Brain Research Bulletin, Vol. 46, No. 3, pp. 189–197, 1998

0361-9230/98 $19.00 + .00

ELSEVIER

PII S0361-9230(98)00011-2

REVIEW ARTICLE

Defective inhibition of dream event memory formation: A hypothesized mechanism in the onset and progression of symptoms of schizophrenia

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[Received 16 July 1997; Revised 21 January 1998; Accepted 22 January 1998]

ABSTRACT: An average person normally spends at least 90 min to 2 h per night dreaming. Nevertheless, memories of dream events are not retrieved while awake unless the person awoke shortly after a dream. It is hypothesized here that schizophrenic delusions initially arise because a system that normally inhibits the formation of memories of dream events is defective. Therefore, memories of dream events or fragments would be occasionally made and placed in the normal memory store. The only reason that we really know anything happened to us in the past is that we have a memory of it, and having a memory of an event is sufficient to really believe it. Therefore, the schizophrenic would believe that the dream events actually happened. It is proposed that this is the basis of primary delusions. Because memories are represented by strengthened neural connections there will be an accumulation of connections that do not correspond to reality. This accumulation may account for other symptoms of schizophrenia such as thought disorder, loosening of associations, and hallucinations. The brain trying to draw conclusions from several memories may be the basis of secondary delusions. Evidence is presented for the ideas that primary delusions are due to memories of dream events, that a substance, with vasotocin-like bioactivity, is released in the brain during dreaming and inhibits memory formation, that the lateral habenula is a brain area involved in vasotocin actions and is affected by neuroleptics, and that brain mechanisms involved in vasotocin actions show pathological alterations in schizophrenia. © 1998 Elsevier Science Inc.

KEY WORDS: Dreams, Memory formation, Delusions, Schizophrenia, Vasotocin.

INTRODUCTION

The term schizophrenia comprises such a wide spectrum of disorders that no single etiology is likely to be responsible for all cases of the disease. Nevertheless, most diagnostic classification systems are in agreement that in many forms of this disorder delusions are a prominent symptom [46,74,80]. Here a hypothesized mechanism in the generation of delusions is presented, and its possible role in some other symptoms of schizophrenia is also discussed. In many cases delusions are an early symptom [12,72]. For example, the great clinician Eugen Bleuler [12] wrote ''the sudden appearance of sharply formulated ideas may be the first perceptible symptoms of the disease. Likewise delusions will often develop from the definite toward the indefinite and vague.'' (p. 134). In the present article, in accordance with many other authors [108,121], a distinction is made between primary and secondary delusions. As used here a primary delusion is defined as a strongly-held false belief that an event occurred that actually involved or was witnessed by the believer. Roberts [108] described it as ''the appearance in consciousness of a fully-formed belief without apparent antecedents.'' Sims [121] regarded it as synonymous with Wernicke's concept of the ''autochthonous idea,'' ''an idea which is 'native to the soil,' aboriginal, arising without external cause'' (p. 85), and indicated similarities to Jasper's concept of un-understandable delusions— unshakable beliefs that certain things happen to the believer that are ultimately not understandable to someone else. As examples were presented the beliefs of a middle-aged schizophrenic spinster that men unlock the door of her flat, anesthetize her and interfere with her sexually, and that the police were using rays to observe her. As used here secondary delusions are reasons worked out by the believer to explain events he believes he was actually involved in or witnessed. Many delusions involve considerable fantasy, such as some of those presented by Lehmann [72]. However, it is pertinent to note that more mundane delusions also occur. Thus, among the examples mentioned by Bleuler [12] are a woman who believed during her puberty ''that she had been engaged to a physician,'' a scientist who ''directs great battles and makes great inventions to honor his beloved,'' and a clerk who believed the Queen of The Netherlands—who had recently figured prominently in the news—wanted to marry him. Lehmann [72, p 1168] also describes a woman who in the early stages of schizophrenia became convinced that she was engaged to a man working in the same office. From personal experience the author is aware of examples such as a person who mentioned, in the course of a

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normal conversation, that by means of helicopters she was being watched by members of a student group she had once belonged to. Due to loss of contact it is not known whether this person became schizophrenic. Another person, at a time of problems with a loved one and on holiday in a foreign country, suddenly believed he was in danger in a war zone. This person was returned home, received neuroleptic treatment, and had no further delusions. The occurrence of such delusions in otherwise normal rational people suggests that delusions are an early symptom that may or may not progress to schizophrenia.

There are three fundamental questions from which the current hypothesis derives. The first is the question of how might such delusions arise. The second is the question of why similarities between schizophrenia and dreaming have been so frequently noted. The third is the question of the function of endogenous systems in the brain that inhibit memory formation.

In answer to these questions, it is hypothesized that one function of endogenous systems that inhibit memory formation is to inhibit the formation of memories of dream events. It is further hypothesized that in schizophrenia this function is defective with the result that memories of dream events are placed, at least occasionally, into the normal memory store. Having a memory that something happened to us is the only reason we really know that this event happened to us. Because having a memory of an event is sufficient for being really convinced that it happened, then the affected person would believe the dream event actually occurred, or in other words would hold a delusion. It is proposed that this mechanism accounts for at least some cases of primary delusions in schizophrenia. Because memories are believed to be represented by strengthened neural connections, then an accumulation of strengthened neural connections that do not correspond to reality could account for the loosening of associations and hallucinations of schizophrenia.

This hypothesis would be supported if a chemical existed that was released in the brain only during dreaming and that inhibited memory formation. According to the hypothesis, the mechanisms involved in the functioning of this chemical might be defective in schizophrenia. Indeed there already exists preliminary evidence that a substance with vasotocin-like bioactivity fits these criteria. This evidence is, therefore, presented together with other evidence supporting the hypothesis.

NORMAL MEMORIES OF DREAM EVENTS ARE NOT GENERALLY MADE

Since the discovery of rapid-eye-movement (REM) sleep [7,8, 32,33] it is well-established that in humans there are generally three to six periods of REM sleep per night and that subjects awakened during such periods are highly likely to report a vivid dream. When a subject is awakened during non-REM (NREM) sleep there is a much lower probability that the subject will report a dream. However, if, instead of being asked if he was dreaming, the subject is asked to report what was going through his head just before he was awakened then more reports of mental imagery are produced [47,130]. It is not presently unequivocal whether these reports are of thought-like nondream mentation, or if those reports obtained after the first REM period include mental imagery from preceding REM dreams, or if there are also actual realistic NREM dreams. A reasonable minimum estimate of the time spent dreaming per night is, therefore, the duration of REM sleep, generally 90 min to 2 h. Nevertheless, during waking a person generally cannot retrieve memories of dream events. When occasionally a dream is remembered on awakening it is thought that this is because the dream immediately preceded an awakening [24,55]. In this situation, presumably because of cues associated with the sleeping place, the person knows that the vivid short-term memory he has of events that happened only moments ago is a memory of a dream. What is proposed here as a basis of schizophrenic delusions is different. It is proposed simply that due to a neurochemical malfunction, a memory of a dream event or fragment may be made and placed in the normal memory store without any evidence that it is a memory of a dream. The affected person then treats this like any other memory in the memory store, which includes being able to retrieve it and believing it.

Here it is assumed that no long-term memories of dream events are normally made. It is possible, however, that memories of dream events are made and placed in a store that is accessible during dreaming, but not during waking. Such a mechanism provides one explanation of recurrent dreams; another is that the conditions that result in particular dreams persist. If indeed two memory stores exist, one for dreaming and the other for waking, then a failure to place a memory of dream events in the correct store could also be the basis of initial delusions.

SIMILARITY OF DREAMS AND DELUSIONS

If the dreams of people destined to become schizophrenic are similar to those who are not, and if those dreams for which the memory-inhibiting system fails do not differ systematically from the population of dreams as a whole, then the current hypothesis predicts some similarity between dream events and delusions. Although this topic has received no or little systematic scientific study, numerous authors have noted similarities between schizophrenia and dreaming. Moreover, relatively common schizophrenic delusions of being younger than one is and of being persecuted are consistent with the properties of dreams. First, we present some statements from respected sources concerning the similarity of dreams and schizophrenia. Some of the similarities observed by Eugen Bleuler are included in a recent review [116]. The most important primary symptom of schizophrenia for Bleuler was the loosening of associations and the generation of logically nonsensical connections like those that Freud had noted in dreams. In both dreams and the beliefs of schizophrenics there can exist, for example, the replacement of ideas by symbols and the condensation of many loved ones or places into the same scenario. C.G. Jung, the founder of Jungian psychotherapy, also noted the similarity of schizophrenia and dreaming as reflected in his oft-quoted statement ''Let the dreamer walk about and act like one awakened, and we have the clinical picture of dementia praecox'' [66, p 79]. The eminent neurologist Hughlings Jackson had earlier also suggested that for elucidating the science of insanity ''Dreaming is for such a purpose as important as any kind of insanity'' [133, p. 5]. Manfred Bleuler also has agreed with the experience of Eugen Bleuler and C.G. Jung that ''The day-and-night dreaming and the thinking revealed in free associations of the healthy proved identical in nature with schizophrenic thinking'' [13].

While it may be difficult experimentally to address the possible similarity of dreams and delusions, several fairly common delusions are consistent with the properties of dreams. One of these is the delusion of being younger than one is. This phenomenon has been called ''age disorientation,'' and is usually interpreted as a manifestation of schizophrenic cognitive impairment. However, the belief of being younger than one is, as a firmly-held false belief, is by definition a delusion and is considered as such here. Crow [26] has recently reviewed a number of studies indicating that this delusion is fairly common among hospitalized or chronic schizophrenics. In extending several early reports of the phenomenon [30,37,69,85], several more recent studies found that approximately 25% of hospitalized or chronic schizophrenics believe they are 5 or more years younger than they actually are [28,125,129].

Moreover, 9%–12% of the populations in these studies believed that their age was within 5 years of their age upon hospital admission, even though, in the study of Crow and Mitchell [28] for example, they were on average 28 years older. At least qualitatively it is possible that this age delusion stems from memories of dream events, because dreams of the past are quite common [36,60,130]. In one particularly long series of dream reports [126] the proportion of dreams exhibiting regression was fairly constant at 15%–40% over several decades with these dreams showing on average 8–21 years of regression. Moreover, dreams of traumatic events often occur in a recurrent fashion. Guerrero and Crocq [59], for example recently studied World War II veterans from Alsace-Lorraine who had been forcibly drafted into the German army and subsequently detained as prisoners of war in Russia. Eighty percent of respondents reported distressing dreams of wartime or captivity even 45 years after the events. Presumably the age of the dreamer in these dreams is that of the time of the dreamed-of event. This topic warrants direct investigation. Assuming it is correct, however, then erroneously-made memories of such dream events could be the basis of an age delusion. In that admission to a mental hospital or the events culminating in this are certainly also often traumatic it is, therefore, possible that memories of recurrent dream events could explain the marked age delusions of a proportion of schizophrenics.

Another class of delusions estimated to affect up to 40% of schizophrenics are the delusional misidentification syndromes, such as the Capgras syndrome and Frégoli syndrome, which share the common theme that persons have been replaced by others or can change into others [39,90,121]. It is tempting to attribute these to the approximately 1% of reported dreams [36,60] in which such metamorphoses occur.

Another common delusion in schizophrenia is of threat to the person or persecution. The fact that such delusions are common in schizophrenia is clear from the term ''paranoid schizophrenia,'' and they are actually the most common form of delusions [121]. In at least a qualitative way this is also consistent with the hypothesis that initial delusions may stem from memories of dream events. For example, in a sample of college students the most common theme of recurrent dreams was of being threatened or pursued [107]. The occurrence of this theme is increased by stress. Thus, 86% of a sample of women undergoing a stressful event of divorce, reported in a single night at least one dream involving threat. Even in the comparison group, not involved in divorce, 56% of the sample reported at least one such dream, and in about one-half of these dreams the threat was directed at the dreamer [134]. Because stress is a precipitating factor in schizophrenia, dreams of threat to the self are probably common in those who become schizophrenic.

These similarities of dreams and delusions support the present hypothesis. Moreover, in support of some disturbance in the inhibition of dream event memory formation at disease onset, Bleuler [12] has noted that ''Before the actual onset of the disease, the patients frequently complain about disturbing dreams which keep haunting them during their waking hours.'' (p. 253). This observation is consistent with an impaired inhibition of formation of memories of dream events, such that dream memories are stronger and even those that are recognized as dreams exert more influence on waking behavior. Similar to this observation of Bleuler, it has been noted in the progression of drug-induced psychosis in Parkinson's disease patients treated with dopaminomimetic drugs, that abnormal dreaming and sleep disturbance often precede other symptoms of psychosis by weeks to months [41].

REM SLEEP AND SCHIZOPHRENIA

There have been numerous studies of REM sleep and schizophrenia. The major conclusion from such studies is that the continuity of sleep is disturbed, whereas the proportion of REM sleep is constant [132]. An early study of Rechtschaffen et al. [105] was prompted by the similarity of schizophrenia and dreaming. These investigators examined whether physiological indices of REM sleep occur during waking in schizophrenics. However, none of the five schizophrenics studied showed two or more indices of REM sleep during waking. The pattern of regional brain glucose utilization, which varies between the stages of sleep and waking, has also been studied by positron emission tomography (PET) [142]. These studies also did not indicate a similarity of REM sleep to the waking state of schizophrenics. One interesting finding is that during acute schizophrenic episodes the rebound increase in REM sleep that normally follows REM sleep deprivation is markedly blunted [49,146]. Despite some controversy, this finding has been confirmed in several laboratories [145]. The significance of this effect is not clear, but may indicate some defect in REM sleep mechanisms in schizophrenia, such that compensatory mechanisms are already activated and working at maximal capacity.

RELEASE OF VASOTOCIN-LIKE ACTIVITY DURING DREAMING

The hypothesis presented here would be strengthened if there existed a chemical that is released during dreaming and inhibits memory formation. Current evidence for such a substance is presented in this section, and evidence that mechanisms involved in the action of this substance are altered in schizophrenia are presented in a following section.

In an experiment with human subjects Pavel et al. [98] took samples of lumbar cerebrospinal fluid (CSF) from sleeping subjects within 5 min of awakening them from a REM sleep or a NREM sleep period. The subjects were also questioned about their dreams. The concentration of a vasotocin-like substance was determined by bioassays that included antidiuretic and hydroosmotic activities. Vasotocin-like bioactivity was detected if the subject was awakened from REM sleep, but not after awakening from NREM sleep. The concentrations were higher when the subject reported a vivid, rather than a vague, dream. Moreover, the concentration declined to undetectable levels within 30 min of the end of a REM period. Although there have apparently been no other studies of the release of vasotocin during sleep, other data are consistent with vasotocin release during REM sleep. Thus, penile erections are well-known to be associated with REM sleep [56, 117] and are produced by intracerebral oxytocin [4]. Because vasotocin is a peptide that differs from oxytocin in only one amino acid and that exhibits most of its effects, these results are also consistent with its release during REM sleep.

INHIBITION OF MEMORY FORMATION BY VASOTOCIN

The effects of vasotocin on memory formation have recently been studied in the passive avoidance paradigm [35]. In agreement with previous results intracerebroventricular (i.c.v.) application of oxytocin (1 ng) immediately after a passive avoidance training trial impaired memory formation, as assessed in a memory retention test 1 or 2 days later, whereas i.c.v. application of vasopressin (1 ng) facilitated it. Low doses of vasotocin (0.03–0.3 ng) acted like oxytocin in that they impaired memory formation, whereas a high dose (10 ng), like vasopressin, facilitated memory formation. Therefore, if the formation of memories of dream events is indeed inhibited by vasotocin, then dysfunction of this mechanism could result either from too little or too much vasotocin.

MECHANISMS INVOLVED IN VASOTOCIN ACTIONS MAY BE DISTURBED IN SCHIZOPHRENIA

Vasotocin is believed to be synthesized in ependymal cells of a pineal region that includes the pineal stalk and associated subcommissural organ [11,93,94,97]. The pineal hormone, melatonin, is believed to be a releasing factor for vasotocin in that intracarotid injection of small amounts of melatonin during the dark, or higher amounts during the light phase, quickly increase the concentration of vasotocin-like bioactivity in CSF and reduce that in the pineal [94,95]. Evidence exists that the lateral habenula is involved in vasotocin actions. For example, the electroencephalogram (EEG) effects of vasotocin in the cat are abolished by a lesion of the habenula [52]. Also, preparations of habenula inactivate vasotocin faster than preparations of neocortex [54], suggesting that receptors for vasotocin are enriched there. Lesions of the lateral habenula increase the vasotocin-like activity in the CSF of cats [53], suggesting the existence of an inhibitory feedback loop.

In light of this evidence it is interesting that it has been reported that pineal calcification (PC) and habenula calcification (HAC) are increased in schizophrenia [113,114]. Unfortunately in neither of these studies was a control group included; values in schizophrenics were compared to control values from the literature. The increased prevalence of PC in schizophrenia was approximately twofold, with 18% of schizophrenics showing a large ($>$ 1 cm) extent of calcification compared to only 1% of controls. On the other hand, HAC was reported in 85% of schizophrenics compared to 15% of controls, indicating an almost sixfold higher prevalence in schizophrenia. Providing further support for pineal alterations in schizophrenia is the markedly lower level of nocturnal melatonin reported in this disorder compared to controls [42,44,86] both in neuroleptic-free patients [44,86] and in patients receiving neuroleptics [42].

Damage to the habenula and its output pathway has recently been suggested to be important in the psychosis resulting from chronic stimulant use. In humans, chronic amphetamine or cocaine use often results in drug-induced psychosis. Because in experimental animals both procedures result in damage to the habenula and its output pathway, the fasciculus retroflexus, Ellison [40] has suggested that this damage may be involved in psychosis. Damage to striatum was suggested to be less relevant because chronic amphetamine, but not chronic cocaine, caused striatal damage.

There have been no direct studies of the secretion of vasotocin-like bioactivity in schizophrenia. Nevertheless in view of the fact that vasotocin mimics most of the actions of vasopressin and oxytocin, and the involvement of these hormones in water and sodium balance, it is remarkable that many schizophrenics have elevated and very variable urine volumes, indulge in polydipsia, and often progress to a state of hyponatremia [63]. Up to 18% of the deaths of schizophrenics under the age of 53 years have been attributed to this syndrome of polydipsia and intermittent hyponatremia [139]. Because of the complexity of interactions between vasopressin and oxytocin and probably also vasotocin, no detailed mechanism can be proposed, but nevertheless these observations are consistent with a disturbance of vasotocin mechanisms. Interestingly, clozapine is reported to markedly improve the polydipsia and intermittent hyponatremia of schizophrenics, whereas the effects of other neuroleptics are equivocal [31,48,62,70,71,76,87,128,138].

A ROLE OF VASOTOCIN MECHANISMS IN THE ACTIONS OF NEUROLEPTICS?

Although this topic has not been explicitly investigated, several findings are consistent with a role of vasotocin in the actions of neuroleptics. As described earlier, the habenula is a region important in the EEG effects of vasotocin, and lesions of it cause alteration of CSF vasotocin levels. It is, therefore, of much interest that neuroleptics cause consistent large increases of deoxyglucose (DOG) uptake in the lateral habenula [78]. This effect is caused by a D_2 antagonist, but not by a D_1 antagonist [91]. Therefore, it is possible that the high correlation between clinical potency of neuroleptics and their potency at D_2 receptors [22,100,106,119,120] reflects a role of the habenula in their therapeutic effects. The effects of the atypical neuroleptic, clozapine, and those of the typical neuroleptic, haloperidol, have been compared [109]. Both drugs significantly elevated DOG uptake in lateral habenula, although at the doses studied (haloperidol 0.1 mg/kg i.v., clozapine 2 mg/kg i.v.) clozapine had a smaller effect than haloperidol in the lateral habenula but a larger effect in thalamic areas. Therefore, if therapeutic action of typical neuroleptics involves an action at the habenula such as to increase its DOG uptake then the superior therapeutic efficacy of clozapine [67] appears to involve additional mechanisms. Although usually interpreted differently the observations that prolonged administration of typical neuroleptics reduces the firing rate of dopaminergic neurons in both A10 and substantia nigra, whereas the atypical neuroleptic clozapine selectively reduces the firing rate of A10 dopaminergic neurons [19,20, 143] are also consistent with a role of the habenula in antipsychotic action, because the dopaminergic innervation of the habenula originates in the A10 area [103,122].

Moreover, several other observations suggest an affinity of clozapine for cells that use transmitters similar to vasotocin. For example, clozapine and amperozide, but not other neuroleptics provoked a large rise in plasma oxytocin [137]. Also, clozapine, but not haloperidol, markedly increased the Fos-like immunoreactivity in the paraventicular and supraoptic nuclei of the hypothalamus, where the cell bodies of vasopressin and oxytocin neurons are located [118]. Direct studies on vasotocin-like bioactivity and on DOG and Fos in the pineal region should be of interest.

CLINICAL TIME-COURSE OF NEUROLEPTIC ACTION IS CONSISTENT WITH THE PRESENT HYPOTHESIS

During prolonged treatment of schizophrenia with neuroleptics there is gradual improvement such that marked improvement may be seen only after weeks or months [2,9,21,27,68,83,84,144]. This presents a problem for theories of the type that the symptoms of schizophrenia are a direct reflection of overactivity of a particular neurotransmitter system, such as the dopaminergic system, because pharmacological blockade occurs much more quickly. The phenomenon is, however, easily explained by the current hypothesis in that, even though neuroleptic treatment may stop the accumulation of further memories of dream events, it will take a long and variable amount of time before the strengthened neural connections that represent already-existing dream-event memories are weakened and the delusions and other symptoms that they may cause (see later) are correspondingly reduced.

CAN THE PROPOSED DEFECT OF DREAM EVENT MEMORY FORMATION ACCOUNT FOR OTHER CHARACTERISTICS OF SCHIZOPHRENIA?

It is generally believed that memories are stored as increased strength of specific synaptic connections in the brain. As envisaged by Hebb [61] a memory is represented by activity in a cell assembly. The increased strength of connections between elements of this assembly has the function of enabling activity in only a part of the assembly (i.e., a partial representation) to eventually elicit activity in the whole assembly. In this way a stimulus containing an element of a memory can eventually elicit a more complete memory, and a memory that contains a certain element can then elicit further memories that contain this element. According to the

present hypothesis there will be in schizophrenia a gradual accumulation of strengthened connections that represent memories of dream events rather than reality. Therefore, a stimulus containing an element of a memory may elicit either dream event memories or reality memories containing the element, which may in turn elicit further dream event memories or reality memories. In view of the frequent association in dreams of actions, objects, and persons that are not associated in reality this mechanism is a plausible explanation of the loosening of associations that is a characteristic symptom of schizophrenia.

If this loosening of associations by accumulation of erroneous connections extends to the sphere of perception then it is capable of explaining the hallucinations that frequently occur in schizophrenics. It is conceivable that by way of erroneously strengthened connections the constellation of feature-specific nerve cells activated by the sight of a particular object will be inappropriate, resulting in distortion of, for example, its perceived size, shape, color, stability, or even its identity. It is also imaginable that stimulation of one sensory modality could elicit a perception in another, so that, for example, a sight could trigger an auditory experience. Auditory experiences are second only to visual experiences in their frequency of occurrence in dreams [77], which may contribute to the predominance of internal voices among the hallucinations of schizophrenics. The previously mentioned mechanism, however, provides no ready explanation of why complaints of visual hallucinations are less frequent.

In the progression of schizophrenia, the situation has the potential to rapidly become complicated as the brain tries to draw conclusions from several memories, including memories of delusions. For example, the delusion of holding a high official position has been mentioned [12]. It is easy to imagine that when the holder of this delusion attempts to exercise his power or confirm his delusion he will be met with amusement and scorn. He may then elaborate the secondary delusion that there exists some kind of a plot to deprive him of his rights. The fact that two types of delusions exist, primary delusions, which originate fully-formed as if from nowhere, and secondary delusions which, can be understood in terms of the patient's other beliefs, has been frequently remarked upon previously [5,108,121,141].

Because the content of dreams is influenced by waking concerns [58], or in other words by the contents of memory, then there will eventually occur dreams that are influenced by delusions. Based on these dreams other delusions may occur. These may influence the content of further dreams and so on, so that eventually the behavior and utterings of late-stage patients may become increasingly unrelated to reality, like those of numerous patients described by Bleuler [12] and Lehmann [72].

Similar implications have been previously drawn from a model of the function of REM sleep. In this model of Crick and Mitchison [23,24] the suggested function of REM sleep is to weaken already existing inappropriately-strengthened synaptic connections. In the current hypothesis inappropriately-strengthened neural connections arise as a result of a neurochemical dysfunction during REM sleep, rather than existing already. The present hypothesis also makes no suggestion about the function of REM sleep. However, according to both hypotheses the consequence of a defect is an accumulation of inappropriately-strengthened synaptic connections. Crick and Mitchison [23] also suggested that such an outcome could result in delusions, hallucinations, and obsessions and therefore, might be involved in some forms of schizophrenia.

The present hypothesis of impaired processes that inhibit memory formation is not in contradiction with the considerable evidence that indicates an impairment of memory processes themselves in schizophrenia [16,17,29,38,50,51,65,79,81,131] because according to this hypothesis the system that inhibits memory formation and is impaired in schizophrenia is active only during REM sleep. A possibility to be considered is whether the accumulation of wrong information in memory stores predicted by the current hypothesis may be a factor contributing to these memory impairments.

In view of the fact that the symptoms of schizophrenia generally appear only after puberty, it is also of interest that there are marked changes in the distribution of oxytocin receptors during development [136] and that gonadal hormones exert numerous influences on vasopressin/oxytocin systems [3,34,135] so that there are many possibilities for something to go wrong at this time. Moreover, the modulation of hippocampal oxytocin receptor binding by glucocorticoids [73] is of interest because stress is often a factor in precipitating psychosis.

IMPLICATIONS FOR THE QUESTION OF EVOLUTIONARY ADVANTAGE OF MECHANISMS PREDISPOSING TO SCHIZOPHRENIA

An interesting question recently raised by Crow [25] concerns the possible survival value of genes that predispose to schizophrenia, to account for the relatively high and constant prevalence of the disorder despite a fecundity disadvantage. According to the present hypothesis, detrimental effects occur due to increased strengthening (because of impaired weakening) of synaptic connections that are the substrate of memories of dream events. If occurring to a lesser degree it seems plausible that facilitation, during REM sleep, of connections between neural representations of objects, ideas, and events that are not normally related could contribute positively to creativity and problem-solving, abilities with evolutionary advantages. Although speculative, this interpretation is consistent with a large body of evidence suggesting some positive role of normal REM sleep in problem-solving, learning, and memory [14,23,24,45,57,99,124,127].

IS THE VASOTOCIN-LIKE BIOACTIVITY RELEASED DURING REM SLEEP ACTUALLY VASOTOCIN?

Arginine vasotocin (AVT) is an evolutionary precursor of the vasopressin/oxytocin superfamily of peptides [1] and is not present in significant amounts in the neurohypophysis of adult mammals. However, the antidiuretic, oxytocic, and frog bladder effects of CSF from anesthetized young men were consistent with the presence of vasotocin [92]. Moreover, in human neonatal CSF and amniotic fluid substantial amounts of vasotocin are measured by radioimmunoassay (RIA), which cannot be accounted for by vasopressin and oxytocin [6]. Similarly in the neurohypohysis from fetal mammals (sheep and seal) the amount of frog bladder activity could not be accounted for by vasopressin and oxytocin and was attributed to vasotocin or a similar peptide [140]. The presence of arginine vasotocin in neurohypophysis of human fetus has been confirmed by high-performance liquid chromatography (HPLC) followed by RIA [123].

In their study of REM sleep in humans, Pavel et al. [98] used bioassays to detect the activity released during REM sleep, which they attributed to vasotocin. The methods used [92,97] included determining the ratio of activity on frog bladder to that on rat uterus, a high ratio (> 200) serving to distinguish vasotocin from vasopressin or oxytocin, which have ratios close to unity [92,115]. Other criteria used were loss of frog bladder activity on incubation with trypsin, which indicates that this activity is not due to oxytocin, and similar chromatographic behavior of the material possessing the biological activities and synthetic arginine vasotocin [97]. Therefore, the criteria used to conclude that the released substance is vasotocin are quite stringent.

Whether the pineal contains actual vasotocin, however, is

somewhat controversial. On one hand the presence of vasotocin-like bioactivity has been confirmed using a different bioassay than that used by Pavel and coworkers. Thus, Pévet et al. [102] showed in bovine pineal the existence of vasotocin-like bioactivity measured by contractile effect on eel ventral aorta strip. On the other hand in studies using immunoassay or immunohistochemistry there are both numerous positive [15,43,82,104,110] and negative [75,88,89,101,102] findings. Likewise, studies using chemical means of identification are conflicting; whereas a gonadotropin-inhibiting compound from bovine pineal had the amino acid composition of AVT and was shown to be AVT by mass spectrometry after degradation to two tetrapeptides [18], no AVT was found in fractions of bovine pineal purified for milk-ejection activity [10]. Many factors may be responsible for such discrepancies. These include the animal species [43] and age, vasotocin-like bioactivity in bovine, and rat pineal showing a marked decline with ontogeny [93,96]. Another important factor is the precise definition of the tissue assayed. Thus, there is considerable evidence that vasotocin-like bioactivity is synthesized in ependymal cells that are present in the pineal stalk and pineal gland of fetal animals, but in the adult are present only in the stalk [11,93,97]. A further factor that may contribute to the variability of results is a pronounced circannual rhythm of pineal/pineal stalk vasotocin immunoreactivity [82,104]. Thus, Prechel et al. [104] using an RIA showed a dramatic seasonal rhythm in rat pineal AVT immunoactivity in two successive years. Moreover, serial dilution of the peak pineal sample from August resulted in an RIA response line parallel to the AVT standard curve. This was not true for serial dilutions of argine-vasopressin or lysine-vasopressin, oxytocin, or mesotocin. Thus, in this assay the pineal constituent was indistinguishable from synthetic AVT. A further factor is the possible presence of vasotocin-like molecules that are recognized by some antibodies but not by others, as suggested by Pévet et al. [102] to explain their detection of AVT-like bioactivity but detection of AVT-like immunoactivity by one antibody but not by another. Interestingly, in nonmammalian vertebrates there exist hydroosmotic peptides such as hydrin 1, hydrin 1′, and hydrin 2, which consist of the amino acid sequence of vasotocin elongated by 1–3 amino acids [64,111,112]. Whether such compounds contribute to vasotocin-like bioactivity in mammals has not yet been examined. Thus, at present, until further chemical identification has been performed there is some uncertainty whether the vasotocin-like bioactivity released during REM sleep can be attributed to vasotocin itself or to a related peptide.

SUMMARY AND CONCLUDING REMARKS

A new hypothesis is presented here to account for the occurrence of schizophrenic delusions. The hypothesis is that a mechanism that normally inhibits the formation of memories of dream events is defective in schizophrenia. Because having a memory of an event is sufficient to be really convinced that it happened then occasional failures of the inhibitory mechanism may account for the formation of primary delusions. The associated gradual accumulation of inappropriately-strengthened synaptic connections can account for other symptoms. The hypothesis is supported by the similarities of dreams and schizophrenic delusions, by the release of a vasotocin-like compound during REM dreams, by inhibition of memory formation by vasotocin over a wide dose-range, and by alterations in schizophrenics of structures such as the habenula and pineal that are involved in the action of vasotocin.

Should the hypothesis of defective inhibition of dream event memory formation be correct then many questions concerning the causes of schizophrenia remain to be elucidated by experiment. First, it is important to know more about the components of this system in terms of brain areas, neuroanatomical pathways, neurotransmitters, receptors, and molecular mechanisms involved in this inhibition. Second, the disturbances of this system that occur in schizophrenia have to be determined and understood. Current evidence that calcification of habenula and pineal are such disturbances has been presented here, while other possible defects in transmitter synthesis, release, or receptor function have not been investigated. However, it is not known if excessive HAC would cause failure of inhibition of dream event memory formation because released vasotocin increases above the range where it inhibits memory formation [35] or because the habenula is part of the mechanism involved in this inhibition. Finally, it would remain to discover how genetic and environmental factors produce these disturbances.

The idea that schizophrenic delusions somehow come from dreams is not new; the psychiatrist Eugen Bleuler, who spent much of his life in close contact with schizophrenics in an era before neuroleptics existed, and who gave schizophrenia its name, wrote:

> At various points of our studies, we have noted that in many respects the disease shows analogies to dreams, a phenomenon which cannot be without significance. In dreams, a similar dissociation of thinking occurs: symbolisms, condensations, predominance of emotions which often remain hidden hallucinations-all these can be found in both states and in the same way. The analogy becomes identity in those cases where the patients handle their dream-hallucinations as real ones, where delusions are formed in dreams, and maintained in the waking state [12, p. 439].

Bleuler made no suggestion why schizophrenics, unlike unaffected individuals, form delusions in dreams that are maintained in the waking state. When he wrote this it was more than 40 years before the discovery of REM sleep and knowledge of the large amount of time we spend dreaming. It was also many years before the discovery of brain mechanisms that inhibit memory formation. In proposing the present hypothesis I have used these new pieces of knowledge to suggest a specific biological mechanism of how dream events become delusions. Naturally I hope that this hypothesis proves to be correct, if not in all its details, then at least in part. At least it is hoped that it will fulfill one important function of a hypothesis in serving to stimulate further research designed to test it.

ACKNOWLEDGEMENTS

It is a pleasure to thank Sarah Copley, Keith Dixon, Anant Dravid, Debra George, Paul Herrling, Tage Honoré, Susan Iversen, Eileen Joyce, Fouzia Laghrissi-Thode, David Laurie, David Moon, Samar Muakkassah-Kelly, Gideon Shapiro, and Karl-Heinz Wiederhold for their interest and comments.

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