 2002), there are several physiological criteria of neuroplasticity during REM sleep (Hennevin et al., 1995; Smith, 1995); also more recently, it was shown that REM sleep-associated P-waves in rats, which are the equivalent of PGO waves in cats, increase after learning (Datta, 2000, 2006). Likewise, elicited PGO spikes in cats have higher amplitudes after fear conditioning (Sanford et al., 2001b), a recall of fear extinction which is altered after REM sleep deprivation (Fu et al., 2007). However, this question of memory processing during REM sleep remains open to debate (Siegel, 2001; Vertes, 2004; Vertes and Eastman, 2000), particularly since noradrenergic silence disturbs the neuroplasticity processes involved in long-term memory (Cirelli and Tononi, 2000, 2004). This could also partly explain the frequent forgetting (non-recording) of dreams, even in the final night-time REM sleep period which, in humans, lasts for up to 50 min (Dement and Kleitman, 1957). Perhaps this long duration is already sufficient to disturb the expression of neuroplasticity genes under noradrenergic control which usually occurs during waking (Cirelli and Tononi, 2000, 2004).

Although the connection with noradrenergic afferents is not directly obvious, tomographic evidence shows that the same deactivation of the dorsolateral prefrontal (Braun et al., 1997; Maquet et al., 1996) and other frontal areas (Lövblad et al., 1999; Madsen et al., 1991) occurs during REM sleep as in schizophrenia, particularly when cognitive tasks are impaired in the latter state (Bunney and Bunney, 2000; Fletcher et al., 1998; Weinberger et al., 1986). This decrease in blood flow that is common to both states and possibly related to the noradrenergic silence (and an overactive pedunculopontine nucleus; Garcia-Rill, 1997) could be responsible for the lower prefrontal efficiency of functioning (as reflected by, among other features, the loss of reflectiveness). Moreover, the posterior cingulate cortex, which is not part of the limbic system, is also deactivated during REM sleep (Braun et al., 1997; Maquet et al., 1996; Nofzinger et al., 1997). As already underlined (Gottesmann, 2007), in one specific case there is a common deactivation of both the prefrontal dorsolateral and

posterior cingulate cortex. This is when pianists are deeply immersed in their performance and "lose themselves" in a state verging on a second consciousness (Parsons et al., 2005). In addition, since the dorsolateral prefrontal cortex is deactivated, it is highly probable that during REM sleep there is descending disfacilitation on the locus coeruleus (see above) (Jodo et al., 1998), which is in agreement with Sakai's assertion, even if postulated to result from another brain stem process (Sakai and Crochet, 2004). Finally, and very significantly, whereas the primary visual area 17 is activated during waking imagery information processing (Kosslyn et al., 1999), it is deactivated during REM sleep (Braun et al., 1998) as well as in schizophrenia, at least as observed in one patient with visual and auditory hallucinations (Silbersweig et al., 1995) (personal communication 2007). Primary visual area deactivation during REM sleep could explain the absence of gamma rhythm reset, in contrast to waking (Llinas and Ribary, 1993). In addition, this occipital deactivation, which is a criteria of disconnection from the periphery, is reinforced by the pre-synaptic inhibition of thalamic afferents in relay nuclei, principally during the eye movement bursts (Dagnino et al., 1969; Gandolfo et al., 1980; Ghelarducci et al., 1970; Steriade, 1970) generally associated with active dreaming (Goodenough et al., 1959; Herman et al., 1984; Roffwarg et al., 1962). It is of interest that voluntary attention to deviant stimuli can increase the P_{400} event-related potential component during the tonic periods of REM sleep and thus when there is no (or only low?) inhibition of sensory afferents. This event-related potential is absent during the phasic events of REM sleep (Takahara et al., 2006), when there is pre-synaptic depolarization (Wall, 1958) at the thalamic level. In contrast to the primary visual cortex, the non-primary visual cortex areas are strongly activated during REM sleep (as shown by the now classic blood flow approach (Braun et al., 1998; Madsen et al., 1991; Maquet, 2000; Maquet et al., 2004) and PGO-like activity (Wehrle et al., 2005), particularly at the onset of the visual ventral stream, which could support the rich visual dreaming activity.

From a neurochemical standpoint, it must be emphasized once again that numerous neurotransmitters and neuromodulators in addition to NA cooperate in mental processes in the cortex, with the modification of their concentrations accounting for the cognitive disturbances that occur during dreaming. (1) Dopamine also inhibits numerous cortical neurons, as was shown long ago (Krnjevic and Phillis, 1963; Reader et al., 1979), by increasing the release of GABA from interneurons via D_2 receptors and also by directly inhibiting pyramidal neurons through D_1 receptors (Abi-Dargham and Moore, 2003; Pirot et al., 1992; Rétaux et al., 1991). However, like NA, dopamine increases the signal-to-noise ratio of synaptic afferents (Luciana et al., 1998), and its prefrontal importance for cognitive processes is underscored by the fact that D_1 receptor gene expression is highest in adolescence and early adulthood, a critical life-stage in schizophrenia. Moreover, the expression of both D_1 and D_2 decreases significantly in old age (Weickert et al., 2007). The decrease in dopamine concentrations in the rat prefrontal cortex during REM sleep (Léna et al., 2005), more than the unchanged glutamate level (Léna et al., 2005), could contribute to the abnormal mental functioning during dreaming, and a similar decrease in dopamine (Abi-Dargham and Moore, 2003) and unmodified glutamate functioning (Lauriat et al., 2005) is observed in schizophrenia. The abnormality of dopaminergic D_1 receptor activation, which appears to be outside a narrow window showing an inverted U-shape relationship with cognitive performance (Meyer-Lindenberg and Weinberger, 2006), together with the NA decrease, can explain, among other things, the reduction or loss of reflectiveness encountered in both states. (2) Serotonergic neurons could also be involved, since they too are silent during REM sleep (McGinty and Harper, 1976; Rasmussen et al., 1984) and this neuromodulator inhibits cortical neurons (Araneda and Andrade, 1991; Reader et al., 1979), thereby inducing complementary disinhibition. (3) In the dorsolateral prefrontal cortex, a decrease in the GABA concentration due to the inhibition of mRNA encoding glutamic acid decarboxylase is one characteristic of schizophrenia (Lewis et al., 2005). The same phenomenon, which remains unexplored to date, could occur during REM sleep. (4) Finally, as already mentioned, the intrinsic or modulatory influences of "trace amines", particularly octopamine for NA (and β-phenylethylamine for dopamine), are strongly hypothesized to intervene at the cortical level in psychiatric syndromes, since they are mainly produced when tyrosine hydroxylase activity is low or absent (i.e. possibly during REM sleep) (Burchett and Hicks, 2006).

4.2.2. Nucleus accumbens

The nucleus accumbens has its main connections with the prefrontal cortex, hippocampus, and amygdala. This forebrain structure exhibits functional disturbances in psycho-affective diseases. It is particularly concerned in the hallucinations and delusions encountered during dreaming as well as in schizophrenia.

The first important fact is that, contrary to the prefrontal cortex, the locus coeruleus only slightly innervates the nucleus accumbens. The major noradrenergic influences are issued from medulla oblongata A_1 and A_2 nuclei (Delfs et al., 1998). The function of these two nuclei has not been studied in as much detail as the locus coeruleus nucleus. However, another noradrenergic nucleus, A_5, displays functional properties identical to those of the locus coeruleus in relation to sleep–waking stages (Fenik et al., 2002). The nucleus accumbens is activated during REM sleep, as evidenced by c-Fos expression after the REM sleep increase following GABA infusion into, or near, the central grey (Sastre et al., 2000). Noradrenaline, dopamine, and glutamate concentrations vary according to the sleep–waking stage. First, there are connections between NA release and glutamate function since their extracellular concentrations vary in parallel (Swanson and Schoepp, 2003). This was confirmed by our sleep–waking study showing similar maximum noradrenaline and glutamate concentrations during waking and minimal concentrations of both during REM sleep (Léna et al., 2005). A related result shows that the lesion of the ventral hippocampus (Lipska et al., 1993, 2003), which is responsible for the generation of psychotic symptoms by decreasing glutamate release (Grace, 2000), increases NA transporter binding in the nucleus accumbens. This phenomenon could give rise to a decreased extracellular level by up-regulating reuptake (Bhardwaj et al., 2004). Noradrenaline certainly plays an important role in the nucleus accumbens, since its concentration in humans is as high as that of dopamine (Tong et al., 2006). The marked decrease that is observed during REM sleep cannot be devoid of functional significance. For example, there is dopamine uptake by noradrenergic neurons in the nucleus accumbens (Carboni and Silvagni, 2004). This should decrease or be suppressed during the REM sleep-associated noradrenergic silence and contribute to the high concentration of dopamine (Léna et al., 2005). Moreover, pre-synaptic noradrenergic α_2-receptor agonists (Pothos et al., 1991) (as well as β-receptor antagonists; Harris et al., 1996) act to increase local dopamine release.

Thus, the nucleus accumbens is activated during REM sleep. Indeed, another argument is that its neurons (3/5) fire more strongly during REM sleep than during waking (Callaway and Henriksen, 1992). As seen above, there are interactions between NA and dopamine. As already described many years ago, an increase in dopamine is responsible for schizophrenic hallucinations and delusions (MacKay et al., 1982). The maximum release of

dopamine during REM sleep (Léna et al., 2005) could explain dreaming mentation, which strongly resembles the disturbances encountered in schizophrenia. Indeed, as carefully analyzed by Hobson's team (Hobson et al., 1998), dreaming is characterized by "sensory motor hallucinations, bizarre imagery . . . diminished self-reflective awareness, orientational instability . . . intensification of emotion, instinctual behaviors", which are all symptoms of schizophrenia. The significant release of dopamine during REM sleep, which is known to induce vivid dreaming (Larsen and Tandberg, 2001), could be supported by NA silence (Carboni and Silvagni, 2004; Pothos et al., 1991); the latter deficit is believed to be involved in schizophrenic disturbances since, once again, new neuroleptics comprise NA transporter blocking agents in addition to antidopaminergic compounds (Friedman et al., 1999; Linner et al., 2002). However, the decrease in glutamate release that takes place in the nucleus accumbens during REM sleep should also be noted, since deficiency of this transmitter is currently believed to mainly account for psychotic symptom occurrence, as shown with NMDA antagonists (Grace, 2000; Heresco-Levy, 2000). It is of the greatest interest that these antagonists also induce vivid dreaming (Reeves et al., 2001). Finally, the disturbances observed in REM sleep-associated dreaming mentation could be intensified by the global disinhibition produced by the greatly decreased level of NA (Léna et al., 2005), which should diminish the local release of GABA (Kombian et al., 2006).

4.2.3. Amygdala

The amygdala is a crucial structure involved in the decoding and memory of emotions. Sensory afferents bring information, mainly about stress-related situations in the environment, and the amygdala triggers appropriate emotional responses.

Some early results showed that the amygdala, like the accumbens nucleus, receives noradrenergic inputs originating from the locus coeruleus and from medulla oblongata A_1 and A_2 nuclei. The centralis and basolateralis nuclei are the most innervated, particularly by fibers with large varicosities (Fallon et al., 1978). It is of interest that there are reciprocal influences between the amygdala and the locus coeruleus (Bouret et al., 2003; Wallace et al., 1992) as well as the medulla oblongata A_2 nucleus, and that there are projections on the C_2 adrenergic nucleus (Wallace et al., 1992). Nucleus centralis activation, which phasically excites locus coeruleus neurons (Bouret et al., 2003), shows "robust expression of α_1 receptors binding sites as well as expression of mRNA encoding specific α_1 receptor subtypes in cells" (p. 1139) (Cecchi et al., 2002). The increased noradrenaline release in the centralis nucleus facilitates a component of the acute behavioral response to immobilization stress (Cecchi et al., 2002), an experimental situation that induces a more than threefold increase in noradrenaline release (Ma and Morilak, 2005). The basolateral nucleus is also significantly modulated by noradrenaline, since the activation of α_2-receptors, through two different pathways, inhibits its glutamatergic functioning, whereas β-receptor activation, in contrast, increases local glutamate release and transmission (Pralong et al., 2002). Thus, "activation of brain noradrenergic neurotransmission by acute stress acts to facilitate an array of neuroendocrine, autonomic, behavioral and cognitive components of the integrated, organismic response to stress (and) it is likely that dysregulation of the brain noradrenergic system may also represent a potential substrate for the interaction between environmental sensitization and individual vulnerability leading to stress-related psychopathology" (p. 1220) (Morilak et al., 2005).

The important role of noradrenaline in regulating responses to stress is sustained by its highest level of release. Indeed, while during alert waking its extracellular concentration is 1.53 pg/μl, the level during REM sleep is only 0.23 pg/μl, a decrease of 85% ($P < 0.05$). In contrast, in the locus coeruleus, it decreases from 2.12 to 0.50 pg/μl, a drop of 76% ($P < 0.05$) (Shouse et al., 2000). A similar finding was reported more recently (Park, 2002), with a 61% decrease during REM sleep ($P < 0.001$) in comparison to waking. Moreover, as the forebrain also intervenes in REM sleep regulation, microinjections of DSP-4 were made into the central nucleus of the rat amygdala. After 10 h of REM sleep deprivation, the usual rebound decreased by 67.28% (Charifi et al., 2000). Thus, the amygdala is involved in REM sleep regulation by noradrenergic processes. It is worth recalling that, more generally, while locus coeruleus neurons become silent, forebrain target neurons become highly sensitive to NA, and that sleep deprivation rapidly up-regulates several plasticity genes, a process mediated by noradrenaline (Payne et al., 2002).

During REM sleep, amygdala functioning is of course highly important for emotional experience in dreams. Freud already stated: "dreaming holds our attention as psychological experience much more by virtue of its affective basis than of its representational content" (pp. 462–463) (Freud, 1900). It is particularly important that the tomographic approach has shown that the amygdala is not only strongly activated during REM sleep (Maquet and Franck, 1997), but is also disinhibited because of the noradrenergic neuron silence (Chen and Sara, 2007). Nucleus centralis stimulation activates the locus coeruleus (Bouret et al., 2003), thus increasing REM sleep-off influences. The output of amygdala influences is increased by nucleus accumbens functioning. Indeed, during the normal waking state, the glutamatergic afferents from both the prefrontal cortex and the hippocampus restrict glutamatergic facilitatory input from the amygdala. During REM sleep (Léna et al., 2005) and in schizophrenia (Grace, 2000), this inhibition decreases or disappears, releasing amygdala influence outputs. Noradrenergic neuron silence (Aston-Jones and Bloom, 1981a; Rasmussen et al., 1986), confirmed by locally decreased release (Park, 2002), is very probably involved in affective disturbances during dreaming by suppressing the amygdala-mediated regulation of its emotional adaptative properties (Cecchi et al., 2002; Morilak et al., 2005): "dysfunction of noradrenergic modulatory activity is a factor in the development of specific psychiatric disorders" (Morilak et al., 2005).

5. Conclusion

Noradrenaline is crucial for the basic processes of REM sleep. The precise mechanism by which a small amount of this essential neuromodulator is available and acts is still open to discussion. Moreover, the fact that NA, in the classic REM sleep-off neuromodulator model, does not modify REM sleep when infused into the REM sleep-on pedunculopontine tegmentum, also needs to be explained (Datta et al., 2003), as do the results raising questions about its true function in REM sleep-generating and sustaining processes (Hunsley and Palmiter, 2003; Sakai and Crochet, 2003, 2004). Similarly, the mechanisms by which noradrenaline recovers its influence in the few seconds preceding behavioral arousal from REM sleep (Aston-Jones and Bloom, 1981a) have still not been fully elucidated.

The function of NA in mental processes is also obvious. Whatever the precise mechanism, even if, as in crustacea, its possible fundamental simple function "is to interrupt the activity of existing functional networks and then to facilitate their reorganization to promote rapid behavioral adaptation" (p. 581) (Bouret and Sara, 2005), the end result is that, in aged primates, there is a parallel decrease in cortical catecholamines and performance (Arnsten and Goldman-Rakic, 1987; Goldman-Rakic and Brown, 1981). More generally, NA depletion increases error

responses to irrelevant stimuli while decreasing responses to relevant stimuli (Milstein et al., 2007; Selden et al., 1990), and increases in cognitive performance are associated with increases in prefrontal NA release (Berridge et al., 2006). However, once again, the need for an optimal noradrenaline stimulation window is proven by the fact that increasing NA availability in well-performing animals impairs performance. There is an "inverted-U relationship between rates of locus coeruleus discharge and vigilance (which) contrasts with a relatively linear relationship between arousal levels and locus coeruleus neuronal activity" (p. 84) (Berridge and Waterhouse, 2003). In any case, stimulating the locus coeruleus for therapeutic purposes in humans induces "well-being (and) improves clarity of ... thinking" (p. 179) (Libet and Gleason, 1994). The silence of noradrenergic neurons during REM sleep contributes without any doubt to cognitive attenuations, e.g., "the loss of restraint upon spontaneous and associative influences" (p. 690) (Johnson, 2003), thus explaining the discontinuity in dreams, and particularly the "loss of self-conscious awareness" (Hofle et al., 1997) characteristic of this sleep stage, as well as of schizophrenia (Gottesmann and Gottesman, 2007). In addition, the narrow range of temperature levels in the hypothalamus (a structure also involved in sleep regulation; Mallick and Alam, 1992) that is crucial for optimal mind functioning, even if only slightly disturbed during REM sleep because of local noradrenergic silence (Bach et al., 2002; Parmeggiani, 2003), could also explain the abnormal associative memory processes. Finally, the sudden recurrence of noradrenergic activity in the few seconds preceding behavioral arousal (Aston-Jones and Bloom, 1981a) could explain the well-documented habitual forgetting of dreams (Gottesmann, 2002). Although there is a latency period between the recovery of consciousness and awareness at REM sleep outcome (Balkin et al., 2002; Garcia-Rill et al., 2003) (which suggests probable complementary neurochemical processes involved in the sometimes rapid but only progressive forgetting of dreams), the decrease in our hypothesized noradrenergic censorship (Gottesmann, 2006b), together with the deficit of dopamine in the cortex and excess in the nucleus accumbens (Léna et al., 2005) could open new vistas in the field of schizophrenia (Kelly, 1998).

In spite of recent questions regarding the sole influence of noradrenaline in the basic processes of REM sleep, Jean-Michel Gaillard's first and sustained powerful assertion of the necessary implication of NA in the underlying processes of REM sleep has to be strongly emphasized. Indeed, although future investigation may possibly slightly modulate its importance in basic REM sleep mechanisms, the silence of noradrenergic neurons during REM sleep retains its interest as an explanation for the disturbances in cognitive processes encountered during dreaming.

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References

Abercrombie, E.D., Zigmond, M.J., 1989. Partial injury to central noradrenergic neurons: reduction of tissue norepinephrine content is greater than reduction of extracellular norepinephrine measured by microdialysis. Neuroscience 9, 4062–4067.

Abi-Dargham, A., Moore, H., 2003. Prefrontal DA transmission at D1 receptors and the pathology of schizophrenia. Neuroscientist 9, 404–416.

Adya, H.V.A., Mallick, B.N., 2000. Uncompetitive stimulation of rat brain Na–K ATPase activity by rapid eye movement deprivation. Neurochem. Int. 36, 249–253.

Aghajanian, G.K., cedarbaum, J.M., Wang, R.Y., 1977. Evidence for norepinephrine-mediated collateral inhibition of locus coeruleus neurons. Brain. Res. 136, 570–577.

Allison, T., 1968. Recovery cycles of primary evoked potentials in cats sensorimotor cortex. Experentia 24, 240–241.

Araneda, R., Andrade, R., 1991. 5-Hydroxytryptamine 2 and 5-hydroxytryptamine 1A receptors mediate opposing responses on membrane excitability in the association cortex. Neuroscience 40, 399–412.

Arnsten, A.F., 1997. Catecholamine regulation of the prefrontal cortex. J. Psychopharmacol. 11, 151–162.

Arnsten, A.F., Dudley, A.G., 2005. Methylphenidate improves prefrontal cortical cognitive function through alpha2 adrenoceptor and dopamine D1 receptor actions: relevance to therapeutic effects in attention deficit hyperactivity disorder. Behav. Brain Funct. 1, 2.

Arnsten, A.F., Goldman-Rakic, P.S., 1987. Noradrenergic mechanisms in age-related cognitive deficit. J. Neural Transm. Suppl. 317–324.

Arnsten, A.F., Jentsch, J.D., 1997. The alpha-1 adrenergic agonist, cirazoline, impairs spatial working memory in aged monkeys. Pharmacol. Biochem. Behav. 58, 55–59.

Arnsten, A.F., Li, B.M., 2005. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol. Psychiat. 57, 1377–1384.

Arnsten, A.F., Mathew, R., Ubriani, R., Taylor, J.R., Li, B.M., 1999. Alpha-1noradrenergic receptor stimulation impairs prefrontal cortical cognitive function. Biol. Psychiat. 45, 26–31.

Aserinsky, E., Kleitman, N., 1953. Regularly occurring periods of eye motility, and concomitant phenomena during sleep. Science 118, 273–274.

Aston-Jones, G., Bloom, F.E., 1981a. Activity of norepinephrine-containing neurons in behaving rats anticipates fluctuations in the sleep–waking cycle. J. Neurosci. 1, 876–886.

Aston-Jones, G., Bloom, F.E., 1981b. Norepinephrine-containing locus coeruleus neurons in behaving rat exhibit pronounced responses to non-noxious environmental stimuli. J. Neurosci. 1, 887–900.

Aston-Jones, G., Cohen, J.D., 2005. An integrative theory of locus coeruleus-norepinephrine function: adaptative gain and optimal performance. Annual Rev. Neurosci. 28, 403–450.

Aston-Jones, G., Ennis, M., Pieribone, V.A., Nickel, T., Shipley, M.T., 1986. The brain nucleus locus coeruleus: restricted afferent control of a broad efferent network. Science 234, 734–737.

Aston-Jones, G., Shirpley, M.T., Chouvet, G., Ennis, M., Van Bockstaele, E., Pieribone, V.A., Shiekhattar, R., Akaoka, H., Drolet, G., Astier, B., Charlety, P., valentino, R., Williams, J.A., 1991. Afferent regulation of locus coeruleus neurons: anatomy, physiology and pharmacology. Prog. Brain Res. 88, 47–75.

Autret, A., Minz, M., Beillevaire, T., Cathala, H.P., Schmitt, H., 1977. Effect of clonidine on sleep patterns in man. Eur. J. Clin. Pharmacol. 12, 319–322.

Bach, V., Telliez, F., Libert, J.P., 2002. The interaction between sleep and thermoregulation in adults and neonates. Sleep Med. Rev. 6, 481–492.

Balkin, T.J., Braun, A.R., Wesensten, N.J., Jeffries, K., Varga, M., Baldwin, P., Belenky, G., Herscovitch, P., 2002. The process of awakening: a PET study of regional brain activity patterns mediating the re-establishment of alertness and consciousness. Brain 125, 2308–2319.

Barratt, E.S., Adams, P.M., Poffenbarger, P.L., Fritz, R.R., Abell, C.W., 1976. Effects of rapid depletion of phenylalanine and tyrosine on sleep and behavior. Pharmacol. Biochem. Behav. 5, 47–53.

Basheer, R., Magner, M., McCarley, R.W., Shiromani, P.J., 1998. REM sleep deprivation increases the levels of tyrosine hydroxylase and norepinephrine transporter mRNA in the locus coeruleus. Mol. Brain Res. 57, 235–240.

Behrendt, R.P., Young, C., 2005. Hallucinations in schizophrenia, sensori impairment and brain disease: an unified model. Behav. Brain Sci. 27, 771–787.

Berger, R., 1961. Tonus of extrinsic laryngeal muscles during sleep and dreaming. Science 134, 840.

Bergmann, B.M., Kushida, C.A., Everson, C.A., Gilliland, M.A., Obermeyer, W., Rechtschaffen, A., 1989. Sleep deprivation in the rat. II. Methodology. Sleep 12, 5–12.

Berlucchi, G., 1997. One or many arousal system? Reflections on some of Guiseppe Moruzzi's foresights and insights about intrinsic regulation of brain activity. Arch. Ital. Biol. 135, 5–14.

Berridge, C.W., Espana, R.A., 2000. Synergic sedative effects of noradrenergic alpha(1)- and beta-receptor blockade on forebrain electroencephalographic and behavior indices. Neuroscience 99, 495–505.

Berridge, C.W., Foote, S.L., 1991. Effects of locus coeruleus activation on electroencephalographic activity in neocortex and hippocampus. Neuroscience 11, 3135–3145.

Berridge, C.W., Waterhouse, B.D., 2003. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res. Rev. 42, 33–84.

Berridge, C.W., Page, M.E., Valentino, R.J., Foote, S.L., 1993. Effects of locus coeruleus inactivation on electroencephalographic activity in neocortex and hippocampus. Neuroscience 55, 381–393.

Berridge, C.W., Devilbiss, D.M., Andrzejewski, M.E., Arnsten, A.F., Kelley, A.E., Schmeichel, B., Hamilton, C., Spencer, R.C., 2006. Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. Biol. Psychiat. 60, 1111–1120.

Betts, T.A., Alford, C., 1985. Beta-blockers and sleep: a controlled trial. Eur. J. Clin. Pharmacol. 28 (Suppl.), 65–68.

Bhardwaj, S.K., Quirion, R., Srivastava, L.K., 2004. Post-pubertal adrenergic changes in rats with neonatal lesions of the ventral hippocampus. Neuropharmacology 46, 85–94.

Bier, M.J., McCarley, R.W., 1994. REM-enhancing effects of the adrenergic antagonist idazoxan infused into the medial pontine reticular formation of the freely moving cat. Brain Res. 634, 333–338.
Bloor, B.C., Flacke, W.E., 1982. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. Anesth. Analg. 61, 741–745.
Bokkon, I., 2005. Dreams and neuroholography: an interdisciplinary interpretation of development of homeotherm state in evolution. Sleep Hypnosis 7, 61–76.
Bouret, S., Sara, S.J., 2005. Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci. 28, 574–582.
Bouret, S., Duvel, A., Onat, S., Sara, S.J., 2003. Phasic activation of locus coeruleus neurons by the central nucleus of the amygdala. J. Neurosci. 23, 3491–3497.
Bouyer, J.J., Montaron, M.F., Rougeul, A., 1981. Fast fronto-parietal rhythms during combined focused attentive behavior and immobility in cat: cortical and thalamic localizations. Electroenceph. Clin. Neurophysiol. 51, 244–252.
Branchey, M., Kissin, B., 1970. The effect of alpha-methyl-*para*-tyrosine on sleep and arousal in the rat. Psychon. Sci. 19, 281–282.
Braun, C.M., Pivik, R.T., 1981. Effects of locus coeruleus lesions upon sleeping and waking in the rabbit. Brain Res. 230, 133–151.
Braun, A.R., Balkin, T.J., Wesensten, N.J., Carson, R.E., Varga, M., Baldwin, P., Selbie, S., Belenky, G., Herscovitch, P., 1997. Regional cerebral blood flow throughout the sleep–wake cycle: an $^{15}0$ PET study. Brain 120, 1173–1197.
Braun, A.R., Balkin, T.J., Wesensten, N.J., Gwardry, f., Carson, R.E., Varga, M., Baldwin, P., Belenky, G., Herscovitch, P., 1998. Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. Science 279, 91–95.
Bunney, W.E., Bunney, B.G., 2000. Evidence for a compromised dorsolateral prefrontal cortical parallel circuit in schizophrenia. Brain Res. Rev. 31, 138–146.
Burchett, S.A., Hicks, T.P., 2006. The mysterious trace amines: protean neuromodulators of synaptic transmission in mammalian brain. Prog. Neurobiol. 79, 223–246.
Caballero, A., De Andres, I., 1986. Unilateral lesions in locus coeruleus area enhance paradoxical sleep. Electroenceph. Clin. Neurophysiol. 64, 339–346.
Callaway, C.W., Henriksen, S.I., 1992. Neuronal firing in the nucleus accumbens is associated with the level of cortical arousal. Neuroscience 51, 547–553.
Cantero, J.L., Atienza, M., Madsen, J.R., Stickgold, R., 2004. Gamma EEG dynamics in neocortex and hippocampus during human wakefulness and sleep. Neuroimage 22, 1271–1280.
Cape, E.G., Jones, B., 1998. Differential modulation of high-frequency gamma-electroencephalogram activity and sleep–wake state by noradrenaline and serotonin into the region of cholinergic basalis neurons. J. Neurosci. 18, 2653–2666.
Carboni, E., Silvagni, A., 2004. Dopamine reuptake by norepinephrine neurons: exception or rule? Crit. Rev. Neurobiol. 16, 121–128.
Cecchi, M., Khoshbouei, H., Morilak, D.A., 2002. Modulatory effects of norepinephrine, acting on alpha 1 receptors in the central nucleus of the amygdala, on behavioral and neuroendocrine response to acute immobilization stress. Neuropharmacology 43, 1139–1147.
Cederbaum, J.M., Aghajanian, G.K., 1976. Noradrenergic neurons of the locus coeruleus: inhibition by epinephrine and activation by the α-antagonist piperoxane. Brain Res. 112, 413–419.
Cespuglio, R., Gomez, M.E., Faradji, H., Jouvet, M., 1982. Alterations in the sleep–waking cycle induced by cooling of the locus coeruleus area. Electroenceph. Clin. Neurophysiol. 54, 570–578.
Charifi, C., Paut-Pagano, L., Debilly, G., Cespuglio, R., Jouvet, M., Valatx, J.L., 2000. Effect of noradrenergic denervation of the amygdala upon recovery after sleep deprivation in the rat. Neurosci. Lett. 287, 41–44.
Charifi, C., Debilly, G., Paut-Pagano, L., Cespuglio, R., Valatx, J.L., 2001. Effect of noradrenergic denervation of medial prefrontal cortex and dentate gyrus on recovery after sleep deprivation in the rat. Neurosci. Lett. 311, 113–116.
Chen, F.J., Sara, S.J., 2007. Locus coeruleus activation by foot shock or electrical stimulation inhibits amygdala neurons. Neuroscience 144, 472–481.
Chiodo, L.A., Acheson, A.L., Zigmond, M.J., Stricker, E.M., 1983. Subtotal destruction of central noradrenergic projections increases the firing rate of locus coeruleus cells. Brain Res. 264, 123–126.
Chu, N.S., Bloom, F.E., 1973. Norepinephrine-containing neurons: changes in spontaneous discharge patterns during sleeping and waking. Science 179, 908–910.
Chu, N.S., Bloom, F.E., 1974. Activity patterns of catecholamine-containing pontine neurons in the dorso-lateral tegmentum of unrestrained cats. J. Neurophysiol. 5, 527–544.
Cirelli, C., Tononi, G., 2000. Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. J. Neurosci. 20, 9187–9194.
Cirelli, C., Tononi, G., 2004. Locus coeruleus control of state-dependent gene expression. J. Neurosci. 24, 5410–5419.
Cirelli, C., Tononi, G., Pompeiano, M., Pompeiano, O., Genneri, A., 1992. Modulation of desynchronized sleep through microinjection of alpha1-adrenergic agonists and antagonists in the dorsal pontine tegmentum of the cat. Pflügers Arch. 422, 273–279.
Claude, M., Braun, M.J., Pivik, R.T., 1981. Effects of locus coeruleus lesions upon sleeping and waking in the rabbit. Brain Res. 230, 133–151.
Crochet, S., Sakai, K., 1999a. Alpha-2 adrenoceptor mediated paradoxical (REM) sleep inhibition in the cat. NeuroReport 10, 2199–2204.
Crochet, S., Sakai, K., 1999b. Effects of microdialysis application in monoamines on the EEG and behavioral states in the cat mesopontine tegmentum. Eur. J. Neurosci. 11, 3738–3752.
Crochet, S., Onoe, H., Sakai, K., 2006. A potent non-monoaminergic paradoxical sleep inhibitory system: a reverse microdialoysis and single-unit recording study. Eur. J. Neurosci. 24, 1404–1412.
Dagnino, N., Favale, E., Loeb, C., Manfredi, M., Seitun, A., 1969. Presynaptic and postsynaptic changes in specific thalamic nuclei during deep sleep. Arch. Ital. Biol. 107, 668–684.
Dahlstrom, A., Fuxe, K., 1964. Evidence for existence of monoamine-containing neurons in the central nervous system. Acta Physiol. Scand. 62 (Suppl. 232), 3–55.
Datta, S., 2000. Avoidance task training potentiates phasic pontine-wave density in the rat: a mechanism for sleep-dependent plasticity. J. Neurosci. 20, 8607–8613.
Datta, S., 2006. Activation of phasic pontine-wave generator: a mechanism for sleep-dependent memory processing. Sleep Biol. Rhyt. 4, 16–26.
Datta, S., Mavanji, V., Patterson, E.H., Ulloor, J., 2003. Regulation of rapid eye movement sleep in the freely moving rat: local microinjection of serotonin, norepinephrine, and adenosine into the brainstem. Sleep 26, 513–520.
De Sarro, G.B., Ascioti, C., Froio, F., Nistisco, G., 1987. Evidence that locus coeruleus is the site where clonidine and drugs acting at alpha-1 and alpha-2 adrenoceptors affect sleep and arousal mechanisms. Br. J. Pharmacol. 90, 675–685.
Delfs, J.M., Zhu, Y., Druhan, J.P., Aston-Jones, G.S., 1998. Origin of noradrenergic afferents to the shell subregion of the nucleus accumbens: anterograde and retrograde tract-tracing studies in the rat. Brain Res. 806, 127–140.
Dement, W.C., 1958. The occurrence of low voltage fast electroencephalogram patterns during behavioral sleep in the cat. Electroenceph. Clin. Neurophysiol. 10, 291–296.
Dement, W., Kleitman, N., 1957. The relation of eye movements during sleep to dream activity: an objective method for the study of dreaming. J. Exp. Psychol. 53, 339–346.
Demetrescu, M., Demetrescu, M., Iosif, G., 1966. Diffuse regulation of visual thalamo-cortical responsiveness during sleep and wakefulness. Electroenceph. Clin. Neurophysiol. 20, 450–469.
Depoortere, H., 1985. Adrenergic agonists and antagonists and sleep–waking stages. In: Wauquier, A., Gaillard, J.M., Monti, J.M., Radulovacki, M. (Eds.), Sleep: Neurotransmitters and Neuromodulators. Raven Press, New York, pp. 79–92.
Depoortere, H., Loew, D.M., 1973. Motor phenomena during sleep in the rat: a mean of improving the analysis of the sleep–wakefulness cycle. In: Jovanovic, U. (Ed.), The Nature of Sleep. Gustav Fisher, Stuttgart, pp. 101–104.
Descarries, L., Watkins, K.C., Lapierre, Y., 1977. Noradrenergic axon terminals in the cerebral cortex of rats. III. Topometric ultrastructural analysis. Brain Res. 133, 197–222.
Devilbiss, D.M., Page, M., Waterhouse, B.D., 2006. Locus coeruleus regulates sensory encoding by neurons and networks in waking animals. J. Neurosci. 26, 9860–9872.
Dewasmes, G., Loos, N., Delanaud, S., Dewasmes, D., Ramadan, W., 2004. Pattern of rapid-eye-movement sleep episode occurrence after an immobilization stress in the rat. Neurosci. Lett. 355, 17–20.
Dunleavy, D.L.F., MacLean, A.W., Oswald, I., 1971. Debrisoquine, guanethidine, propanolol and human sleep. Psychopharmacologia 21, 101–110.
Dusan-Peyrethon, D., Peyrethon, J., Jouvet, M., 1968. Suppression élective du sommeil paradoxal chez le Chat par α méthyl DOPA. C. R. Soc. Biol. 162, 116–118.
Ennis, M., Aston-Jones, G., 1986. A potent excitatory input to the locus coeruleus from the ventrolateral medulla. Neurosci. Lett. 71, 299–305.
Ennis, M., Aston-Jones, G., 1987. Two physiologically distinct populations of neurons in the ventrolateral medulla innervate the locus coeruleus. Brain Res. 425, 275–282.
Ennis, M., Aston-Jones, G., 1988. Activation of locus coeruleus from nucleus paragigantocellularis: a new excitatory amino acid pathway in brain. J. Neurosci. 8, 3644–3657.
Ennis, M., Aston-Jones, G., 1989a. GABA-mediated inhibition of locus coeruleus from the dorsomedial rostral medulla. J. Neurosci. 9, 2973–2981.
Ennis, M., Aston-Jones, G., 1989b. Potent inhibitory input to the locus coeruleus from the nucleus prepositus hypoglossi. Brain Res. Bull. 22, 793–803.
Evarts, E.V., 1964. Temporal patterns of discharge of pyramidal tract neurons during sleep and waking in the monkey. J. Neurophysiol. 27, 152–171.
Fallon, J.H., Koziell, D.A., Moore, R.Y., 1978. Catecholamine innervation of the basal forebrain. II. Amygdala, suprarhinal cortex and entorhinal cortex. J. Comp. Neurol. 180, 509–532.
Fenik, V., Marchenko, V., Janssen, P., davies, R.O., Kubin, L., 2002. A5 cells are silenced when REM sleep-like signs are elicited by pontine carbachol. J. Appl. Physiol. 93, 1448–1456.
Ferster, D., 1988. Spatially opposed excitation and inhibition in simple cells of the cat visual cortex. J. Neurosci. 8, 1172–1180.
Fletcher, P.C., McKenna, P.J., Frith, C.D., Grasby, P.M., Friston, K.J., Dolan, R.J., 1998. Brain activation in schizophrenia during a graded memory task studied with functional neuroimaging. Arch. Gen. Psychiat. 55, 1001–1008.
Foote, S.L., Freedman, R., Oliver, A.P., 1975. Effects of putative neurotransmitters on neuronal activity on monkey auditory cortex. Brain Res. 86, 229–242.
Foote, S.L., Bloom, F.E., Aston-jones, G., 1983. Nucleus locus coeruleus: new evidence of anatomical and physiological specificity. Physiol. Rev. 63, 846–914.
Franken, P., Djik, D.J., Tobler, I., Borbely, A.A., 1994. High-frequency components of the rat electrocorticogram are modulated by the vigilance states. Neurosci. Lett. 167, 89–92.
Frederickson, R.C.A., Jordan, L.M., Phillis, J.W., 1971. The action of noradrenaline on cortical neurons: effects of pH. Brain Res. 35, 556–560.

Freud, S., 1900. The Interpretation of Dreams, The Hogart Press, London.
Friedman, J.I., Adler, D.N., Davis, K.L., 1999. The role of norepinephrine in the physiopathology of cognitive disorders: potential applications to the treatment of cognitive dysfunction in schizophrenia and Alzheimer's disease. Biol. Psychiat. 46, 1243–1252.
Fritschy, J.M., Grzanna, R., 1991. Selective effects of DSP-4 on locus coerileus axons: are there pharmacologically different types of noradrenergic axons in the central nervous system? In: Barnes, C.D., Pompeiano, O. (Eds.), Progress in Brain Research, vol. 88. Elsevier, Amsterdam, pp. 257–267.
Fu, J., Li, P., Ouyang, X., Gu, C., Song, Z., Gao, J., Han, L., Feng, S., Tian, S., Hu, B., 2007. Rapid eye movement sleep deprivation selectively impairs recall of fear extinction in hippocampus-independent tasks in rats. Neuroscience 144, 1186–1192.
Fuxe, K., Hamberger, B., Hökfelt, T., 1968. Distribution of noradrenaline nerve terminals in cortical areas if the rat. Brain Res. 8, 125–131.
Fuxe, K., Lidbrink, P., Hökfelt, T., Bolme, P., Goldstein, M., 1974. Effects of piperoxane on sleep and waking in the rat: evidence for increased waking by blocking inhibitory adrenaline receptors on the locus coeruleus. Acta Physiol. Scand. 91, 566–567.
Gaillard, J.M., 1983. Biochemical pharmacology of paradoxical sleep. Br. J. Pharmacol. 16, 205s–230S.
Gaillard, J.M., 1985. Brain noradrenergic activity in wakefulness and paradoxical sleep: the effect of clonidine. Neuropsychobiology 13, 23–25.
Gaillard, J.M., Kafi, S., 1978. Brain catecholaminergic control of paradoxical sleep: pharmacological studies. Adv. Biosci. 21, 85–94.
Gaillard, J.M., Kafi, S., 1979. Involvement of pre- and postsynaptic receptors in catecholaminergic control of paradoxical sleep in man. Eur. J. Clin. Pharmacol. 15, 83–89.
Gaillard, J.M., Simmen, A.E., Tissot, R., 1971. Analyse automatique des enregistrements polygraphiques de sommeil. Electroenceph. Clin. Neurophysiol. 30, 557–561.
Gaillard, J.M., Kafi, S., Justafre, J.C., 1982. On the role of brain alpha-adrenergic systems in the production of paradoxical sleep. L'Encephale 8, 413–434.
Gaillard, J.M., Iorio, G., Kafi, S., Blois, R., 1983. Paradoxical sleep rebound without previous debt: the effect of minute doses of clonidine in man. Sleep 6, 60–66.
Gandolfo, G., Arnaud, C., Gottesmann, C., 1980. Transmission in the ventrobasal complex of rat during the sleep–waking cycle. Brain Res. Bull. 5, 921–927.
Garcia-Rill, E., 1997. Disorders of the reticular activating system. Med. Hypoth. 49, 379–387.
Garcia-Rill, E., Kobahashi, T., Good, C., 2003. The developmental decrease in REM sleep. Thal. Rel. Syst. 46, 1–17.
Gentili, A., Godschalk, M.F., Gheorghiu, D., Nelson, K., Julius, D.A., Mulligan, T., 1996. Effect of clonidine and yohimbine on sleep in healthy men: a double-blind, randomized, controlled trial. Eur. J. Clin. Pharmacol. 50, 463–465.
Gerber, U., Greene, R.W., McCarley, R.W., Haas, H.L., 1990. Excitation of brain stem neurons by noradrenaline and histamine. J. Basic Clin. Physiol. Pharmacol. 1, 71–76.
Ghelarducci, B., Pisa, M., Pompeiano, M., 1970. Transformation of somatic afferent volleys across the prethalamic and thalamic components of the lemniscal system during the rapid eye movements of sleep. Electroenceph. Clin. Neurophysiol. 29, 348–357.
Goldman-Rakic, P.S., Brown, R.M., 1981. Regional changes of monoamines in cerebral cortex and subcortical structures of aged rhesus monkeys. Neuroscience 6, 177–187.
Gonzalez, M.M., Debilly, G., Valatx, J.L., Jouvet, M., 1995. Sleep increase after immobilization stress: role of the noradrenergic locus coeruleus system in the rat. Neurosci. Lett. 202, 5–8.
Goodenough, D.R., Shapiro, A., Holden, M., Steinschriber, L., 1959. A comparison of ''dreamers'' and ''nondreamers'': eye movements, electroencephalograms, and the recall of dreams. J. Abnorm. Soc. Psychol. 59, 295–302.
Gordon, C.R., Lavie, P., 1984. Effect of adrenergic blockers on the dog's sleep–wake pattern. Physiol. Behav. 32, 345–350.
Gottesmann, C., 1964. Données sur l'activité corticale au cours du sommeil profond chez le Rat. C. R. Soc. Biol. 158, 1829–1834.
Gottesmann, C., 1966. Réserpine et vigilance chez le Rat. C. R. Soc. Biol. 160, 2056–2061.
Gottesmann, C., 1967. Recherche sur la psychophysiologie du sommeil chez le Rat. Presses du Palais Royal, Paris. Still available, discussion and summary in English.
Gottesmann, C., 1970. La psychophysiologie du sommeil. Bull. Psychol. 24, 520–528.
Gottesmann, C., 1971. Psychophysiologie du sommeil. Ann. Psychol. 71, 451–488.
Gottesmann, C., 1972. Le stade intermédiaire du sommeil chez le Rat. Rev. EEG Neurophysiol. 3, 65–68.
Gottesmann, C., 1996. The transition from slow wave sleep to paradoxical sleep: evolving facts and concepts of the neurophysiological processes underlying the intermediate stage of sleep. Neurosci. Biobehav. Rev. 20, 367–387.
Gottesmann, C., 1999. Neurophysiological support of consciousness during waking and sleep. Prog. Neurobiol. 59, 469–508.
Gottesmann, C., 2002. The neurochemistry of waking and sleeping mental activity. The disinhibition-dopamine hypothesis. Psychiat. Clin. Neurosci. 56, 345–354.
Gottesmann, C., 2005. Dreaming and schizophrenia. A common neurobiological background. Sleep Biol. Rhyt. 3, 64–74.
Gottesmann, C., 2006a. The dreaming sleep stage: a new neurobiological model of schizophrenia? Neuroscience 140, 1105–1115.
Gottesmann, C., 2006b. Neurobiological disturbances during the dreaming-sleep stage can explain dream bizarreness without recourse to censorship. Neuro-Psychoanalysis 8, 27–32.
Gottesmann, C., 2007. A neurobiological history of dreaming. In: McNamara, P., Barrett, D. (Eds.), The Science of Dreaming, vol. 1. Greenwood Publishers, Westport, pp. 1–51.
Gottesmann, C., Gottesman, I.I., 2007. The neurobiological characteristics of the rapid eye movement (REM) dreaming sleep stage are candidate endophenotypes of depression, schizophrenia, mental retardation and dementia. Prog. Neurobiol. 81, 237–250.
Gottesmann, C., Juan de Mendoza, J.L., Lacoste, G., Lallement, B., Rodrigues, L., Tasset, M., 1971. Etude sur l'analyse et la quantification automatiques des différents états de veille et de sommeil chez le Rat. C. R. Acad. Sci. 272, 301–302.
Grace, A.A., 2000. Gating information flow within the limbic system and the pathophysiology of schizophrenia. Brain Res. Rev. 31, 330–341.
Greene, R.W., Carpenter, D.O., 1985. Actions of neurotransmitters on pontine medial reticular formation neuron of the cat. J. Neurophysiol. 54, 520–531.
Gulyani, S., Mallick, B.N., 1993. Effect of rapid eye movement sleep deprivation on rat brain Na–K ATPase activity. J. Sleep Res. 2, 45–50.
Gulyani, S., Mallick, B.N., 1995. Possible mechanism of rapid eye movement sleep deprivation induced increase in Na–K-ATPase activity. Neuroscience 64, 255–260.
Gulyani, S., Majumdar, S., Mallick, B.N., 2000. Rapid eye movement sleep and significance of its deprivation studies. A review. Sleep Hypnosis 2, 49–68.
Harris, G.C., Hedaya, M.A., Pan, W.J., Kalivas, P.W., 1996. Beta-adrenergic antagonism alters the behavioral and neurochemical response to cocaine. Neuropsychopharmacology 14, 195–204.
Hartmann, E., 1966. Reserpine: its effect on the sleep–dream cycle in man. Psychopharmacologia 9, 242–247.
Hartmann, E., Schildkraut, J.J., 1973. Desynchronized sleep and MHPG excretion: an inverse correlation. Brain Res. 61, 412–416.
Hartmann, E., Zwilling, G., 1976. The effect of alpha and beta adrenergic receptor blockers on sleep in the rat. Pharmacol. Biochem. Behav. 5, 135–138.
Hartmann, E., Chung, R., Draskoczy, P.R., Schildkraut, J.J., 1971. Effects of 6-hydroxydopamine on sleep in the rat. Nature 233, 425–427.
Heister, D.S., Hayar, A., Charlesworth, A., Yates, C., Zhou, Y.H., Garcia-Rill, E., 2008. Evidence for electrical coupling in the subCoeruleus (SubC) nucleus. J. Neurophysiol. 97, 3142–3147.
Henley, K., Morrison, A.R., 1974. A re-evaluation of the effects of lesions of the pontine tegmentum and locus coeruleus on phenomena of paradoxical sleep in the cat. Acta Neurobiol. Exp. 34, 215–232.
Hennevin, E., Hars, B., Maho, C., Bloch, V., 1995. Processing of learned information in paradoxical sleep: relevance for memory. Behav. Brain Res. 69, 125–135.
Heresco-Levy, U., 2000. *N*-Methyl-D-aspartate (NMDA) receptor-based treatment approaches in schizophrenia: the first decade. Int. J. Neuropharmacol. 3, 243–258.
Herman, J.H., Erman, M., Boys, R., Peiser, L., Taylor, M.E., Roffwarg, H., 1984. Evidence for a directional correspondence between eye movements and dream imagery in REM sleep. Sleep 7, 52–63.
Hilakivi, I., 1983. The role of β- and α-adrenoceptors in the regulation of the stages of the sleep–waking cycle in the cat. Brain Res. 277, 109–118.
Hilakivi, I., Leppävuori, A., 1984. Effects of methoxamine, an alpha-1 adrenoceptor agonist, and prazosin, an alpha-1 antagonist, on the stages of the sleep–waking cycle in the cat. Acta Physiol. Scand. 120, 363–372.
Hilakivi, I., Mäkelä, J.P., Leppävuori, A., Putkonen, P.T.S., 1978. Effects of two adrenergic β-receptor blockers on the sleep cycle of the cat. Med. Biol. 56, 138–143.
Hilakivi, I., Leppävuori, A., Putkonen, P.T.S., 1980. Prazosin increases paradoxical sleep. Eur. J. Clin. Pharmacol. 65, 417–420.
Hishikawa, Y., Nakai, K., Ida, H., Kaneko, Z., 1965. The effect of imipramine, desmethylimipramine and chlorpromazine on the sleep–wakefulness cycle of the cat. Electroenceph. Clin. Neurophysiol. 19, 518–521.
Hobson, J.A., Pace-Schott, E.F., 2002. The cognitive neuroscience of sleep: neuronal systems, consciousness and learning. Nat. Rev. Neurosci. 3, 679–693.
Hobson, J.A., McCarley, R.W., Wyzinski, P.W., 1975. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 189, 55–58.
Hobson, J.A., Stickgold, R., Pace-Schott, E.F., 1998. The neuropsychology of REM sleep dreaming. NeuroReport 9, R1–R14.
Hobson, J.A., Pace-Schott, E., Stickgold, R., 2000. Dreaming and the brain: towards a cognitive neuroscience of conscious states. Behav. Brain Sci. 23, 793–842.
Hofle, N., Paus, T., Reutens, D., Fiset, P., Gotman, J., Evans, A.C., Jones, B.E., 1997. Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep. J. Neurosci. 17, 4800–4808.
Holdefer, R.N., Jacobs, B.L., 1994. Phasic stimulation of the locus coeruleus: effects on activity in the lateral geniculate nucleus. Exp. Brain Res. 100, 444–452.
Hou, Y.P., Manns, I.D., Jones, B.E., 2002. Immunostaining of cholinergic pontomesencephalic neurons for alpha1 versus alpha2 adrenergic receptors suggests different sleep–wake state activities and roles. Neuroscience 114, 517–521.
Hunsley, M.S., Palmiter, R.D., 2003. Norepinephrine-deficient mice exhibit normal sleep–wake states but have shorter sleep latency after mild stress and low doses of amphetamine. Sleep 26, 521–526.
Iskander, T.N., Kaelbling, R., 1970. Catecholamines, a dream sleep model, and depression. Am. J. Psychiat. 127, 43–50.
Jacobs, B.L., 1986. Single unit activity of locus coeruleus neurons in behaving animals. Prog. Neurobiol. 27, 183–194.
Jodo, E., Chiang, C., Aston-Jones, G., 1998. Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus. Neuroscience 83, 63–79.

Johnson, J.D., 2003. Noradrenergic control of cognition: global attenuation and an interrupt function. Med. Hypoth. 60, 689–692.
Jones, B., 1972. The respective involvement of noradrenaline and its deaminated metabolites in waking and paradoxical sleep: a neuropharmacological model. Brain Res. 39, 121–136.
Jones, B.E., 1991. Paradoxical sleep and its chemical/structural substrates in the brain. Neuroscience 40, 637–656.
Jones, B.E., 2004. Paradoxical sleep promoting and permitting neural networks. Arch. Ital. Biol. 142, 379–396.
Jones, B., Moore, R.Y., 1974. Catecholamine-containing neurons of the locus coeruleus in the cat. J. Comp. Neurol. 157, 43–52.
Jones, B., Harper, S.T., Halaris, A.E., 1977. Effects of locus coeruleus lesions upon cerebral monoamine content, sleep–wakefulness states and the response to amphetamine in the cat. Brain Res. 124, 473–496.
Jouvet, M., 1962. Recherches sur les structures nerveuses et les mécanismes responsables des différentes phases du sommeil physiologique. Arch. Ital. Biol. 100, 125–206.
Jouvet, M., 1969. Biogenic amines and the states of sleep. Science 163, 32–41.
Jouvet, M., 1972. The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep–waking cycle. Ergib. Physiol. 64, 166–307.
Jouvet, M., Delorme, F., 1965. Locus coeruleus et sommeil paradoxal. C. R. Soc. Biol. 159, 895–899.
Jouvet, M., Michel, F., 1960. Nouvelles recherches sur les structures responsables de la "phase paradoxale" du sommeil. J. Physiol. (Paris) 52, 130–131.
Jouvet, M., Mounier, D., 1960. Effets des lésions de la formation réticulaire pontique sur le sommeil du Chat. C. R. Soc. Biol. 154, 2301–2305.
Jouvet, M., Michel, F., Courjon, J., 1959. Sur la mise en jeu de deux mécanismes à expression électro-encéphalographique différente au cours du sommeil physiologique chez le Chat. C. R. Acad. Sci. 248, 3043–3045.
Jouvet, M., Vimont, P., Delorme, F., 1965. Suppression éléctive du sommeil paradoxal chez le Chat par les inhibiteurs de la monoamineoxydase. C. R. Soc. Biol. 159, 1595–1599.
Justafre, J.C., Gaillard, J.M., 1981. Diminution du sommeil paradoxal chez le Rat sous antidépresseur tricyclique: rôle de l'inhibition collatérale. Rev. EEG Neurophysiol. 11, 228–235.
Kafi, S., Gaillard, J.M., 1980. The effect of presynaptic alpha blocker yohimbine on rat paradoxical sleep. Waking Sleeping 4, 131–137.
Kafi, S., Gaillard, J.M., 1981. Effect of alpha-stimulation by clonidine on the evolution of paradoxical sleep. J. Psychiat. Biol. Therapy 1, 13–20.
Kafi, S., Bouras, C., Constantinidis, J., Gaillard, J.M., 1977. Paradoxical sleep and brain catecholamines in the rat after single and repeated administration of alpha-methyl-paratyrosine. Brain Res. 135, 123–134.
Kanno, O., Clarenbach, P., 1985. Effect of clonidine and yohimbine on sleep in man: polygraphic EEG analysis by normalized slope descriptors. Elecroenceph. Clin. Neurophysiol. 60, 478–484.
Karczmar, A.G., Longo, V.G., De Carolis, A.S., 1970. A pharmacological model of paradoxical sleep: the role of cholinergic and monoamine systems. Physiol. Behav. 5, 175–182.
Kaur, S., Saxena, R.N., Mallick, B.N., 1997. GABA in locus coeruleus regulates spontaneous rapid eye movement sleep by acting on $GABA_A$ receptors in freely moving rats. Neurosci. Lett. 223, 105–108.
Kaur, S., Saxena, R.N., Mallick, B.N., 2001. GABAergic neurons in prepositus hypoglossi regulate REM sleep by its action on locus coeruleus in freely moving rats. Synapse 42, 141–150.
Kaur, S., Panchal, M., Madan, V., Nangia, P., Mallick, B.N., 2004. Long term blocking of GABA-A receptor in locus coeruleus by bilateral microinfusion of picrotoxin reduced rapid eye movement sleep and increased brain NA–K ATPase activity in freely moving normally behaving rats. Behav. Brain Res. 151, 185–190.
Kawahara, Y., Kawahara, H., Westerink, B.H., 1999. Tonic regulation of the activity of noradrenergic neurons in the locus coeruleus of the conscious rat studied by dual-probe microdialysis. Brain Res. 823, 42–48.
Kelly, P.H., 1998. Defective inhibition of dream event memory formation: a hypothesized mechanism in the onset and progression of symptoms of schizophrenia. Brain Res. Bull. 46, 189–197.
King, C.D., Jewett, R.E., 1971. The effects of α-methyltyrosine on sleep and brain norepinephrine in cats. J. Pharm. Exp. Therap. 177, 188–195.
Kisley, M.A., Olincy, A., Robbins, E., Polk, S.D., Adler, L.E., Waldo, M.C., Freedman, R., 2003. Sensory gating impairment associated with schizophrenia persists into REM sleep. Psychophysiology 40, 29–38.
Klaue, R., 1937. Die bioelektrische Tätigkeit der Grosshirnrinde im normalen Schlaf und in der Narkose durch Schlafmittel. J. Psychol. Neurol. 47, 510–531.
Kleinlogel, H., Scholtysik, G., Sayers, A.C., 1975. Effects of clonidine and BS 100-141 on the EEG sleep pattern in rats. Eur. J. Pharmacol. 33, 159–163.
Knight, R.T., Hillyard, S.A., Woods, D.L., Neville, H.J., 1981. The effects of frontal cortex lesions on event-related potentials during auditory selective attention. Electroenceph. Clin. Neurophysiol. 52, 571–582.
Kombian, S.B., Ananthalakshmi, K.V., Edafiogho, I.O., 2006. Enaminones and norepinephrine employ convergent mechanisms to decrease excitatory synaptic transmission in the rat nucleus accumbens in vitro. Eur. J. Neurosci. 24, 2781–2788.
Kosslyn, S.M., Pascual-Leone, A., Felician, O., Camposano, S., Keena, J.P., Thompson, W.L., Ganis, G., Sukel, K.E., Alpert, N.M., 1999. The role of area 17 in visual imagery: convergent evidence from PET and rTMS. Science 284, 167–170.
Koyama, Y., Sakai, K., 2000. Modulation of presumed cholinergic mesopontine tegmental neurons by acetylcholine and monoamines applied iontophoretically in unaenesthetized cats. Neuroscience 96, 723–733.
Krnjevic, K., Phillis, J.W., 1963. Actions of certain amines on cerebral cortex neurons. Br. J. Pharmacol. 20, 471–490.
Laguzzi, R., Petitjean, F., Pujol, J.F., Jouvet, M., 1972. Effets de l'injection intraventriculaire de 6-hydroxydopamine. II. Sur le cycle veille-sommeil du Chat. Brain Res. 48, 295–310.
Lanfumey, L., Dugovic, C., Adrien, J., 1985. β_1 and β_2 adrenergic receptors: their role in the regulation of paradoxical sleep in the rat. Elecroenceph. Clin. Neurophysiol. 60, 558–567.
Lapiz, M.D.S., Morilak, A., 2006. Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. Neuroscience 1039–1049.
Larsen, J.P., Tandberg, E., 2001. Sleep disorders with Parkinson's disease: epidemiology and management. CNS Drugs 15, 267–275.
Lauriat, T.L., Dracheva, S., Chin, B., Schmeidler, J., McInnes, L.A., Haroutunian, V., 2005. Quantitative analysis of glutamate transporter mRNA expression in prefrontal and primary visual cortex in normal and schizophrenic brain. Neuroscience 137, 843–851.
Leconte, P., Hennevin, E., 1981. Post-learning paradoxical sleep, reticular activation and noradrenergic activity. Physiol. Behav. 26, 587–594.
Léna, I., Parrot, S., Deschaux, O., Muffat, S., Sauvinet, V., Renaud, B., Suaud-Chagny, M.F., Gottesmann, C., 2005. Variations in the extracellular levels of dopamine, noradrenaline, glutamate and aspartate across the sleep–wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. J. Neurosci. Res. 81, 891–899.
Leppävuori, A., Putkonen, P.T.S., 1980. Alpha-adrenoceptive influences on the control of the sleep–waking cycle in the rat. Brain Res. 193, 95–115.
Levit, P., Moore, R.Y., 1978. Noradrenaline neuron innervation on the neocortex in the cat. Brain Res. 139, 219–232.
Lewis, D.A., Hashimoto, T., Volk, D.W., 2005. Cortical inhibitory neurons in schizophrenia. Nat. Rev. Neurosci. 6, 312–324.
Libet, B., Gleason, G.A., 1994. The human locus coeruleus and anxiogenesis. Brain Res. 634, 178–180.
Linner, L., Wiker, C., Wadenberg, M.L., Schalling, M., Svensson, T.H., 2002. Noradrenaline reuptake inhibition enhances the antipsychotic-like effect of raclopride and potentiates D2-blockade-induced dopamine release in the medial prefrontal cortex of the rat. Neuropsychopharmacology 27, 691–698.
Lipska, B.K., Jaskiw, G., Weinberger, D.R., 1993. Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: a potential animal model of schizophrenia. Neuropsychopharmacology 9, 67–75.
Lipska, B.K., Lerman, D.N., Khaing, Z.Z., Weinberger, D.R., 2003. The neonatal ventral hippocampal lesion model of schizophrenia: effects on dopamine and GABA mRNA markers in the rat midbrain. Eur. J. Neurosci. 18, 3097–3104.
Llinas, R., Paré, D., 1991. Of dreaming and wakefulness. Neuroscience 44, 521–535.
Llinas, R., Ribary, U., 1993. Coherent 40 Hz oscillation characterizes dream state in humans. Proc. Natl. Acad. Sci. U.S.A. 90, 2078–2081.
Llinas, R., Grace, A.A., Yarom, Y., 1991. In vitro neurons in mammalian cortical layer 4 exhibits intrinsic oscillatory activity in the 10- to 50-Hz frequency range. Proc. Natl. Acad. Sci. U.S.A. 88, 897–901.
Loomis, A.L., Harvey, E.N., Hobart, G.A.I., 1937. Cerebral states during sleep, as studied by human brain potentials. J. Exp. Psychol. 21, 127–144.
Lövblad, K.O., Thomas, R., Jakob, P.M., Scammel, T., Bassetti, C., Griswold, M., Ives, J., Matheson, J., Edelman, R.R., Warach, S., 1999. Silent functional magnetic resonance imaging demonstrates focal activation in rapid eye movement sleep. Neurology 53, 2193–2195.
Lu, J., Devor, M., Saper, C.B., 2006. A putative flip-flop switch for control of REM sleep. Nature 441, 589–594.
Luciana, M., Collins, P.F., Depue, R.A., 1998. Opposing role for dopamine and serotonin in the modulation of human spatial working memory functions. Cerebral Cortex 8, 218–226.
Luppi, P.H., Aston-Jones, G., Akaoka, H., Chouvet, G., Jouvet, M., 1995. Afferent projections to the rat locus coeruleus demonstrated by retrograéde and anterograde tracing with cholera-toxin-B subunit and *Phaseolus vulgaris* leucoagglutinin. Neuroscience 65, 119–160.
Luppi, P.H., Gervasoni, D., Verret, L., Goutagny, R., Peyron, C., Salvert, D., Leger, L., Fort, P., 2006. Paradoxical (REM) sleep genesis: the switch from an aminergic-cholinergic to a GABAergic-glutamatergic hypothesis. J. Physiol. (Paris) 100, 271–283.
Ma, S., Morilak, A., 2005. Norepinephrine release in medial amygdala facilitates activation of hypothalamic–pituitary–adrenal axis in response to acute immobilization stress. J. Neuroendocrinol. 17, 22–28.
MacKay, A.V., Iversen, L.L., Rossor, M., Spokes, E., Bird, E., Arregui, A., Snyder, S., 1982. Increased brain dopamine and dopamine receptors in schizophrenia. Arch. Gen. Psychiat. 39, 991–997.
Madsen, P.L., Holm, S., Vorstrup, S., Friberg, L., Lassen, N.A., Wildschiodtz, G., 1991. Human regional cerebral blood flow during rapid-eye-movement sleep. J. Cerbral Blood Flow Metab. 11, 502–507.
Majumbar, S., Faisal, M., Madan, V., Mallick, B.N., 2003. Increased turnover of Na–K-ATPase molecules in rat brain after rapid eye movement sleep deprivation. J. Neurosci. Res. 73, 870–875.
Majumdar, S., Mallick, B.N., 2003. Increased levels of tyrosine hydroxylase and glutamic acid decarboxylase in locus coeruleus after rapid eye movement sleep deprivation in rats. Neurosci. Lett. 338, 193–196.
Mäkelä, J.P., Hilakivi, I.T., 1986. Effect of alpha-adrenoceptor blockade on sleep and wakefulness in the rat. Pharmacol. Biochem. Behav. 24, 613–616.

Mallick, B.N., Adya, H.V.A., 1999. Norepinephrine induced alpha-adrenoceptor mediated increase in rat brain Na–K-ATPase activity is dependent on ion channel. Neurochem. Int. 34, 499–507.
Mallick, B.N., Alam, N., 1992. Different types of norepinephrinergic receptors are involved in preoptic area mediated independent modulation of sleep–wakefulness and body temperature. Brain Res. 591, 8–19.
Mallick, B.N., Gulyani, S., 1993. Rapid eye movement sleep deprivation increases chloride-sensitive Mg-ATPase activity in the rat brain. Pharmacol. Biochem. Behav. 45, 359–362.
Mallick, B.N., Siegel, J.M., Fahringer, H.M., 1990. Changes in pontine unit activity with REM sleep deprivation. Brain Res. 515, 94–98.
Mallick, B.N., Thankachan, S., Islam, F., 1998. Differential responses of brain stem neurons during spontaneous and stimulation-induced desynchronization of the cortical EEG in freely moving cats. Sleep Res. Online 1, 132–146.
Mallick, B.N., Anupama, H.V., Thankachan, S., 1999a. REM sleep deprivation alters factors affecting neuronal excitability: role of norepinephrine and its possible mechanism of action. In: Mallick, B.N., Inoué, S. (Eds.), Rapid Eye Movement Sleep. Narosa Publishing House, New Delhi, pp. 338–354.
Mallick, B.N., Kaur, S., Jha, S.K., Siegel, J.M., 1999b. Possible role of GABA in the regulation of REM sleep with special reference to REM-off neurons. In: Mallick, B.N., Inoué, S. (Eds.), Rapid Eye Movement Sleep. Narosa Publishing House, New Delhi, pp. 153–166.
Mallick, B.N., Anupama, H.V., Faisal, M., 2000. Norepinephrine-stimulated increase in Na^+, K^+-ATPase activity in the rat brain is mediated through α_{1A}-adrenoceptor possibly by dephosphorylation of the enzyme. J. Neurochem. 74, 1574–1578.
Mallick, B.N., Majumdar, S., Faisal, M., Yadav, V., Madan, V., Pal, D., 2002. Role of norepinephrine in the regulation of rapid eye movement sleep. J. Biosci. 27, 539–551.
Mallick, B.N., Thankachan, S., Islam, F., 2004. Influence of hypnogenic brain areas on wakefulness- and rapid-eye-movement sleep-related neurons in the brainstem of freely moving cats. J. Neurosci. Res. 75, 133–142.
Mallick, B.N., Singh, S., Pal, D., 2005. Role of alpha and beta adrenoceptors in locus coeruleus stimulation-induced reduction in rapid eye movement sleep in freely moving rats. Behav. Brain Res. 158, 9–21.
Maloney, K.J., Cape, E.G., Gotman, J., Jones, B.E., 1997. High-frequency-electroencephalogram activity in association with sleep–wake states and spontaneous behaviors in the rat. Neuroscience 76, 541–555.
Maloney, K.J., Mainville, L., Jones, B.E., 1999. Differential c-Fos expression in cholinergic, monoaminergic, and GABAergic groups of the pontomesencephalic tegmentum after paradoxical sleep deprivation and recovery. J. Neurosci. 19, 3057–3072.
Manunta, Y., Edeline, J.M., 1999. Effects of noradrenaline on frequency tuning of auditory cortex neurons during wakefulness and slow wave sleep. Eur. J. Neurosci. 11, 2134–2150.
Mao, Z.M., Arnsten, A.F., Li, B.M., 1999. Local infusion of an alpha-1 adrenergic agonist into the prefrontal cortex impairs spacial working memory performance in monkeys. Biol. Psychiat. 46, 1259–1265.
Maquet, P., 2000. Functional neuroimaging of normal sleep by position emission tomography. J. Sleep Res. 9, 207–231.
Maquet, P., Franck, G., 1997. REM sleep and amygdala. Mol. Psychiat. 2, 195–196.
Maquet, P., Peters, J.M., Aerts, J., Delfiore, G., Degueldre, C., Luxen, A., Franck, G., 1996. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 383, 163–166.
Maquet, P., Ruby, P., Schw artz, S., Laurey, S., Albouy, T., Dang-Vu, T., Desseilles, M., Boly, M., Melchior, G., Peigneux, P., 2004. Regional organisation of brain activity during paradoxical sleep. Arch. Ital. Biol. 142, 413–419.
Marantz, R., Rechtschaffen, A., 1967. Effects of alpha-methyltyrosine on sleep in the rat. Percept. Motor Skills 25, 805–808.
Marantz, R., Rechtschaffen, A., Lowell, R.A., Whitehead, P.K., 1968. Effect of alpha-methyltyrosine on the recovery from paradoxical deprivation in the rat. Commun. Behav. Biol. 2, 161–164.
Mark, J., Heiner, L., Mandel, P., Godin, Y., 1969. Norepinephrine turnover in brain and stress reactions in rats during paradoxical sleep deprivation. Life Sci. 8, 1085–1093.
Marrosu, F., Portas, C., Mascia, M.F., Casu, M.A., Fa, M., Giagheddu, M., Imperato, A., Gessa, G.L., 1995. Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep–wake cycle in freely moving cats. Brain Res. 671, 329–332.
Masserano, J.M., King, C., 1982. Effects on sleep of phentolamine and epinephrine infused into the locus coeruleus of cats. Eur. J. Pharmacol. 84, 199–204.
Massimini, M., Ferrarelli, F., Huber, R., Esser, S.K., Singh, H., Tononi, G., 2005. Breakdown of cortical effective connectivity during sleep. Science 309, 2228–2232.
Mastrangelo, D., De Saint Hilaire-Kafi, Z., Gaillard, J.M., 1994. Effects of clonidine and α-methyl-*p*-tyrosine on the carbachol stimulation of paradoxical sleep. Pharmacol. Biochem. Behav. 48, 93–100.
Masuko, S., Nakajima, Y., Nakajima, S., Yamaguchi, K., 1986. Noradrenergic neurons from the locus coeruleus in dissociated cell culture: culture methods, morphology, and electrophysiology. J. Neurosci. 6, 3229–3241.
Matsumoto, J., Jouvet, M., 1964. Effets de la réserpine, DOPA et 5 HTP sur les deux états de sommeil. C. R. Soc. Biol. 158, 2137–2140.
Matsumoto, J., Watanabe, S., 1967. Paradoxical sleep: effects of adrenergic blocking agents. Proc. Jpn. Acad. 43, 680–683.
Matsuyama, S., Coindet, J., Mouret, J., 1973. 6-Hydroxydopamine intracisternale et sommeil chez le Rat. Brain Res. 57, 85–95.
McCormick, D.A., 1992. Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. Prog. Neurobiol. 39, 337–388.
McCormick, D.A., Wang, Z., Huguenard, J., 1993. Neurotransmitter control of neocortical neuronal activity and excitability. Cerebral Cortex 3, 387–398.
McGinty, D.J., Harper, R.M., 1976. Dorsal raphe neurons: depression of firing during sleep in cats. Brain Res. 101, 569–575.
Meyer-Lindenberg, A., Weinberger, D.R., 2006. Intermediate phenotypes and genetic mechanism of psychiatric disorders. Nat. Neurosci. Rev. 7, 818–827.
Meyer-Lindenberg, A., Poline, J.B., Kohn, P.D., Holt, J.L., Egan, M.F., Weinberger, D.R., Berman, K.F., 2001. Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. Am. J. Psychiat. 158, 1809–1817.
Meyer-Lindenberg, A., Olsen, R.K., Kohn, P.D., Brown, T., Egan, M.F., Weinberber, D.R., Berman, K.F., 2005. Regionally specific disturbance of dorsolateral prefrontal-hippocampal function connectivity in schizophrenia. Arch. Gen. Psychiat. 62, 379–386.
Milon, H., Enslen, M., 1980. Effect of repeated administration of alpha-methyl-*para*-tyrosine on the rat brain catecholamines, spontaneous locomotor activity and sleep states. Eur. J. Mass Spectrom. Biochem. Med. Env. Res. 1, 117–120.
Milstein, J.A., Lehmann, O., Theobald, D.E., Dalley, J.W., Robbins, E., 2007. Selective depletion of cortical noradrenaline by anti-domaine beta-hydroxylase-saporin impairs attentional function and enhances the effect of guafacine in the rat. Psychopharmacology 190, 51–63.
Mirmiran, M., 1983. "Oneiric" behavior during active sleep induced by bilateral lesions of the pontine tegmentum in juvenile rats. In: Koella, W.P. (Ed.), Sleep 1982. Karger, Basel, pp. 236–239.
Mirmiran, M., 1986. The role of the central monoaminergic system and rapid eye movement sleep in development. Brain Dev. 8, 382–389.
Mogilnicka, E., Arbilla, S., Depoortere, H., Langer, S.Z., 1980. Rapid-eye-movement sleep deprivation decreases the density of ^{3}H-dihydroalprenolol and ^{3}H-imipramine binding sites in the rat cerebral cortex. Eur. J. Pharmacol. 65, 289–292.
Mogilnicka, E., Przewlocka, B., Van Luijtelaar, E.L.J.M., Klimek, V., Coenen, A.M.L., 1986. Effects of REM sleep deprivation on central α1- and β-adrenoceptors in rat brain. Pharmacol. Biochem. Behav. 25, 329–332.
Mons, L., D'hondt, E., Pijcke, K., Vandesande, F., 1995. Noradrenergic system in the chicken brain: immunocytochemical study with antibodies to noradrenaline and dopamine-beta-hydroxylase. Comp. Neurol. 360, 331–348.
Monti, J.M., 1983. Catecholamines and the sleep–wake cycle. II. REM sleep. Life Sci. 32, 1401–1415.
Monti, J.M., D'Angelo, L., Jantos, H., Barbeito, L., Abo, V., 1988. Effect of DSP-4, a noradrenergic neurotoxin, on sleep and wakefulness and sensitivity to drugs acting on adrenergic receptors in the rat. Sleep 11, 370–377.
Morilak, D.A., Barrera, G., Echevarria, D.J., Garcia, A.S., Hernandez, A., Ma, S., Petre, C.O., 2005. Role of brain norepinephrine in the behavioral response to stress. Prog. Neuropsychopharmacol. Biol. Psychiat. 29, 1214–1224.
Moruzzi, G., 1972. The sleep–waking cycle. In: Egibnisse der Physiologie, Springer–Verlag, Berlin, pp. 1–165.
Mouret, J., Delorme, F., 1967. Lesions du tegmentum pontique et sommeil chez le Rat. C. R. Soc. Biol. 161, 1603–1606.
Mühlethaler, M., Khateb, A., Serafin, M., 1990. Effects of monoamines and opiates on pedunculopontine neurons. In: Mancia, M., Marini, G. (Eds.), The Diencephalon and Sleep. Raven Press Ltd., New York, pp. 367–377.
Murphy, V.N., Fetz, E.E., 1992. Coherent 25- to 35-Hz oscillations in the sensorimotor cortex of awake behaving monkeys. Proc. Natl. Acad. Sci. U.S.A. 89, 5670–5674.
Nelson, C.N., Hoffer, B.J., Chu, N.S., Bloom, F.E., 1973. Cytochemical and pharmacological studies on polysensory neurons in the primate frontal cortex. Brain Res. 62, 115–133.
Nicholson, A.N., Pascoe, P.A., 1991. Presynaptic alpha$_2$-adrenoceptor function and sleep in man: studies with clonidine and idazoxan. Neuropharmacology 30, 367–372.
Nicholson, A.N., Pascoe, P.A., Stone, B.M., 1986. Modulation of catecholamine transmission and sleep in man. Neuropharmacology 25, 271–274.
Nicoll, R.A., Malenka, R.C., Kauer, J.A., 1990. Functional comparison of neurotransmitter receptor subtypes in mammalian central nervous system. Physiol. Rev. 70, 513–566.
Nofzinger, E.A., Mintun, M.A., Wiseman, M.B., Kupfer, J., 1997. Forebrain activation during REM sleep: an FDG PET study. Brain Res. 770, 192–201.
Oswald, I., Thacore, V.R., Adam, K., Brezinova, V., 1975. α-Adrenergic receptor blockade increases human REM sleep. Br. J. Clin. Pharmacol. 2, 107–110.
Ouyang, M., Hellman, K., Abel, T., Thomas, S.A., 2004. Adrenergic signaling plays a critical role in the maintenance of waking and in the regulation of REM sleep. J. Neurophysiol. 92, 2071–2082.
Pal, D., Mallick, B.N., 2006. Role of noradrenergic and GABA-ergic inputs in pedunculopontine tegmentum for regulation of rapid eye movement sleep in rats. Neuropharmacology 51, 1–11.
Pal, D., Mallick, B.N., 2007. Neural mechanism of rapid eye movement sleep generation with reference to REM-OFF neurons in locus coeruleus. Ind. J. Med. Res. 125, 721–739.
Pal, D., Madan, V., Mallick, B.N., 2005. Neural mechanism of rapid eye movement sleep generation: cessation of locus coeruleus neurons is a necessity. Acta Physiol. Sin. 57, 401–413.
Panksepp, J., Jalowiec, J.E., Morgane, P.J., Zolovick, A.J., Stern, W.C., 1973. Noradrenergic pathways and sleep–waking states in cats. Exp. Neurol. 41, 233–245.

Park, S.P., 2002. In vivo microdialysis measures of extracellular norepinephrine in the rat amygdala during sleep–wakefulness. J. Korean Med. Sci. 17, 395–399.
Parmeggiani, P.L., 2003. Thermoregulation and sleep. Front. Biosci. 8, s557–s567.
Parsons, L.M., Sergent, J., Hodges, D.A., Fox, P.T., 2005. The brain basis of piano performance. Neuropsychologia 43, 199–215.
Payne, J.L., Quiroz, J.A., Zarate, C.A.J., Manji, H.K., 2002. Timing is everything: does the robust upregulation of noradrenergically regulated plasticity genes underlie the rapid antidepressant effects of sleep deprivation. Biol. Psychiat. 52, 921–926.
Peled, A., Geva, A.B., Kremen, W.S., Blankfeld, H.M., Esfandiarfard, R., Nordahl, T.E., 2000. Functional connectivity and working memory in schizophrenia: an EEG study. Int. J. Neurosci. 106, 47–61.
Pellejero, T., Monti, J.M., Baglietto, J., Jantos, H., Pazos, S., Cichevski, V., Hawkins, M., 1984. Effects of methoxamine and α-adrenoceptor antagonists, prazosin and yohimbine, on the sleep–wake cycle of the rat. Sleep 7, 365–372.
Perez-Garci, E., del Rio-Portilla, Y., Guevara, M.A., Arce, C., Corsi-cabrera, M., 2001. Paradoxical sleep is characterized by uncoupled gamma activity between frontal and perceptual cortical regions. Sleep 24, 118–126.
Petitjean, F., Laguzzi, R., Sordet, F., Jouvet, M., Pujol, J.F., 1972. Effets de l'injection intravntriculaire de 6-hydroxydopamine. I. Sir les monoamines cérébrales du Chat. Brain Res. 48, 281–293.
Pierpibone, V.A., Aston-Jones, G., Bohn, M.C., 1988. Adrenergic and non-adrenergic neurons in the C1 and C3 areas project to locus coeruleus: a fluorescent double labeling study. Neurosci. Lett. 85, 297–303.
Pineda, J.A., Foote, S.L., Neville, H.J., 1989. Effects of locus coeruleus lesions on auditory, long-latency, event-related potentials in monkeys. J. Neurosci. 9, 81–93.
Pirot, S., Godbout, R., Mantz, J., Tassin, J.P., Glowinski, J., Thierry, A.M., 1992. Inhibitory effects of ventral tegmental area stimulation on the activity of the prefrontal cortex neurons: evidence for the involvement of both dopaminergic and GABAergic components. Neuroscience 49, 857–865.
Porkka-Heiskanen, T., Smith, S.E., Taira, T., Urban, J.H., Levine, J.E., Turek, F.W., Stenberg, D., 1995. Noradrenergic activity in rat brain during rapid eye movement sleep deprivation and rebound sleep. Am. J. Physiol. 268, R1456–R1463.
Pothos, E., Rada, P., Mark, G.P., Hoebel, B.G., 1991. Dopamine microdialysis in the nucleus accumbens during acute and chronic morphine, naloxone-precipitated withdrawal and clonidine treatment. Brain Res. 566, 348–350.
Pralong, E., Magistretti, P., Stoop, R., 2002. Cellular perspectives on the glutamate-monoamine interactions in limbic lobe structures and their relevance for some psychiatric disorders. Prog. Neurobiol. 67, 173–202.
Pujol, J.F., Jouvet, M., Glowinski, J., 1968. Increased turnover of central norepinephrine during rebound of paradoxical sleep in the rat. Science 158, 112–114.
Putkonen, P.T.S., Leppävuori, A., 1977. Increase in paradoxical sleep in the cat after phentolamine, an alpha-adrenoceptor antagonist. Acta Physiol. Scand. 100, 488–490.
Putkonen, P.T.S., Leppävuori, A., Stenberg, D., 1977. Paradoxical sleep inhibition by central alpha-adrenoceptor stimulant clonidine antagonized by alpha-receptor blocker yohimbine. Life Sci. 21, 1059–1066.
Python, A., Charnay, Y., Mikolajewski, R., Merica, H., de Saint Hilaire, Z., 1997. Effects of nisoxetine, a selective noradrenaline transporter blocker, on sleep in rats. Pharmacol. Biochem. Behav. 58, 369–372.
Radulovacki, M., Micovic, N., 1982. Effects of REM sleep deprivation and desipramine on β-adrenergic binding sites in rat brain. Brain Res. 235, 393–396.
Radulovacki, M., Wojcik, W.J., Fornal, C., Miletich, R., 1980. Elimination of REM sleep rebound in rats by α-adrenoreceptor blockers, phentolamine and phenoxybenzamine. Pharmacol. Biochem. Behav. 13, 51–55.
Radulovacki, M., wojcik, W.J., Walovitch, R., Brodie, M., 1981. Phenoxybenzamine and bromocriptine attenuate need for REM sleep in rats. Pharmacol. Biochem. Behav. 14, 371–375.
Ramm, P., 1979. The locus coeruleus, catecholamines, and REM sleep: a critical review. Behav. Neural Biol. 25, 415–448.
Ramos, B.P., Colgan, L., Ovadia, S., Wilson, S.R., Arnsten, A.F., 2005. The beta-1 adrenergic antagonist, betaxolol, improves working memory performance in rats and monkeys. Biol. Psychiat. 58, 894–900.
Rasch, B., Dodt, C., Mölle, M., Born, J., 2007. Stage -sleep- specific regulation of plasma catecholamine concentration. Psychoneuroendocrinology 32, 884–891.
Rasmussen, K., Heym, J., Jacobs, B.L., 1984. Activity of serotonin-containing neurons in nucleus centralis superior of freely moving cats. Exp. Neurol. 83, 302–317.
Rasmussen, K., Morilak, D.A., Jacobs, B.L., 1986. Single unit activity of locus coeruleus neurons in the freely moving cat. I. Naturalistic behaviors and in response to simple and complex stimuli. Brain Res. 371, 324–334.
Reader, T.A., Ferron, A., Descarries, L., Jasper, H.H., 1979. Modulatory role for biogenic amines in the cerebral cortex. Microiontopheric studies. Brain Res. 160, 219–229.
Reeves, M., Lindholm, D.E., Myles, P.S., Fletcher, H., Hunt, J.O., 2001. Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: a double-blind, randomized trial. Anesth. Analg. 93, 116–120.
Renouard, A., Widdowson, P.S., Millan, M.J., 1994. Multiple alpha 2 adrenergic receptor subtypes. I. Comparison of (3H)RX821002-labelled rat R alpha-2A adrenergic receptors in cerebral cortex to human H alpha2A adrenergic receptor and other populations of alpha-2 adrenergic subtypes. J. Pharmacol. Exp. Ther. 1994, 946–957.
Rétaux, R., Besson, M.J., Penit-Soria, J., 1991. Opposing effects of dopamine D2 receptor stimulation on the spontaneous and electrically-evoked release of 3H GABA on rat prefrontal cortex slices. Neuroscience 42, 61–72.
Ribary, U., Ionnides, A.A., Singh, K.D., Hasson, R., Bolton, J., Lado, F., Mogilner, A., Llinas, R., 1991. Magnetic field tomography of coherent thalamocortical 40 Hz oscillations in humans. Proc. Natl. Acad. Sci. U.S.A. 88, 11037–11041.
Rochette, L., Bralet, A.M., Bralet, J., 1974. Influence de la clonidine sur la synthèse et la libération de la noradrénaline dans différentes structures cérébrales du Rat. J. Pharmacol. (Paris) 5, 209–220.
Roffwarg, H.P., Dement, W.C., Muzio, J.N., Fisher, C., 1962. Dream imagery: relationship to rapid eye movements of sleep. Arch. Gen. Psychiat. 7, 235–258.
Rossi, G.F., Palestini, M., Pisano, M., Rosadini, G., 1965. An experimental study of the cortical reactivity during sleep and wakefulness. In: Aspects anatomo-fonctionnels de la physiologie du sommeil, CNRS, Paris, pp. 509–532.
Sakai, K., 1980. Some anatomical and physiological properties of ponto-mesencephalic tegmental neurons with special reference to PGO waves and postural atonia during paradoxical sleep in the cat. In: Hobson, J.A., Brazier, M.A.B. (Eds.), The Reticular Formation Revisited. Raven Press, New York, pp. 427–447.
Sakai, K., 1985. Anatomical and physiological basis of paradoxical sleep. In: Drucker-Colin, R., Morrison, A.R., Parmeggiani, P.L. (Eds.), Brain Mechanisms of Sleep. pp. 111–137.
Sakai, K., 1988. Executive mechanisms of paradoxical sleep. Arch. Ital. Biol. 126, 239–257.
Sakai, K., 1991. Physiological properties and afferent connections of the locus coeruleus and adjacent tegmental neurons involved in the generation of paradoxical sleep in the cat. In: Barnes, C.D., Pompeiano, O. (Eds.), Progress in Brain Research, vol. 18. Elsevier Science Publishing, Amsterdam, pp. 31–45.
Sakai, K., Crochet, S., 2003. A neural mechanism of sleep and wakefulness. Sleep Biol. Rhyt. 1, 29–42.
Sakai, K., Crochet, S., 2004. Role of the locus coeruleus in the control of paradoxical sleep generation in the cat. Arch. Ital. Biol. 142, 421–427.
Sanford, L.D., Cheng, C.S., Silvestri, A.J., Tang, X., Mann, G.L., Ross, R.J., Morrison, A.R., 2001a. Sleep and behavior in rats with pontine lesions producing REM without atonia. Sleep Res. Online 14, 1–5.
Sanford, L.D., Silvestri, A.J., Ross, R.J., Morrison, A.R., 2001b. Influence of fear conditioning on elicited ponto-geniculo-occipital waves and rapid eye movement sleep. Arch. Ital. Biol. 139, 169–183.
Sastre, J.P., Jouvet, M., 1979. Oneiric behavior in cats. Physiol. Behav. 22, 979–989.
Sastre, J.P., Buda, C., Lin, J.S., Jouvet, M., 2000. Differential c-fos expression in the rhinencephalon and striatum after enhanced sleep–wake states in the cat. Eur. J. Neurosci. 12, 1397–1410.
Satoh, T., Tanaka, R., 1973. Selective suppression of rapid eye movement sleep (REM) by fusaric acid, an inhibitor of dopamine-b-oxidase. Experientia 29, 177–178.
Schildkraut, J.J., Hartmann, E., 1971. Turnover and metabolism of norepinephrine in rat brain after 72 h on a D-deprivation island. Psychopharmacologia 27, 17–27.
Seguela, P., Watkons, K.C., Geffard, M., Descarries, L., 1990. Noradrenaline axon terminals in adult rat neocortex: an immunocytochemical analysis in serial thin sections. Neuroscience 35, 249–264.
Selden, N.R.W., Robbins, T.W., Everitt, B.J., 1990. Enhanced behavioral conditioning to context and impaired behavioral and neuroendocrine responses to conditioned stimuli following ceruleocortical noradrenergic lesions: support for an attentional hypothesis of central noradrenergic function. J. Neurosci. 10, 531–539.
Shouse, M.N., Staba, R.J., Saquib, S.F., Farber, P.R., 2000. Monoamines and sleep: microdialysis findings in pons and amygdala. Brain Res. 860, 181–189.
Siegel, J.M., 2001. The REM sleep–memory consolidation hypothesis. Science 294, 1058–1063.
Siegel, J., Rogawski, M.A., 1988. A function for REM sleep: regulation of noradrenergic receptor sensitivity. Brain Res. Rev. 13, 213–233.
Silbersweig, D.A., Stern, E., Frith, C.D., Cahill, C., Holmes, A., Grootoonk, S., Seaward, J., McKenna, P., Chua, S.E., Schnorr, L., Jones, T., Frackowiak, R.S.J., 1995. A functional neuroanatomy of hallucinations in schizophrenia. Nature 378, 176–179.
Singh, S., Mallick, B.N., 1996. Mild electrical stimulation of pontine tegmentum around locus coeruleus reduces rapid eye movement sleep in rats. Neurosci. Res. 24, 227–235.
Sinha, A.K., Ciaranello, R.D., Dement, W.C., Barchas, J.D., 1973. Tyrosine hydroxylase activity in rat brain following "REM" sleep deprivation. J. Neurochem. 20, 1289–1290.
Smeets, W.J., Steinbusch, H.W.M., 1989. Distribution of noradrenaline immunoreactivity in the forebrain and midbrain of the lizzard Gekko gecko. Comp. Neurol. 285, 453–466.
Smith, C., 1995. Sleep states and memory processes. Behav. Brain Res. 69, 137–145.
Spector, S., Sjoerdsma, A., Underfriend, S., 1965. Blockade of endogenous norepinephrine synthesis by a α-methyl-tyrosine hydroxylase. J. Pharmacol. Exp. Ther. 147, 86–95.
Spencer, K.M., Nestor, P.G., Niznikiewicz, A., Salisbury, D.F., Shenton, M.E., McCarley, R.W., 2003. Abnormal neural synchrony in schizophrenia. J. Neurosci. 23, 7407–7411.
Spiegel, R., Devos, J.E., 1980. Central effects of guanfacine and clonidine during wakefulness and sleep in healthy subjects. Brit. J. Clin. Pharmacol. 10, 165S–168S.
Steere, J.C., Arnsten, A.F., 1997. The alpha-2 noradrenergic receptor agonist guanfacine improves visual object discrimination reversal performance in aged rhesus monkeys. Behav. Neurosci. 111, 883–891.

Stein, D., Jouvet, M., Pujol, J.F., 1974. Effects of α-methyl-*p*-tyrosine upon amine metabolisms and sleep in the cat. Brain Res. 72, 360–365.
Steriade, M., 1970. Ascending control of thalamic and cortical responsiveness. Int. Rev. Neurobiol. 12, 87–144.
Steriade, M., Curro dossi, R., Paré, D., Oakson, G., 1991. Fast oscillations (20–40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. Proc. Natl. Acad. Sci. U.S.A. 88, 4396–4400.
Steriade, M., Amzica, F., Contreras, D., 1996a. Synchronization of fast (30–40 Hz) spontaneous cortical rhythms during brain activation. J. Neurosci. 16, 392–417.
Steriade, M., Contreras, D., Amzica, F., Timofeev, I., 1996b. Synchronization of fast (30–40 Hz) spontaneous oscillations in the intrathalamus and thalamocortical networks. J. Neurosci. 16, 2788–2808.
Stern, W.C., Morgane, P.J., 1973a. Effects of α-methyltyrosine on REM sleep and brain amine levels in the cat. Biol. Psychiat. 6, 301–306.
Stern, W.C., Morgane, P.J., 1973b. Effects of reserpine on sleep and brain biogenic amine levels in the cat. Psychopharmacologia 28, 275–286.
Stern, W.C., Morgane, P.J., 1974. Theoretical view of REM sleep function: maintenance of cathecolamine systems in the central nervous system. Behav. Biol. 11, 1–32.
Stevens, D.R., McCarley, R.W., Greene, R.W., 1994. The mechanism of noradrenergic alpha1 excitatory modulation of pontine reticular formation neurons. J. Neurosci. 14, 6481–6487.
Swanson, C.J., Schoepp, D.D., 2003. A role for noradrenergic transmission in the actions of phencyclidine and the antipsychotic and antistress effects of mGlu2/3 receptor agonists. Ann. N. Y. Acad. Sci. 1003, 309–317.
Swick, D., Pineda, J.A., Foote, S.L., 1994. Effects of systemic clonidine on auditory event-related potentials in squirrel monkeys. Brain Res. Bull. 33, 79–86.
Tait, D.S., Brown, V.J., Farovik, A., Theobald, D.E., Dalley, J.W., Robbins, T.W., 2007. Lesions of the dorsal noradrenergic bundle impair set-shifting in the rat. Eur. J. Neurosci. 25, 3719–3733.
Takahara, M., Nittono, H., Hori, T., 2006. Effect of voluntary attention on auditory processing during REM sleep. Sleep 29.
Thakkar, M., Mallick, B.N., 1993. Effect of rapid eye movement sleep deprivation on rat brain monoamine oxidase. Neuroscience 55, 677–683.
Thankachan, S., Islam, F., Mallick, B.N., 1999. Adrenergic and cholinergic modulation of spontaneous and brain stem reticular formation stimulation induced desynchronization of the cortical EEG in freely moving behaving cats. Sleep Hypnosis 1, 14–21.
Thankachan, S., Islam, F., Mallick, B.N., 2001. Role of wake inducing brain stem area on rapid eye movement sleep regulation in freely moving cats. Brain Res. Bull. 55, 43–49.
Tissot, R., 1965. The effects of certain drugs on the sleep cycle in man. In: Akert, K., Bally, C., Schadé, J.P. (Eds.), Progress in Brain Research, Sleep Mechanisms, vol. 18. Elsevier, Amsterdam, pp. 175–177.
Tong, J., Hornykiewicz, O., Kish, S.J., 2006. Identification of a noradrenaline-rich subdivision of the human nucleus accumbens. J. Neurochem. 96, 349–354.
Tononi, G., Edelman, G.M., 2000. Schizophrenia and the mechanism of conscious integration. Brain Res. Rev. 31, 391–400.
Tononi, G., Pompeiano, M., Cirelli, C., 1991a. Suppression of desynchronized sleep through microinjection of alpha2-adrenergic agonist clonidine in the dorsal pontine tegmentum of the cat. Pflügers Arch. 418, 512–518.
Tononi, G., Pompeiano, M., Cirelli, C., 1991b. Effects of local pontine injection of noradrenergic agents on desynchronized sleep of the cat. Prog. Brain Res. 88, 545–553.
Toppila, J., Stenberg, D., Alanko, L., Asikainen, M., Urban, J.H., Turek, F.W., Porkka-Heiskanen, T., 1995. REM sleep deprivation induces galanin gene expression in the rat brain. Neurosci. Lett. 183, 171–174.
Torda, C., 1968. Effect of changes of brain norepinephrine content on sleep cycle in the rat. Brain Res. 10, 200–207.
Toyoda, J., 1964. The effects of chlorpromazine and imipramine on the human nocturnal sleep electroencephalogram. Folia Psychiat. Neurol. 18, 198–221.
Tsai, L.L., Bergmann, B.M., Perry, B.D., Rechtschaffen, A., 1993. Effects of chronic total sleep deprivation on central noradrenergic receptors in rat brain. Brain Res. 602, 221–227.
Tulen, J.H., Man in't Veld, A.J., Melchese, K., Boomsma, F., 1990. Sleep patterns in congenital dopamine beta-hydroxylase deficiency. J. Neurol. 237, 98–102.
Tulen, J.H., Man in't Veld, A.J., Dzoljic, M.R., Melchese, K., Moleman, P., 1991. sleeping with and without norepinephrine: effects of metoclopramide and D,L-thyreo-3,4-dihydroxyphenylserine on sleep in dopamine beta-hydroxylase deficiency. Sleep 14, 32–38.
Vanderwolf, C.H., 2000. Are neocortical gamma waves related to consciousness. Brain Res. 855, 217–224.
Vanini, G., Torterolo, P., McGregor, R., Chase, M.H., Morales, F.R., 2007. GABAergic processes in the mesencephalic tegmentum modulate the occurrence of active (rapid eye movement) sleep in guinea pigs. Neuroscience 145, 1157–1167.
Vasquez, J., Baghdoyan, H.A., 2001. Basal forebrain acetylcholine release during REM sleep is significantly greater than during waking. Am. J. Physiol. 280, R598–R601.
Verret, L., Fort, P., Gervasoni, D., Léger, L., Luppi, P.H., 2006. Localization of the neurons active during paradoxical (REM) sleep and projecting to the locus coeruleus noradrenergic neurons in the rat. J. Comp. Neurol. 495, 573–586.
Vertes, R.P., 2004. Memory consolidation in sleep; dream or reality. Neuron 44, 135–148.
Vertes, R.P., Eastman, K.E., 2000. The case against memory consolidation in REM sleep. Behav. Brain Sci. 23, 867–876.
Vogel, G., 1983. Evidence for REM sleep deprivation as the mechanism if action of antidepressant drugs. Prog. Neuro-Psychopharmacol. Biol. Psychiat. 7, 343–349.
Wall, P.D., 1958. Excitability changes in afferent fiber terminations and their relation to slow potential. J. Physiol. Lond. 142, 1–21.
Wallace, D.M., Magnuson, D.J., Gray, T.C., 1992. Organization of amygdaloid projections to brainstem dopaminergic, norazdrenergic, and adrenergic cell groups in the rat. Brain Res. Bull. 28, 447–454.
Wang, Z., McCormick, D.A., 1993. Control of firing mode of corticotectal and corticopontine layer V burst-generating neurons by norepinephrine, acetylcholine and 1*S*,3*R*-ACPD. J. Neurosci. 13, 2199–2216.
Warren, R.A., Dykes, R.W., 1996. Transient and long-lasting effects of iontophoretically administered norepinephrine on somatosensory cortical neurons in halothane-anesthetized cats. Can. J. Physiol. Pharmacol. 74, 38–57.
Waterhouse, B.D., Azizi, S.A., Burne, R.A., Woodward, D., 1990. Modulation of rat cortical area 17 neuronal responses to moving visual stimuli during norepinephrine and serotonin microiontophoresis. Brain Res. 514, 276–292.
Wehrle, R., Czisch, M., Kaufmann, C., Wetter, T.C., Holsboer, F., Auer, D.P., Pollmächer, T., 2005. Rapid eye movement-related brain activation in human sleep: a functional magnetic resonance imaging study. NeuroReport 16, 853–857.
Weickert, C.S., Webster, M.J., Gondipalli, P., Rothmond, D., Fatula, R.J., Herman, M.M., Kleinman, J.E., Akil, M., 2007. Postnatal alterations in dopaminergic markers in the human prefrontal cortex. Neuroscience 144, 1109–1119.
Weinberger, D.R., Berman, K.F., Zec, R.F., 1986. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. 1. Regional cerebral blood flow evidence. Arch. Gen. Psychiat. 43, 114–124.
Weiss, T., Adey, W.R., 1965. Excitability changes during paradoxical sleep in the rat. Experentia 21, 1–4.
Weitzman, E., McGregor, P., Moore, C., Jacoby, J., 1969. The effect of alpha-methyl-*para*-tyrosine on sleep patterns of the monkey. Life Sci. 8, 751–757.
Williams, J.A., Reiner, P.B., 1993. Noradrenaline hyperpolarizes identified rat mesopontine cholinergic neurons in vitro. J. Neurosci. 13, 3878–3883.
Woods, D.L., Knight, R.T., 1986. Electrophysiological evidence of increased distractibility after dorsolateral prefrontal lesions. Neurology 36, 212–216.
Wyatt, R.J., Chase, T.N., Kupfer, D.J., Scott, J., Snyder, F., 1971. Brain catecholamines and human sleep. Nature 133, 63–65.
Yamaguchi, N., Ling, G.M., Marczynski, T.J., 1964. The effects of chemical stimulation of the preoptic region, nucleus centralis medialis, or brain stem reticular formation with regard to sleep and wakefulness. In: Wortis, I. (Ed.), Recent Advances in Biological Psychiatry, vol. VI. Plenum Press, New York, pp. 9–20.
Yamuy, J., Sampogna, S., Morales, F.R., Chase, M.H., 1998. c-Fos expression in mesopontine noradrenergic and cholinergic neurons of the cat during carbachol-induced active sleep: a double-labelling study. Sleep Res. Online 1, 28–40.
Yeragani, V.K., Cashmere, D., Miewald, J., Tancer, M., Keshavan, M.S., 2006. Decreased coherence in higher frequency ranges (beta and gamma) between central and frontal EEG in patients with schizophrenia: a preliminar report. Psychiat. Res. 141, 53–60.
Young, C.E., Beach, T.G., Falkai, P., Honer, W.G., 1998. SNAP-25 deficit and hippocampal connectivity in schizophrenia. Cerebral Cortex 8, 261–268.
Zoli, M., Torri, C., Ferrari, R., Jansson, A., Zini, I., Fuxe, K., Agnati, I.F., 1998. The emergence of the volume transmission concept. Brain Res. Rev. 26, 136–147.
Zolovick, A.J., Stern, W.C., Jalowiec, J.E., Panksepp, J., Morgane, P.J., 1973. Sleep–waking patterns and brain biogenic amine levels in cats after administration of 6-hydroxydopamine into the dorsolateral pontine tegmentum. Pharmacol. Biochem. Behav. 1, 557–567.