Pergamon

www.neuroscience-ibro.com

PII: S0306-4522(02)00034-9

Neuroscience Vol. 111, No. 2, pp. 231–239, 2002

0306-4522/02 $22.00+0.00

COMMENTARY

GABA MECHANISMS AND SLEEP

CLAUDE GOTTESMANN*

Laboratoire de Psychophysiologie, Faculté des Sciences, Université de Nice-Sophia Antipolis, 06108 Nice Cedex 2, France

Abstract—GABA is the main inhibitory neurotransmitter of the CNS. It is well established that activation of $GABA_A$ receptors favors sleep. Three generations of hypnotics are based on these $GABA_A$ receptor-mediated inhibitory processes. The first and second generation of hypnotics (barbiturates and benzodiazepines respectively) decrease waking, increase slow-wave sleep and enhance the intermediate stage situated between slow-wave sleep and paradoxical sleep, at the expense of this last sleep stage. The third generation of hypnotics (imidazopyridines and cyclopyrrolones) act similarly on waking and slow-wave sleep but the slight decrease of paradoxical sleep during the first hours does not result from an increase of the intermediate stage. It has been shown that $GABA_B$ receptor antagonists increase brain-activated behavioral states (waking and paradoxical sleep: dreaming stage). Recently, a specific $GABA_C$ receptor antagonist was synthesized and found by i.c.v. infusion to increase waking at the expense of slow-wave sleep and paradoxical sleep.

Since the sensitivity of $GABA_C$ receptors for GABA is higher than that of $GABA_A$ and $GABA_B$ receptors, $GABA_C$ receptor agonists and antagonists, when available for clinical practice, could open up a new era for therapy of troubles such as insomnia, epilepsy and narcolepsy. They could possibly act at lower doses, with fewer side effects than currently used drugs. This paper reviews the influence of different kinds of molecules that affect sleep and waking by acting on GABA receptors.

Key words: $GABA_A$, $GABA_B$, $GABA_C$, biological rhythm.

CONTENTS

$GABA_A$ RECEPTOR COMPLEX	232
$GABA_A$ binding site	232
Barbiturate binding site	234
Benzodiazepine binding site	234
New-generation hypnotics	234
Steroid binding site	235
$GABA_B$ RECEPTORS	235
$GABA_C$ RECEPTORS	235
CONCLUSION	235
NOTE ADDED IN PROOF	236
ACKNOWLEDGEMENTS	236
REFERENCES	236

Insomnia is one of the most frequent complaints encountered in a doctor's office. Although it is most often related to anxiety, it commonly reflects a lack of central inhibitory processes. Bubnoff and Heidenhain (1881) seem to have been the first to describe such central inhibitory processes. They showed that low-intensity peripheral and cortical stimulations were able to inhibit cortical stimulation-induced motor activities. For sleep–waking behavior, it was Hess (1931) who first claimed that sleep involved inhibitory processes: 'the essential mechanism of sleep cannot be explained differently as by active inhibition of some functions of the organism'. Although Creutzfeldt et al. (1956) observed true inhibitory phenomena at the cortical cellular level, it was Evarts et al. (1960) who studied the recovery cycle of cortical evoked potentials induced by radiation stimulation and demonstrated inhibitory mechanisms during sleep–waking behavior. From the neurochemical standpoint, since the pioneering work of Krnjevic et al. (1966), it has been acknowledged that GABA is the principal inhibitory transmitter and nowadays it is estimated that 20% at least of brain neurons are GABAergic (Parades and Agmo, 1992).

The pentameric $GABA_A$ ionotropic receptor (Fig. 1, top) was the first to be identified, with several classes of

*Tel.: +33-4-92-07-61-66; fax: +33-4-92-07-61-62.

E-mail address: gottesma@unice.fr (C. Gottesmann).

Abbreviations: CACA, *cis*-4-amino crotonic acid; EEG, electroencephalogram; TPMPA, (1,2,5,6-tetrahydropyridine)-methylphosphonic acid.

subunits α, β, γ, ρ, δ, π, ε and θ: α comprising six subunits in rats, β four subunits, γ three subunits, and ρ three subunits (Möhler et al., 1990; Duncan et al., 1995; Schmid et al., 1995; Barnard et al., 1998; Davies et al., 2000); the γ2 binding site has been shown to comprise two variants, γ2L and γ2S, which differ by eight amino acids (Duncan et al., 1995). The $GABA_A$ receptor complex consists of a Cl^- ionophore principally coupled to GABA, barbiturate, benzodiazepine, steroid, and picrotoxin binding sites (McDonald and Olsen, 1994). GABA's influence on its own binding site has been most often studied by the antagonist bicuculline and the agonist muscimol (Sieghart, 1995). However, many compounds binding to other sites have given rise to numerous studies on sleep. The second receptor to be identified was the $GABA_B$ receptor (Hill and Bowery, 1981) which is coupled to Ca^{2+} and K^+ ion channels and functions by a metabotropic pathway with a second messenger. The affinity of GABA to $GABA_B$ receptors is lower than for $GABA_A$ receptors (Chu et al., 1990). This receptor was first blocked by phaclofen and the agonist most often used is baclofen. The modulation of this receptor has given rise to only a few studies on sleep. The third receptor identified is that for $GABA_C$ (Fig. 1, bottom). Indeed, as early as 1975 (Johnston et al., 1975) and again later (Parades and Agmo, 1992), it appeared that some GABA analogues acted on bicuculline- and baclofen-insensitive receptors. These $GABA_C$ receptors (Drew et al., 1984) were first observed at the retinal level (Feigenspan et al., 1993; Quian and Dowling, 1994), then at the central brain level (Bormann and Feigenspan, 1995; Boue-Grabot et al., 2000). This receptor comprises a Cl^- ionophore and several subunits (ρ1, ρ2, ρ3) (Ogurusu et al., 1997). It is also more sensitive to GABA than the $GABA_A$ receptor and its desensitization is also different (Quian and Dowling, 1994): 'while the amplitude of $GABA_A$ receptor-mediated currents decreases notably in the presence of agonists, the time-course of $GABA_C$ receptor responses is more sustained' (Bormann and Feigenspan, 1995).

Up to now, insomnia has been principally treated by compounds acting at the $GABA_A$ receptor level. I propose to analyze the function of the different kind of GABA receptors and their clinical potentialities.

$GABA_A$ RECEPTOR COMPLEX

$GABA_A$ binding site

The function of the GABA receptor binding site is to open a chloride channel. Some time ago it was shown that the global central increase of GABA by i.c.v. infusion of GABA or inhibition of GABA transaminase increased slow-wave sleep and induced a 64% drop of paradoxical sleep without rebound effect in cats (Karadzic, 1966; Holmes and Sugden, 1975), and did not influence the recovery of paradoxical sleep after selective deprivation in rats (Juan de Mendoza et al., 1973). In humans it seemed to have no significant influence on paradoxical sleep but decreased sleep latency and the amount of waking (Schneider et al., 1977). More recent data have established that inhibition of uptake (Fink-Jensen et al., 1992) has little or no effect on the duration of sleep stages (Lancel et al., 1998). The more specific influence of GABA on sleep mechanisms was principally studied through the action of its agonist muscimol. Mendelson and Martin (1990) found no influence on slow-wave sleep and paradoxical sleep in rats. Lancel et al. (1996a, 1997a) found an increase in both and the low frequencies of electroencephalogram (EEG) (2–6 c/s) were increased during slow-wave sleep. A similar enhancement of slow-wave activity and the corresponding sleep stage was observed by Lancel (1997) in rats with another agonist (gaboxadol), the same effect occurring in humans (Faulhaber et al., 1997). Muscimol was also used by infusion to identify local structure functions. Injection in the anterior hypothalamus which is involved in sleep-generating processes (Von Economo, 1928; Nauta, 1946; Sterman and Clemente, 1962; Bremer, 1973; Szymusiak and McGinty, 1986; Ogawa and Kawamura, 1988; Sallanon et al., 1989; Cirelli et al., 1995) produced transient insomnia (Lin et al., 1989), and recent results have confirmed that anterior hypothalamic neurons (of the ventrolateral preoptic nucleus) favoring sleep are GABAergic (Gallopin et al., 2000). Moreover, it is known that anterior hypothalamic GABAergic neurons project to the posterior hypothalamus (Gritti et al., 1994) and muscimol injection to posterior hypothalamus target neurons which are involved in the generation of wakefulness (Von Economo, 1928; Ranson, 1939; Nauta, 1946; McGinty, 1969; Lin et al., 1999) promoted slow-wave sleep and inhibited paradoxical sleep (Lin et al., 1989) even in cats with anterior hypothalamic lesions (Sallanon et al., 1989). Furthermore, there is an increased release of GABA during slow-wave sleep in this posterior hypothalamic area (Nitz and Siegel, 1996). At the brainstem level, muscimol infusion in the rat pontine reticular formation increases waking and decreases slow-wave sleep, and the latency of paradoxical sleep occurrence is prolonged (Camacho-Arroyo et al., 1991) in such a way that it seems to correspond to a suppression followed by a rebound of this sleep stage. Similar results were obtained recently in cats (Xi et al., 1999a), where antisense nucleotide against glutamic acid decarboxylase (when injected in the pons) induces an increase of paradoxical sleep (Xi et al., 1999b). Other data suggest that brainstem 'GABAergic neurons could be responsible for inhibiting 'paradoxical sleep-on' neurons during slow-wave sleep and waking and disinhibiting them during paradoxical sleep' (Mallick et al., 1999; Maloney et al., 2000). All conclusions based on results with muscimol have to be approached with caution since this compound is also a $GABA_C$ receptor agonist (Bormann and Feigenspan, 1995) and, as already mentioned, the sensitivity of this receptor for GABA is higher than for the $GABA_A$ receptor. Several studies related to GABA were also undertaken at midbrain and pontine monoaminergic levels. Nitz and Siegel (1997a) showed the highest amount of GABA release during paradoxical sleep in the dorsal raphe nucleus which contains glutamic acid decarboxylase-labeled neu-

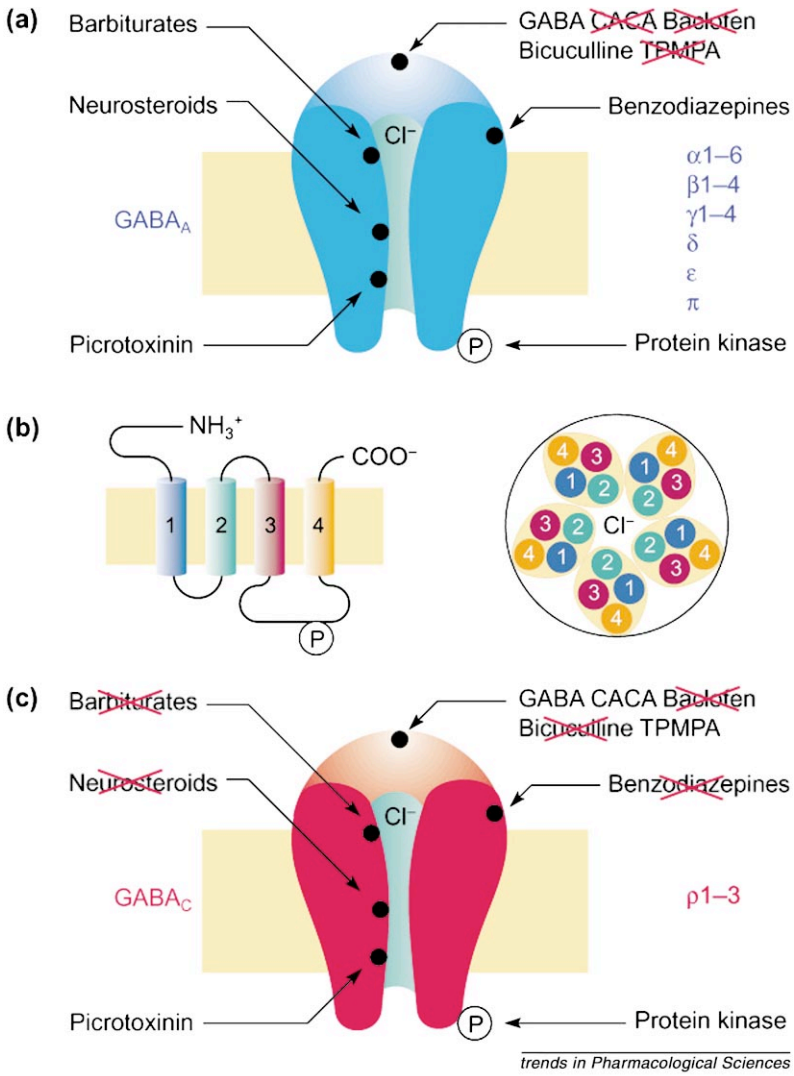

Fig. 1. Schematic illustration of the $GABA_A$ and $GABA_C$ receptors. (a) The $GABA_A$ receptor, which is a Cl^- pore, has binding sites for barbiturates, benzodiazepines and neurosteroids. The GABA responses are blocked competitively by bicuculline and non-competitively by picrotoxinin. The $GABA_B$ receptor agonist baclofen is without effect, like the $GABA_C$ receptor agonist, CACA, and antagonist, TPMPA. The vertebrate $GABA_A$ receptor is built from several subunits, some examples of which are shown on the right-hand side. (b) Each subunit comprises four transmembrane domains. (c) The $GABA_C$ receptor is activated by CACA and antagonized by TPMPA. It is blocked by picrotoxinin. It comprises three subunits (see on the right). Both receptors are modulated intracellularly by protein kinases. Reprinted from Bormann (2000) with permission of Elsevier.

rons (Ford et al., 1995) and receives afferents from different brain levels (Gervasoni et al., 2000). Moreover, the infusion of muscimol increases the amount of paradoxical sleep (Sastre et al., 1996, 1999; Nitz and Siegel, 1997a). The locus coeruleus, which also contains some GABAergic interneurons (Ijima and Ohtomo, 1988), receives GABAergic terminals from the medullary prepositus hypoglossi nucleus (Ennis and Aston-Jones, 1989). Recent findings show that the highest amount of GABA occurs in the locus coeruleus during paradoxical sleep (Nitz and Siegel, 1997b) and that the local infusion of the GABA receptor antagonist picrotoxin reduces the duration of paradoxical sleep phases (Kaur et al., 1997). It is noteworthy that the locus coeruleus and the dorsal raphe nucleus have been shown to be permissive structures for paradoxical sleep appearance (Hobson et al., 1975). However, partial results involving only few cells show that neurons of the locus coeruleus are able to fire without suppressing paradoxical sleep (Gervasoni et al., 1998) as can dorsal raphe nucleus neurons in the normal animal (Gervasoni et al., 2000) or in the cat with abolition of paradoxical sleep atonia (by pontine lesions) (Trulson et al., 1981). These data strongly suggest that the GABAergic inhibition of one of these neuron areas is sufficient for the appearance of this sleep stage. It should be noted that, for the raphe nucleus, the inhibition of serotonergic neuron firing during paradoxical sleep could be partly consecutive to disfacilitation of serotonergic neurons (Levine and Jacobs, 1992; Sakai and Crochet, 2000). At the level of the medulla itself, which plays an important role in processes inducing slow-wave sleep (Batini et al., 1958; Magnes et al., 1961; Bonvallet and

Allen, 1963) and paradoxical sleep (Webster et al., 1986; Vanni-Mercier et al., 1991; Gottesmann et al., 1995; Jouvet et al., 1995), there are GABAergic interneurons. These 'could ... be responsible for the inhibition of paradoxical sleep-off cells presumed to be in part serotonergic or (indirectly for) the disinhibition of paradoxical sleep-on cells, presumed to be in part cholinergic' (Holmes et al., 1994; Holmes and Jones, 1994).

Barbiturate binding site

Barbiturates stimulate α1 and β1 sites and favor the binding of GABA. 'At higher doses, barbiturate molecules can activate the chloride channel directly, in the absence of GABA' (Möhler, 1992). Barbiturates (synthesized in 1862) have long been known to induce sleep and they have had clinical applications since 1903. They promote slow-wave sleep and inhibit paradoxical sleep (with a rebound effect) (Oswald, 1968). However, in rats (Gottesmann, 1964, 1996) and cats (Gottesmann et al., 1995; Gottesmann, 1996) these first-generation hypnotics, at low and medium doses, massively extend the 'intermediate stage' (Gottesmann, 1967, 1972), the turning point at the junction of slow-wave sleep and paradoxical sleep. This stage, also identified in mice (Glin et al., 1991), is characterized by high-amplitude cortical spindles and a low-frequency hippocampal theta rhythm. Several arguments suggest that it corresponds to a transient disconnection of the forebrain from the brainstem, thus constituting a physiological cerveau isolé stage (Bremer, 1935). Indeed, the thalamic responsiveness which is controlled by midbrain facilitating influences (Dumont and Dell, 1958; Steriade, 1970) is the lowest of all sleep–waking stages (Gandolfo et al., 1980) and intercollicular transections induce a continuous intermediate stage in rats (Gottesmann et al., 1980) and cats (Gottesmann et al., 1984). Finally, barbiturates suppress pontine activation responsible for the central and peripheral characteristics of paradoxical sleep (Gottesmann, 1967, 1969, 1996). Consequently, stimulation of the barbiturate binding site inhibits the midbrain as well as the pontine and mesopontine reticular core responsible for waking (Moruzzi and Magoun, 1949; Steriade, 1996) and paradoxical sleep (Jouvet and Mounier, 1960; Sakai, 1988; Datta and Siwek, 1997) respectively.

Benzodiazepine binding site

In 1971 the era of benzodiazepines came fully into being with flurazepam (Mitler, 2000). The binding site of benzodiazepines on the $GABA_A$ receptor complex 'is distinct, but is nonetheless functionally coupled with the $GABA_A$ binding site and they regulate each other in an allosteric manner. Benzodiazepine agonists enhance the affinity of GABA for its receptor and hence its inhibitory function. Similarly, GABA (or $GABA_A$ receptor agonists, like muscimol) increases the affinity of benzodiazepine agonists for their receptor' (Sadzot and Frost, 1990). However, it is worth mentioning two studies which show that there is no potentiation of sleep by stimulation of the $GABA_A$ and benzodiazepine binding sites (Mendelson and Martin, 1990; Lancel et al., 1997a). The stimulation of the benzodiazepine binding site promotes slow-wave sleep in humans, particularly stage II (with spindle enhancement) at the expense of stages III and IV, and inhibits paradoxical sleep (and its eye movements) (Gaillard et al., 1973; Monti and Altier, 1973; Borbely et al., 1985; Mendelson and Martin, 1990; Lancel et al., 1996a). In animals most benzodiazepines, like barbiturates, increase the intermediate stage and decrease or suppress paradoxical sleep (Gandolfo et al., 1994), except for midazolam which increases both the intermediate stage and paradoxical sleep in rats at 1 and 3 mg/kg injected i.p. (Gandolfo et al., 1994) and increases paradoxical sleep in rabbits at 1 mg/kg injected i.v. (Scherschlicht and Marias, 1983), while Lancel et al. (1996a) found a decrease of paradoxical sleep at 3 mg/kg i.p. in rats. At the central level, benzodiazepines injected in the dorsal raphe nucleus increase waking (Mendelson et al., 1987); this result recalls the insomnia induced by raphe nucleus lesion in cats (Jouvet and Renault, 1966).

New-generation hypnotics

The third generation of sedative-hypnotic compounds comprises principally the imidazopyridines (zolpidem) and the cyclopyrrolones (zopiclone) which also bind to the $GABA_A$ receptor complex. Zolpidem (Depoortere et al., 1986), which binds to α1, β2, γ2 subunits with a preference for the γ2L variant (Duncan et al., 1995), induces sleep at much lower doses than benzodiazepines (Depoortere et al., 1986). It reduces sleep latency in humans (Lund et al., 1988; Declerck et al., 1992), but does not induce significant changes in night sleep distribution although there is a decrease of EEG low frequency bands (≤10 Hz), an enhancement of the frequency range of spindles (Lancel and Steiger, 1999) and a decrease of paradoxical sleep (Brunner et al., 1991; Declerck et al., 1992). In rats, zolpidem increases slow-wave sleep (Depoortere et al., 1995), and decreases paradoxical sleep during the first 2 h (Gottesmann et al., 1994) but not on a 6-h recording (Gottesmann et al., 1994; Depoortere et al., 1995). Zopiclone (Stutzmann et al., 1993) acts as a partial agonist at the benzodiazepine receptor level (Concas et al., 1994). 'The differences between zopiclone and the classical benzodiazepines that have been reported previously must be due to distinct interactions of these ligands with recognition site domains other than that represented by histidine 101' (Davies et al., 2000). It reduces sleep latency in humans, decreases stage I, increases stage II, has almost no effect on stages III and IV and reduces paradoxical sleep (Stutzmann et al., 1993; Lancel and Steiger, 1999). In rats, it also decreases sleep latency and increases the latency of the intermediate stage and paradoxical sleep. This last stage is decreased by up to 6 h, but the intermediate stage is never increased as is observed under barbiturates and most benzodiazepines (Gauthier et al., 1997a,b; Gottesmann et al., 1998).

Steroid binding site

Only a few studies have been specifically devoted to the steroid binding site for sleep mechanisms. It is well known that pregnancy is often associated with sleepiness and a tendency to increased daily sleeping time. Lancel et al. (1997b) studied allopregnanolone, which is a neuroactive steroid, and Edgar et al. (1997) studied pregnanolone, another neuroactive steroid, and an active analogue of it. They induced an increase in slow-wave sleep, allopregnanolone decreasing the EEG slow frequencies ($\leq$7 c/s) and increasing the spindle frequencies ($\geq$13 c/s). A steroid precursor, pregnenolone, did not change the sleep–waking cycle distribution but promoted the cortical slow waves (0.5–4 c/s) within slow-wave sleep (Lancel et al., 1994). However, studying the influence of progesterone and allopregnanolone with more detailed sleep stages, Lancel et al. (1996b, 1997b) were able to observe a pronounced increase in the intermediate stage and a decrease of paradoxical sleep with progesterone. This effect could be related to the bioconversion (of progesterone) into neuroactive metabolites (Lancel, 1999) like allopregnanolone and, to a lesser extent, pregnanolone.

Consequently, all agonists of $GABA_A$ receptor binding sites (except the picrotoxin binding site) favor sleep, although physiological sleep is better respected only with third generation hypnotics.

$GABA_B$ RECEPTORS

These receptors are involved in sleep–waking regulation as shown by lethargic (*lh/lh*) mice which have increased numbers of $GABA_B$ receptors in the cortex and thalamus (Lin et al., 1993, 1995). Moreover, $GABA_B$ receptor antagonists infused in the thalamus decrease EEG slow waves and deep slow-wave sleep while light slow-wave sleep is increased (Juhasz et al., 1994). These compounds are used to alleviate absence-epilepsy in humans (Marescaux et al., 1992; Bittinger et al., 1993) partly because of their thalamic impact on relay and reticular nuclei (Lin et al., 1992), this brain level having the highest number of $GABA_B$ receptors (Crunelli and Leresche, 1991). At this level, the reduction of $GABA_A$ receptor-mediated inhibition markedly enhances $GABA_B$ receptor inhibitory postsynaptic potentials in relay cells (Krosigk et al., 1993). Sleep studies were also undertaken in humans. Guilleminault and Flagg (1984), in a double-blind study, found a dose-related increase in slow-wave sleep and a reduction of paradoxical sleep with the agonist baclofen, while Finnimore et al. (1995) observed an increase in both slow-wave sleep and paradoxical sleep. In rats the receptor antagonist (CGP 35348) increased slow-wave sleep and paradoxical sleep in one study (Puigcerver et al., 1996) and increased waking and paradoxical sleep in another (Gauthier et al., 1997a,b). The findings of the last study are more in accordance with expected physiological results since these two behavioral stages are characterized by activation of the midbrain (Moruzzi and Magoun, 1949; Steriade, 1996) and pons (Gottesmann, 1967, 1969; McCarley and Hobson, 1971; McGinty et al., 1974; Moroz et al., 1977; Vertes, 1977). In the same way, phaclofen, another antagonist, increased paradoxical sleep when infused in the pontine reticular oralis nucleus of the cat, while waking and slow-wave sleep were not affected (Xi et al., 2001).

The study of these agonists and antagonists of the $GABA_B$ receptor confirms the sleep-inducing properties of this receptor.

$GABA_C$ RECEPTORS

Hitherto, it has been difficult to study the influence of the $GABA_C$ receptor on behavior since the agonist *trans*-4-aminocrotonic acid (TACA) and its *cis*-enantiomer CACA, the first compounds acting on this receptor to be identified, were not specific, like the first antagonists (Bormann and Feigenspan, 1995; Quian and Dowling, 1996). However, in 1996 the first selective antagonist was uncovered: (1,2,5,6-tetrahydropyridine)-methylphosphonic acid (TPMPA) (Murata et al., 1996; Ragozzino et al., 1996).

The first results show that GABA acting at these receptors is also involved in sleep–waking regulation. Indeed, TPMPA increases both quiet and active waking (with hippocampal theta rhythm), decreases total slow-wave sleep, essentially by decreasing the slow-wave stage (spindles and the intermediate stage are not significantly modified), and also decreases paradoxical sleep (Arnaud et al., 2001).

Regarding the decrease in paradoxical sleep, there are conflicting results with compounds acting on $GABA_A$ and $GABA_B$ receptors. It can be hypothesized that the decrease in this sleep stage induced by the $GABA_C$ receptor antagonist is related to corresponding receptors located at the neuron level in the dorsal raphe and locus coeruleus nuclei (Nitz and Siegel, 1997a,b; Gervasoni et al., 1998, 2000). Their blockade may induce a disinhibition of monoaminergic influences antagonistic to this sleep stage (and otherwise favoring waking; Berlucchi, 1997). The contradictory result obtained with $GABA_A$ and $GABA_B$ receptor acting compounds seems to be linked to an inhibition of paradoxical executive processes (Gottesmann, 1967, 1969, 1996; McCarley and Hobson, 1971; Sakai, 1988; Xi et al., 1999b, 2001).

CONCLUSION

The three currently identified GABA receptors have similar hypnotic effects when stimulated. Some differences appear when the quality of sleep is examined. Slow-wave sleep is enhanced in all cases. It can be strongly hypothesized that when antagonists promote waking, agonists, where available, will increase sleep. The intermediate stage is extended at the expense of paradoxical sleep by barbiturates, most benzodiazepines and steroids but not by new-generation hypnotics. $GABA_B$ and $GABA_C$ receptor antagonists used so far are not appropriate compounds for the study of this

effect on the intermediate stage, because of its natural shortness; specific agonists would be more appropriate. Finally, paradoxical sleep is decreased by agonistic modulators of $GABA_A$ receptors, and increased by $GABA_B$ receptor antagonists – parallel results – whereas the first available $GABA_C$ receptor antagonist decreases this sleep stage. Altogether, these results show the complexity and richness of brain regulation processes and could explain why a global *in vivo* increase in extracellular GABA by various methods leads to different results.

It seems probable that future research will be directed towards $GABA_C$ receptors which could have an important function in global behavior organization. Indeed, they are more sensitive to GABA than $GABA_A$ and $GABA_B$ receptors and their desensitization is much slower (Chebib and Johnston, 1999; Bormann, 2000). Thus, low concentrations of GABA should act preferentially on $GABA_C$ receptors. To speculate somewhat, specific agonists, when identified, could be useful compounds in clinical use as hypnotics and perhaps anti-epileptics, with fewer side effects than current medications. It is also not excluded that antagonists could be effective on narcoleptic attacks since there is GABAergic participation in recent molecules which relieve this disease (Lin et al., 2000).

NOTE ADDED IN PROOF

Kauer et al. (2001) confirmed that the medulla prepositus hypoglossi nucleus regulates paradoxical sleep by GABAergic neurons which inhibit locus coeruleus neurons.

Acknowledgements—I thank Professor G. Morgan for correction of the English.

REFERENCES

Arnaud, C., Gauthier, P., Gottesmann, C., 2001. Study of a $GABA_C$ receptor antagonist on sleep–waking behavior in rats. Psychopharmacology 154, 415–419.

Barnard, E.A., Skolnick, P., Olsen, R.W., Mohler, H., Sieghart, W., Bioggio, G., Braestrup, C., Bateson, A.N., Langer, S.Z., 1998. International union of Pharmacology. XV. Subtypes of γ-aminobutyric $acid_A$ receptors: Classification on the basis of subunit structure and receptor function. Pharmacol. Rev. 50, 291–313.

Batini, C., Moruzzi, G., Palestini, M., Rossi, G.F., Zanchetti, A., 1958. Persistent patterns of wakefulness in the pretrigeminal midpontine preparation. Science 128, 30–32.

Berlucchi, G., 1997. One or many arousal systems? Reflection on some of Giuseppe Moruzzi's foresights and insights about the intrinsic regulation of brain activity. Arch. It. Biol. 135, 5–14.

Bittinger, H., Froestl, W., Mickel, S.J., Olpe, H.R., 1993. $GABA_B$ receptor antagonists: from synthesis to therapeutic applications. Trends Pharmacol. Sci. 14, 391–394.

Bonvallet, M., Allen, M.B., 1963. Prolonged spontaneous and evoked reticular activation following discrete bulbar lesions. Electroencephalogr. Clin. Neurophysiol. 15, 969–988.

Borbely, A.A., Mattmann, P., Loepfe, M., Strauch, I., Lehman, D., 1985. Effect of benzodiazepine hypnotics on all-night sleep. EEG spectra. Hum. Neurobiol. 4, 189–194.

Bormann, J., 2000. The 'ABC' of GABA receptors. Trends Pharmacol. Sci. 21, 16–19.

Bormann, J., Feigenspan, A., 1995. $GABA_C$ receptors. Trends Neurosci. 18, 515–518.

Boue-Grabot, E., Taupignon, A., Tramu, G., Garre, M., 2000. Molecular and electrophysiological evidence for a GABAC receptor in therotropin-secreting cells. Endocrinology 141, 1627–1632.

Bremer, F., 1935. Cerveau 'isolé' et physiologie du sommeil. C.R. Soc. Biol. 118, 1235–1241.

Bremer, F., 1973. Preoptic hypnogenic area and reticular activating system. Arch. It. Biol. 111, 85–111.

Brunner, D.P., Diik, D.J., Münch, M., Borbely, A.A., 1991. Effect of zolpidem on sleep and sleep EEG spectra in healthy young men. Psychopharmacology 104, 1–5.

Bubnoff, N., Heidenhain, R., 1881. Ueber Erregungs-Hemmungsvorgänge innerhalb der motorischen Hirncentren. In: Pflüger, E.F.W. (Ed.), Arch. Gesam. Physiol. Emil Strauss Verlag, Bonn, pp. 137–202.

Camacho-Arroyo, I., Alvarado, R., Manjarrez, J., Tapia, R., 1991. Microinjections of muscimol and bicuculline into the pontine reticular formation modify the sleep–waking cycle in the rat. Neurosci. Lett. 129, 95–97.

Chebib, M., Johnston, G.A.R., 1999. The 'ABC' of GABA receptors: a brief review. Clin. Exp. Pharmacol. Physiol. 26, 937–940.

Chu, D.C.M., Albin, R.L., Young, A.B., Penney, J.B., 1990. Distribution and kinetics of GABAB binding sites in rat central nervous system: a quantitative autoradiographic study. Neuroscience 34, 341–357.

Cirelli, C., Pompeiano, M., Arrighi, P., Tononi, G., 1995. Sleep–waking changes after c-*fos* antisense injections in the medial preoptic area. NeuroReport 6, 801–805.

Concas, A., Serra, M., Santoro, G., Maciocco, E., Cuccheddu, T., Biggio, G., 1994. The effect of cyclopyrrolones on GABAA receptor function is different from that of benzodiazepines. Naunyn Schmiedeberg's Arch. Pharmacol. 350, 294–300.

Creutzfeldt, O., Baumgartner, G., Schoen, L., 1956. Reaktionen einzelner Neurons des senso-motorischen Cortex nach elektrischen Reizen. I Hemmung und Erregung nach direkten und contralateralen Einzelreizen. Arch. Psychiat. Nervenkrankh. 194, 597–619.

Crunelli, V., Leresche, N., 1991. A role of $GABA_B$ receptors in excitation and disinhibition of thalamocortical cells. Trends Neurosci. 14, 16–21.

Datta, S., Siwek, D.F., 1997. Excitation of the brain stem pedunculopontine tegmentum cholinergic cells induces wakefulness and REM sleep. J. Neurophysiol. 77, 2975–2988.

Davies, M., Newell, J.G., Derry, J.M.C., Martin, I.L., Dunn, S.M., 2000. Characterization of the interaction of zopiclone with γ-aminobutyric acid type A receptors. Mol. Pharmacol. 58, 756–762.

Declerck, A.C., Ruwe, F., O'Hanlon, J.F., Wauquier, A., 1992. Effects of Zolpidem and flunitrazepam on nocturnal sleep of women subjectively complaining of insomnia. Psychopharmacology 106, 497–501.

Depoortere, H., Françon, D., van Luijtelaar, E.L.J.M., Drinkenburg, W.H.I.M., Coenen, A.M.L., 1995. Differential effects of midazolam and zolpidem on sleep–wake states and epileptic activity in WAG/Rij rats. Pharmacol. Biochem. Behav. 51, 571–576.

Depoortere, H., Zivkovic, B., Lloyd, K.G., Sanger, D.J., Perrault, G., Langer, S.Z., Bartholini, G., 1986. Zolpidem, a novel nonbenzodiazepine hypnotic. I. Neuropharmacological and behavioral effects. J. Pharmacol. Exp. Ther. 237, 649–658.

Drew, C.A., Johnston, G.A.R., Weatherby, R.P., 1984. Bicuculline insensitive GABA receptors: studies on the binding of (−)-baclofen to rat cerebellar membranes. Neurosci. Lett. 52, 317–321.
Dumont, S., Dell, P., 1958. Facilitations spécifiques et non spécifiques des réponses visuelles corticales. J. Physiol. (Paris) 50, 261–264.
Duncan, G.E., Breese, G.R., Criswell, H.E., Mccown, T.J., Herbert, J.S., Devaud, L.L., Morrow, A.L., 1995. Distribution of (^{3}H) zolpidem binding sites in relation to messenger RNA encoding the α1, β2 and γ2 subunits of $GABA_A$ receptors in rat brain. Neuroscience 64, 1113–1128.
Edgar, D.M., Seidel, W.F., Gee, K.W., Lan, N.C., Field, G., Xia, H., Hawkinson, J.E., Wieland, S., Carter, R.B., Wood, P.L., 1997. CCD-3693: An orally bioavailable analog of the endogenous neuroactive steroid, pregnanolone, demonstrates potent sedative hypnotic actions in the rat. J. Pharmacol. Exp. Ther. 282, 420–429.
Ennis, M., Aston-Jones, G., 1989. Potent inhibition input to the locus coeruleus from the nucleus prepositus hypoglossi. Brain Res. Bull. 22, 793–803.
Evarts, E.V., Fleming, T.C., Huttenlocher, P.R., 1960. Recovery cycle of visual cortex of the awake and sleeping cat. Am. J. Physiol. 199, 373–376.
Faulhaber, J., Steiger, A., Lancel, M., 1997. The $GABA_A$ agonist THIP produces slow wave sleep and reduces spindling activity in NREM sleep in humans. Psychopharmacology 130, 285–291.
Feigenspan, A., Wässle, H., Bormann, J., 1993. Pharmacology of GABA receptor Cl^- channels in rat retinol bipolar cells. Nature 361, 159–162.
Fink-Jensen, A., Suzdak, P.D., Sweberg, M.B.D., Judge, M.E., Hansel, L., Nielsen, P.G., 1992. The GABA uptake inhibitor triagabine increases extracellular brain levels of GABA in awake rats. Eur. J. Pharmacol. 220, 197–201.
Finnimore, A.J., Roebuck, M., Sajkow, D., Mcevoy, R.D., 1995. The effect of the GABA agonist, baclofen, on sleep and breathing. Eur. Resp. 8, 230–234.
Ford, B., Holmes, C.J., Mainville, L., Jones, B.E., 1995. GABAergic neurons in the rat pontomesencephalic tegmentum: codistribution with cholinergic and other tegmental neurons projecting the posterior lateral hypothalamus. J. Comp. Neurol. 363, 177–196.
Gaillard, J.M., Schultz, P., Tissot, R., 1973. Effects of three benzodiazepines (nitrazepam, flunitrazepam and bromazepam) on sleep of normal subjects, studied with an automatic scoring system. Pharmakopsychiatrie 6, 207–217.
Gallopin, T., Fort, P., Eggermann, E., Caul, B., Luppi, P.H., Rossier, J., Audinat, E., Mühlethaler, M., Serafin, M., 2000. Identification of sleep-promoting neurons *in vitro*. Nature 404, 922–995.
Gandolfo, G., Arnaud, C., Gottesmann, C., 1980. transmission in the ventrobasal complex of rats during the sleep–waking cycle. Brain Res. Bull. 5, 553–562.
Gandolfo, G., Scherschlicht, R., Gottesmann, C., 1994. Benzodiazepines promote the intermediate stage at the expense of paradoxical sleep in the rat. Pharmacol. Biochem. Behav. 49, 921–927.
Gauthier, P., Arnaud, C., Gottesmann, C., 1997a. Influence of a $GABA_B$ receptor antagonist on sleep–waking cycle in the rat. Brain Res. 773, 8–14.
Gauthier, P., Arnaud, C., Stutzmann, J.M., Gottesmann, C., 1997b. Influence of zopiclone, a new generation hypnotic, on the intermediate stage and paradoxical sleep in the rat. Psychopharmacology 130, 139–143.
Gervasoni, D., Darracq, L., Fort, P., Soulière, F., Chouvet, G., Luppi, P.H., 1998. Electrophysiological evidence that noradrenergic neurons of the locus coeruleus are tonically inhibited by GABA during sleep. Eur. J. Neurosci. 10, 964–970.
Gervasoni, D., Peyron, C., Barbagli, B., Chouvet, G., Urbain, N., Fort, P., Luppi, P.H., 2000. Role and origin of the GABAergic innervation of dorsal raphe serotonergic neurons. J. Neurosci. 20, 4217–4225.
Glin, L., Arnaud, C., Berracochea, D., Galey, D., Jaffard, R., Gottesmann, C., 1991. The intermediate stage of sleep in mice. Physiol. Behav. 50, 951–953.
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., 1967. Recherche sur la psychophysiologie du sommeil chez le Rat. Presses du Palais-Royal, Paris (discussion and summary in English).
Gottesmann, C., 1969. Etude sur les activités électrophysiologiques phasiques chez le Rat. Physiol. Behav. 4, 495–504.
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., Gandolfo, G., Arnaud, C., Gauthier, P., 1998. The intermediate stage and paradoxical sleep in the rat: influence of three generations of hypnotics. Eur. J. Neurosci. 10, 409–414.
Gottesmann, C., Gandolfo, G., Zernicki, B., 1984. Intermediate stage of sleep in the cat. J. Physiol. (Paris) 79, 365–374.
Gottesmann, C., Gandolfo, G., Zernicki, B., 1995. Sleep–waking cycle in chronic rat preparation with brain stem transected at the caudopontine level. Brain Res. Bull. 36, 573–580.
Gottesmann, C., Trefouret, S., Depoortere, H., 1994. Influence of Zolpidem, a novel hypnotic, on the intermediate stage and paradoxical sleep in the rat. Pharmacol. Biochem. Behav. 47, 359–362.
Gottesmann, C., User, P., Gioanni, H., 1980. Sleep: a physiological 'cerveau isolé' stage? Waking Sleep 4, 111–117.
Gritti, I., Mainville, L., Jones, B.E., 1994. Projections of GABAergic and cholinergic basal forebrain and GABAergic preoptic-anterior hypothalamic neurons to the posterior lateral hypothalamus of the rat. J. Comp. Neurol. 339, 251–268.
Guilleminault, C., Flagg, W., 1984. Effect of baclofen on sleep related periodic limb movements. Ann. Neurol. 15, 234–239.
Hess, W.R., 1931. Le sommeil. C.R. Soc. Biol. 107, 1333–1364.
Hill, D.R., Bowery, N.G., 1981. ^{3}H-baclofen and ^{3}H-GABA bind to bicuculline insensitive $GABA_B$ sites in rat brain. Nature 290, 149–152.
Hobson, J.A., McCarley, R.W., Wyzinski, P.W., 1975. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 189, 55–58.
Holmes, C.J., Jones, B.E., 1994. Importance of cholinergic, GABAergic, serotonergic and other neurons in the medial medullary reticular formation for sleep–wake states studied by cytotoxic lesions in the cat. Neuroscience 62, 1179–1200.
Holmes, C.J., Mainville, L.S., Jones, B.E., 1994. Distribution of cholinergic, GABAergic and serotonergic neurons in the medial medullary reticular formation and their projections studied by cytotoxic lesions in the cat. Neuroscience 62, 1155–1178.
Holmes, S.W., Sugden, D., 1975. The effects of GABAtransaminase (GABA-T) inhibition on sleep and behavior of the cat. Sleep Res. 4, 78.
Ijima, K., Ohtomo, K., 1988. Immunocytochemical study using a GABA antiserum for the demonstration of inhibitory neurons in the rat locus coeruleus. Am. J. Anat. 181, 43–52.
Johnston, G.A.R., Curtis, D.R., Beart, P.M., Game, C.J.A., McCulloch, R.M., Twitclin, B., 1975. Cis-and trans-4-aminocrotonic acid as GABA analogues of restricted conformation. J. Neurochem. 24, 157–160.
Jouvet, M., Buda, C., Sastre, J.P., 1995. Existe-t-il un pacemaker bulbaire responsable du rythme ultradien du sommeil paradoxal? Arch. It. Biol. 134, 39–56.
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., Renault, J., 1966. Insomnie persistante après lésions des noyaux du raphé chez le Chat. C.R. Soc. Biol. 160, 1461.

Juan de Mendoza, J.L., Gauthier, P., Rodi, M., Roux, R., Gottesmann, C., 1973. Influence de l'élévation du taux de l'acide gamma-amino-butyrique dans le système nerveux central sur les différentes phases du cycle veille-sommeil chez le Rat. C.R. Soc. Biol. 167, 73–80.
Juhasz, G., Emri, Z., Kékesi, K.A., Salfay, O., Grunelli, V., 1994. Blockade of thalamic $GABA_B$ receptors decreases EEG synchronization. Neurosci. Lett. 172, 155–158.
Karadzic, V., 1966. Effect of raised levels of gamma-aminobutyric acid in the central nervous system on sleep phases in the cat. Acta Med. Jugosl. 20, 282–290.
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 paradoxical sleep by its action on locus coeruleus in freely moving rats. Synapre 42, 141–150.
Krnjevic, K., Randic, M., Straughan, D.W., 1966. Pharmacology of cortical inhibition. J. Physiol. (London) 184, 78–105.
Krosigk, M., von Bal, T., McCormick, D.A., 1993. Cellular mechanisms of a synchronized oscillation in the thalamus. Science 261, 361–364.
Lancel, M., 1997. The $GABA_A$ agonist THIP increases non-REM sleep and enhances non-REM sleep-specific delta activity in the rat during dark period. Sleep 20, 1099–1104.
Lancel, M., 1999. Role of GABAA receptors in the regulation of sleep: initial sleep responses to peripherally administered modulators and agonists. Sleep 22, 33–42.
Lancel, M., Crönlein, T.A.M., Preuss, P., Holsboer, F., 1994. Pregnenolone enhances EEG delta activity during non-rapid eye movement sleep in the rat, in contrast to midazolam. Brain Res. 646, 85–94.
Lancel, M., Faulhaber, J., Deisz, R.A., 1998. Effect of the GABA uptake inhibition triagabine on sleep and EEG power spectra in the rat. Br. J. Pharmacol. 123, 1471–1477.
Lancel, M., Faulhaber, J., Holsboer, F., Ruppert, R., 1996b. Progesterone induces changes in sleep comparable to those of agonists $GABA_A$ receptor modulations. Am. J. Physiol. 34, E763–E772.
Lancel, M., Faulhaber, J.M., Schiffelholz, T., Mathias, S., Deisz, R.A., 1997a. Muscimol and midazolam do not potentiate each other's effects on sleep EEG in the rat. J. Neurophysiol. 77, 1624–1629.
Lancel, M., Faulhaber, J., Schiffelholz, T., Romeo, E., di Michele, D., Holsboer, F., Ruppecht, R., 1997b. Allopregnanolone affects sleep in a benzodiazepine-like fashion. J. Pharmacol. Exp. Ther. 282, 1213–1218.
Lancel, M., Grönlein, T.A.M., Faulhaber, J., 1996a. Role of $GABA_A$ receptors in sleep regulation. Differential effects of muscimol and midazolam on sleep in rats. Neuropsychopharmacology 15, 63–74.
Lancel, M., Steiger, A., 1999. Sleep and its modulation by drugs that affect $GABA_A$ receptor function. Angew. Chem. Int. Ed. 111, 2852–2864.
Levine, E.S., Jacobs, B.L., 1992. Neurochemical afferents controlling the activity of serotonergic neurons in the dorsal raphe nucleus: micro-iontophoretic studies in the awake cat. J. Neurosci. 12, 4037–4044.
Lin, F.H., Cao, Z., Hosford, D.A., 1993. Increased number of $GABA_B$ receptors in the lethargic (*lh*/*lh*) mouse model of absence epilepsy. Brain Res. 608, 101–106.
Lin, F.H., Wang, Y., Lin, S., Cao, Z., Hosford, D.A., 1995. $GABA_B$ receptor-mediated effects in synaptosomes of lethargic (*lh*/*lh*) mice. J. Neurochem. 65, 2087–2095.
Lin, J.S., Gervasoni, D., Hou, Y., Vanni-Mercier, G., Rambert, F., Frydman, A., Jouvet, M., 2000. Effects of amphetamine and modafinil on the sleep–wake cycle during experimental hypersomnia induced by sleep deprivation in the cat. J. Sleep Res. 9, 89–96.
Lin, J.S., Sakai, K., Vanni-Mercier, G., Jouvet, M., 1989. A critical role of the posterior hypothalamus in the mechanisms of wakefulness determined by microinjection of muscimol in freely moving cats. Brain Res. 479, 225–240.
Lin, J.S., Yao, Y.Z., Parmentier, R., Sakai, K., Vanni-Mercier, G., Jouvet, M., 1999. Importance of histaminergic ascending projections in cortical activation demonstrated with H_1 and H_3 receptor ligands and C-Fos labeling in mesencephalic cats. Sleep Res. Online 2 (Suppl. 1), 54.
Lin, Z., Vergnes, M., Depaulis, A., Marescaux, C., 1992. Involvement of intrathalamic $GABA_B$ neurotransmission in the control of absence seizures in the rat. Neuroscience 48, 87–93.
Lund, R., Rüther, E., Wober, W., Hippius, H., 1988. Effects of Zolpidem (10 and 20 mg), lormetazepam, triazolam and placebo on night sleep and residual effects during the day. In: Sauvanet, J.P., Langer, S.Z., Morselli, P.L. (Eds.), Imidazopyridines in Sleep Disorders. Raven Press, New York, pp. 193–203.
Magnes, J., Moruzzi, G., Pompeiano, O., 1961. Synchronization of the EEG produced by low frequency electrical stimulation of the region of the solitary tract. Arch. It. Biol. 99, 33–67.
Mallick, B.N., Kaur, S., Jha, S., Siegel, J.M., 1999. 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.
Maloney, K.J., Mainville, L., Jones, B.E., 2000. c-Fos expression in GABAergic, serotonergic, and other neurons of the pontomedullary reticular formation and raphe after paradoxical sleep deprivation and recovery. J. Neurosci. 20, 4669–4679.
Marescaux, C., Vergnes, M., Bernasconi, R., 1992. $GABA_B$ receptor antagonists: potential new anti-absence drugs. J. Neural Transm. 35 (Suppl.), 179–187.
McCarley, R.W., Hobson, J.A., 1971. Single neuron activity in cat giganto cellular tegmental field: selectivity of discharge in desynchronized sleep. Science 174, 1250–1252.
McDonald, R.L., Olsen, R.W., 1994. $GABA_A$ receptor channels. Annu. Rev. Neurosci. 17, 569–602.
McGinty, D.J., 1969. Somnolence, recovery and hyposomnia following ventromedial diencephalic lesion in the rat. Electroencephalogr. Clin. Neurophysiol. 26, 70–79.
McGinty, D.J., Harper, R.M., Fairbank, M.K., 1974. Neuronal unit activity and the control of sleep states. In: Weitzmann, E. (Ed.), Advances in Sleep Research, Vol 1. Spectrum, New York, pp. 173–216.
Mendelson, W.B., Martin, J.V., 1990. Effects of muscimol and flurazepam on the sleep EEG in the rat. Life Sci. 47, PL99–PL101.
Mendelson, W.B., Martin, J.V., Perlis, M., Wagner, R., 1987. Arousal induced by injection of triazolam into the dorsal raphe nucleus of rats. Neuropsychopharmacology 1, 85–88.
Mitler, M.M., 2000. Nonselective and selective benzodiazepine receptor agonists – where are we today? Sleep 23 (Suppl. 1), S39–S47.
Möhler, H., 1992. GABAergic synaptic transmission. Regulation by drugs. Arzneim.-Forsch. Drug Res. 42, 211–214.
Möhler, H., Malherbe, P., Draguhn, A., Sigel, E., Sequier, J.M., Persohn, E., Richards, J.G., 1990. $GABA_A$-receptor subunits: functional expression and gene localisation. In: Biggio, G., Costa, E. (Eds.), GABA and Benzodiazepine Receptor Subtypes. Raven Press, New York, pp. 23–34.
Monti, J.M., Altier, H., 1973. Flunitrazepam (Ro 5-4200) and sleep cycle in normal subjects. Psychopharmacologia 32, 343–349.
Moroz, G., Foutz, A., Gottesmann, C., 1977. Paradoxical sleep and pontine activation in the rat. In: Koella, W.P., Levin, P. (Eds.), Sleep 1976. Karger, Basel, pp. 186–188.
Moruzzi, G., Magoun, H.W., 1949. Brain stem reticular formation and activation of the EEG. Electroencephalogr. Clin. Neurophysiol. 1, 455–473.

Murata, Y., Woodward, R.M., Miledi, R., Overman, L.E., 1996. The first selective antagonist for $GABA_C$ receptor. Bioorg. Med. Chem. Lett. 6, 2073–2076.
Nauta, W.J.H., 1946. Hypothalamic regulation of sleep in rats. J. Neurophysiol. 9, 285–316.
Nitz, D., Siegel, J., 1996. GABA release in posterior hypothalamus across sleep–wake cycle. Am. J. Physiol. 271, R1707–R1712.
Nitz, D., Siegel, J., 1997a. GABA release in the dorsal raphe nucleus: role in the control of REM sleep. Am. J. Physiol. 273, R451–R455.
Nitz, D., Siegel, J., 1997b. GABA release in the locus coeruleus as a function of sleep–wake state. Neuroscience 78, 795–801.
Ogawa, Y., Kawamura, H., 1988. Increase of multiple unit activity during slow wave sleep in the cat preoptic area. Brain Res. Bull. 20, 897–902.
Ogurusu, T., Eguchi, G., Schingai, R., 1997. Localization of γ-aminobutyric acid (GABA) receptor ρ3 subunit in rat retina. NeuroReport 8, 925–927.
Oswald, I., 1968. Drugs and sleep. Pharmacol. Rev. 20, 273–303.
Parades, R.G., Agmo, A., 1992. GABA and behavior: the role of receptor subtypes. Neurosci. Biobehav. Rev. 16, 145–170.
Puigcerver, A., van Luijtelaar, E.L.J.M., Drinkenburg, W.H.I., Coenen, A.L.M., 1996. Effects of the $GABA_B$ antagonist CGP 35348 on sleep–wake states, behavior and spike-wave discharges in old rats. Brain Res. Bull. 40, 157–162.
Quian, H., Dowling, J.E., 1994. Pharmacology of novel GABA receptors found on rod horizontal cells of the white perch retina. J. Neurosci. 14, 4299–4307.
Quian, H., Dowling, J.E., 1996. Selective agonists for $GABA_C$ receptors. Trends Neurosci. 19, 109.
Ragozzino, D., Woodward, R.M., Murata, Y., Eusebi, F., Overman, L.E., Miledi, R., 1996. Design an *in vitro* pharmacology of a selective γ-aminobutyric $acid_c$ receptor antagonist. Mol. Pharmacol. 50, 1024–1030.
Ranson, S.W., 1939. Somnolence caused by hypothalamic lesion in the monkey. Arch. Neurol. Psychiat. 41, 1–23.
Sadzot, B., Frost, J.J., 1990. Benzodiazepine receptors. In: Frost, J.J., Wagner, H.N. (Eds.), Quantitative Imaging: Neuroreceptors, Neurotransmitters and Enzymes. Raven Press, New York, pp. 109–127.
Sakai, K., 1988. Executive mechanisms of paradoxical sleep. Arch. It. Biol. 126, 239–257.
Sakai, K., Crochet, S., 2000. Serotonergic dorsal raphe neurons cease firing by disfacilitation during paradoxical sleep. NeuroReport 11, 3237–3241.
Sallanon, M., Denoyer, M., Kitahama, K., Aubert, C., Gay, N., Jouvet, M., 1989. Long-lasting insomnia induced by preoptic neuron lesions and its transient reversal by muscimol injection into the posterior hypothalamus in the cat. Neuroscience 32, 669–683.
Sastre, J.P., Buda, C., Kitahama, K., Jouvet, M., 1996. Importance of the ventrolateral region of the periaqueductal gray and adjacent tegmentum in the control of paradoxical sleep as studied by muscimol microinjections in the cat. Neuroscience 74, 415–426.
Sastre, J.P., Buda, C., Lin, J.S., Jouvet, M., 1999. Expression of the proto-oncogene c-fos in the cat brain after selective increase in paradoxical sleep, slow wave sleep and wake induced by unilateral microinjection of muscimol in the periaqueductal grey matter. Sleep Res. Online 2 (Suppl. 1), 77.
Scherschlicht, R., Marias, J., 1983. Effects of oral and intravenous midazolam, triazolam and flunitrazepam on the sleep–wakefulness cycle of rabbits. Br. J. Pharmacol. 16, 29S–35S.
Schmid, L., Bottlaender, M., Fuseau, C., Fournier, D., Brouillet, E., Mazière, M., 1995. Zolpidem displays heterogeneity in its binding to the nonhuman primate benzodiazepine receptor *in vivo*. J. Neurochem. 65, 1880–1886.
Schneider, E., Ziegler, B., Maxion, H., 1977. The influence of di-n-propylacetate acid on sleep in man. Eur. J. Pharmacol. 15, 146–152.
Sieghart, W., 1995. Structure and pharmacology of γ-aminobutyric $acid_A$ receptor subtypes. Pharmacol. Rev. 47, 181–234.
Steriade, M., 1970. Ascending control of thalamic and cortical responsiveness. Int. Rev. Neurobiol. 12, 87–144.
Steriade, M., 1996. Arousal: revisiting the reticular system. Science 272, 225–226.
Sterman, M.B., Clemente, C.D., 1962. Forebrain inhibitory mechanisms: cortical synchronization induced by basal forebrain stimulation in the behaving cat. Exp. Neurol. 6, 102–103.
Stutzmann, J.M., Delahaye, C., Alain, H., 1993. Zopiclone. Données de pharmacologie expérimentale et de clinique. Thérapie 48, 33–42.
Szymusiak, R., McGinty, D., 1986. Sleep-related neuronal discharge in the basal forebrain of cats. Brain Res. 370, 82–92.
Trulson, M.E., Jacobs, B.L., Morrison, A.R., 1981. Raphe unit activity during REM sleep in normal cats and in pontine lesioned displaying REM sleep without atonia. Brain Res. 226, 75–91.
Vanni-Mercier, G., Sakai, K., Lin, J.S., Jouvet, M., 1991. Carbachol microinjections in the mediodorsal pontine tegmentum are unable to induce paradoxical sleep after caudal pontine and prebulbar transections in the cat. Neurosci. Lett. 130, 41–45.
Vertes, R.P., 1977. Selective firing of rat pontine giganto cellular neurons during movement and REM sleep. Brain Res. 128, 146–152.
Von Economo, C., 1928. Théorie du sommeil. J. Neurol. Psychiat. 7, 437–464.
Webster, H.H., Friedman, L., Jones, B.E., 1986. Modification of paradoxical sleep following transections of the reticular formation at the pontomedullary junction. Sleep 9, 1–23.
Xi, M.C., Morales, F.R., Chase, M.H., 1999a. A GABAergic pontine reticular system is involved in the control of wakefulness and sleep. Sleep Res. Online 12, 43–48.
Xi, M.C., Morales, F.R., Chase, M.H., 1999b. Evidence that wakefulness and REM sleep are controlled by a GABAergic pontine mechanism. J. Neurophysiol. 82, 2015–2019.
Xi, M.C., Morales, F.R., Chase, M.H., 2001. Induction of wakefulness and inhibition of active (REM) sleep by GABAergic processes in the nucleus pontis oralis. Arch. It. Biol. 139, 125–145.

(*Accepted* 21 *January* 2002)