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NEUROPHYSIOLOGICAL SUPPORT OF CONSCIOUSNESS DURING WAKING AND SLEEP

C. GOTTESMANN*

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

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Abstract—The aim of this review was to try to establish the current neurophysiological knowledge capable of explaining the differences of mental functioning during the different stages of sleep and waking. The analysis focused on the cortical state. Waking is characterized by electrophysiological activities (low voltage and gamma range EEG field patterns, unitary activities) and cerebral blood flow reflecting an activated state.

On the contrary, neurochemical influences are marked by inhibitory afferent processes since dopamine, noradrenaline, serotonine and histamine tend, for the most part, to inhibit cortical neurons by diffuse release at the level of varicosities. During slow wave sleep, all these brain stem influences sustaining the cortical state decrease and transiently disappear just prior to onset of REM sleep.

During REM sleep, pontine and mesopontine ascending activating influences invade the cortex in their turn while neurochemical inhibitory influences disappear with the exception of dopaminergic ones.

We hypothesize that the activating influences acting on the cortex allow the latter to function, just as petrol makes an engine run, but that the diffuse inhibitory influences somehow regulate cortex functioning. Therefore, it is understandable that, during waking, mental activity is reflective and rational, and that psychological content is less intense during slow wave sleep.

During REM sleep, the activated and mostly disinhibited state might induce the characteristic dream activity which appear to be rather ill-considered and illogical. Persistent dopaminergic input combined with the absence of noradrenergic input may induce psychological activities somewhat similar to those related to psychotic syndromes.

Deactivation of part of the prefrontal cortex could contribute to this unusual mental activity.

CONTENTS

* Tel.: +33 4 92 07 61 66; fax: +33 4 92 07 61 62;
email: gottesman@unice.fr.

ABBREVIATIONS

cAMP	Cyclic adenosine monophophate	LTD	Long-term depression
DC potential	Direct current potential	LTP	Long-term potentiation
EEA	Excitatory amino acid	NMDA	*N*-methyl-D-aspartate
EEG	Electroencephalogram	PGO	Ponto-geniculo-occipital wave
GABA	Gamma aminobutyric acid	REM sleep	Rapid eye movement sleep
5-HT	Serotonin	VIP	Vasoactive intestinal peptide.

1. INTRODUCTION

Mental functioning remains a mystery in spite of major progresses made in our knowledge of brain mechanisms. The problem is still more complex since considerable differences appear between thinking modalities during waking and sleep. The discoveries of the last decades have emphasized the similarities of the cortical activation state during waking and dreaming. However, our own experience shows the significant differences of psychological content and logical organization in these two behavioral states. Consequently, activation processes are not sufficient to explain these differences of mental functioning. Moreover, the leading French psychiatrist, Henri Ey (1967), said 30 years ago "il est évident, il ne peut pas ne pas être évident que le rêve et la folie jaillissent des mêmes sources" (p. 575)[1]. Are there today neurophysiological bases to support such assertion?

Since psychological features are principally generated in the cortex, we would like to analyze the processes which possibly underpin the differences of psychological activity during waking and sleep.

2. RESULTS

2.1. Electrophysiological Approach

2.1.1. *Activation*

To speak about the concept of cortical activation is somewhat of a truism. This assertion is already implicit in the hypothesis of Gall (1825) hypothesis on cerebral localization of functions and in their detection by cranioscopy. Before discussing the true cortical activation processes, it is worth recalling the history of the first steps toward the discovery of its electrophysiological activity (EEG).

The first author describing electrical currents in the cortex was Richard Caton (1875). Working on rabbits and monkeys—quite a feat at this time in the north of England (Liverpool)—and by means of a galvanometer, he observed potential variations of "the grey matter (which) appear to have a relation to its function. When any part of the grey matter is in a state of functional activity, its electrical current usually exhibits negative variation" (p. 278).

It was Hans Berger (1929) who first described the electrocorticogram and EEG in humans during waking and sleep. Indeed, in many observations the electrodes were directly situated on the cortex after trephination. However, other observations, particularly those made on his son, used electrodes placed under the skin and on the scalp (Fig. 1). Several later on papers by the same author developed these initial findings [see Loomis et al. (1938) for references][2].

However, 1937 was a significant year for cortical electrical activity during paradoxical sleep, also called rapid eye movement (REM) sleep or rapid sleep. The first paper on this topic, I found mentioned for the first time by Kleitman (1965) (it was probably already mentioned in the previous edition of 1939), is R. Klaue (1937) who described the different stages of sleep and waking in cats. Distinguishing the various stages of sleep, he called one "tiefer Schlaf" (deep sleep) which occurred after a stage with irregular 8 Hz large amplitude waves (Fig. 2). This stage was characterized by what he termed "Beruhigung in Strombilde" (quiet electrical current), that is, low amplitude EEG, "eine völlige Entspannung der Muskulatur…und häufige Zunkungen in einzelne extremitäten" (p. 514) (a complete muscular relaxation…and numerous jerks of single extremities).

The second important finding, the same year, was made by the team of Loomis who published two preliminary papers (Loomis et al., 1935a, 1935b) followed by two full papers (Loomis et al., 1937, 1938). In the first paper (Loomis et al., 1935a) the authors clearly distinguished waking and sleep EEG recordings. But for our topic, the 1937 paper (Loomis et al., 1937) is of particular interest. Besides the fact that it showed hypnograms (apparently for the first time), almost a page is devoted to EEG recordings during dreams (Fig. 3). Their results established that during dreaming the EEG is in the 'B' category, that is to say of low amplitude.

However, in those days, the authors did not speak explicitly about cortical activation during this sleep stage. In fact, it was Dement (1958) who first spoke about 'activated' sleep, although Aserinski and Kleitman (1953, 1955), Dement (1955) and Dement and Kleitman (1957a, 1957b) had definitively established EEG low voltage activity during REM sleep. Nevertheless, since Bremer (1936) and, above all Moruzzi and Magoun (1949), it has been known

[1]It is obvious, it cannot be but obvious that dream and madness spurt out from the same source.

[2]The whole work of Berger was translated in English by P. Gloor (1969).

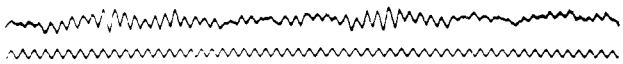


Fig. 1. Berger (1929) recorded trephined electrocorticogram and Electroencephalogram on humans and dogs. Shown here is the EEG recorded on his son by an occipital-forehead lead. Clearcut alpha rhythm can be observed (below, electrical 1/10 sec oscillations). Reprinted from Archiv für Psychiatrie und NervenKrankheiten, with permission of Springer Verlag.

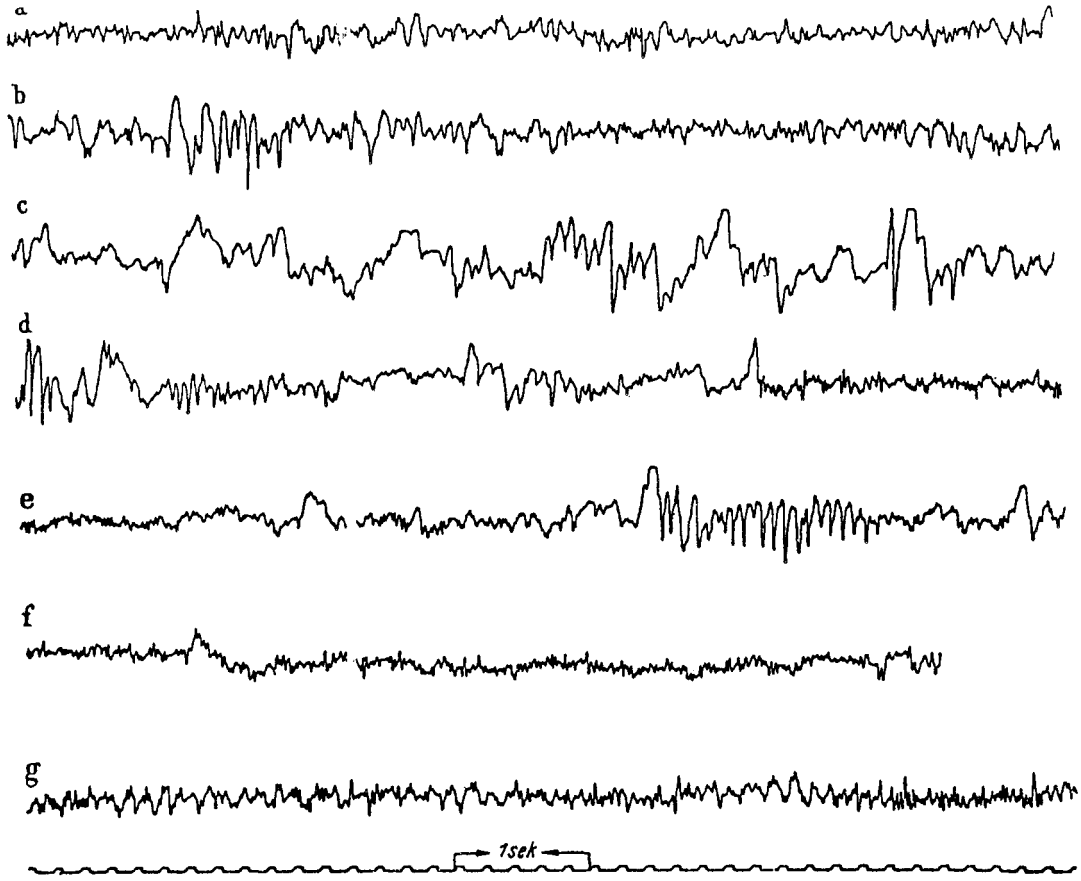


Fig. 2. Klaue (1937) described in cats a sleep stage with low amplitude cortical activity which was called 'deep sleep'. (A) Waking: the cat is purring; (B) falling asleep; (C) sleep; (D and E) instead of appearance of high amplitude waves at 8 c/sec, as previously, there is incipient of low amplitude activity. Jerks occur during this stage; (F) 'deep sleep'; (G) arousal. Reprinted from *Journal für Psychologie und Neurologie*, with permission.

that cortical low voltage activity is usually related to waking, that is, activation state. Soon after Dement (1958), Jouvet called this stage paradoxical sleep because of its cortical similarities with waking activation patterns[3].

The nature of the cortical state during paradoxical sleep was further studied by unitary recording. Evarts (1962) observed that the neurons of the primary visual cortex were more activated during paradoxical sleep, particularly during the eye movements, than during slow wave sleep. There were no clear differences between paradoxical sleep and waking. Like Klaue (1937) and Benoit and Bloch (1960), he referred to the "deepest stage of sleep" (p. 815) because of the high threshold of awakening by reticular stimulation. In a later paper (Evarts, 1965), on the same subject, the author found a similar high neuronal discharge rate during paradoxical sleep and waking during eye movements, the lowest discharge level during slow wave

[3]Jouvet et al. (1959) already alluded to a "paradoxical stage" back in 1959. He definitively adopted the term "paradoxical sleep" in 1965 (Jouvet, 1965). Meanwhile, he used the designation of "telencephalic" and "rhombencephalic" sleep (personal communication).

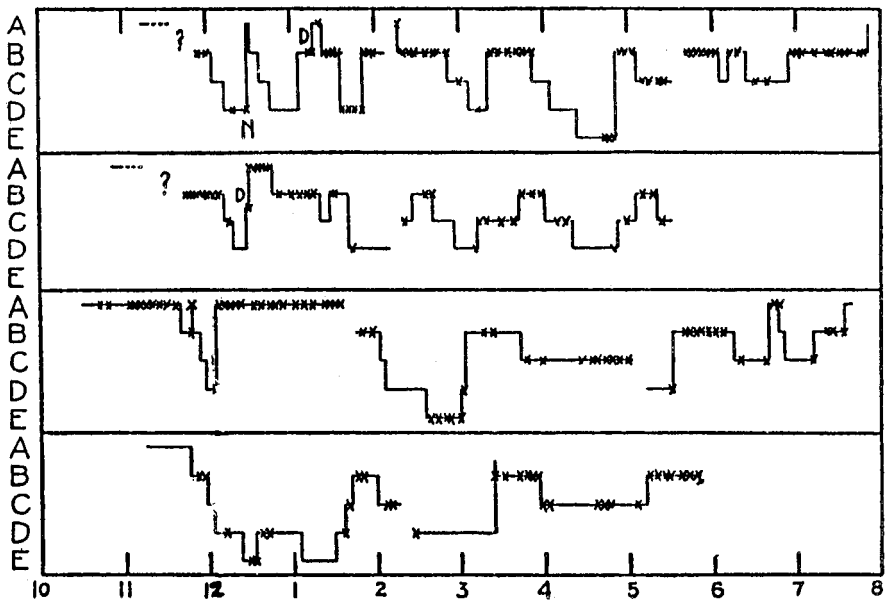


Fig. 3. Loomis et al. (1937) published in humans probably the first hypnogram. They observed that during dreaming (D) the subject shifted from a spindle stage to a B stage (low amplitude EEG activity). Reprinted from *Journal of Experimental Psychology*, with permission.

sleep and a slightly higher rate during waking without visual stimulation (Fig. 4).

The year after, Arduini et al. (1963) studied the pyramidal cell discharges during sleep–waking stages by recording the integrated pyramidal tract activity at the pes pedunculi level: "the overall pyramidal discharge reaches during the stage of fast, desynchronized sleep a steady level which is definitively higher than that maintained during the inter-spindle lulls of the slow synchronized sleep (Fig. 5). This level of activity is of the same order as that observed in conditions of quiet wakefulness" (p. 539). Soon afterwards, Morrison and Pompeiano (1965) showed, using true pyramidal tract unitary recording, that the pyramidal cells issued from the somatosensory cortex increase their firing rate from the steady waking state to arousal and decrease their activity during slow wave sleep with a peak of

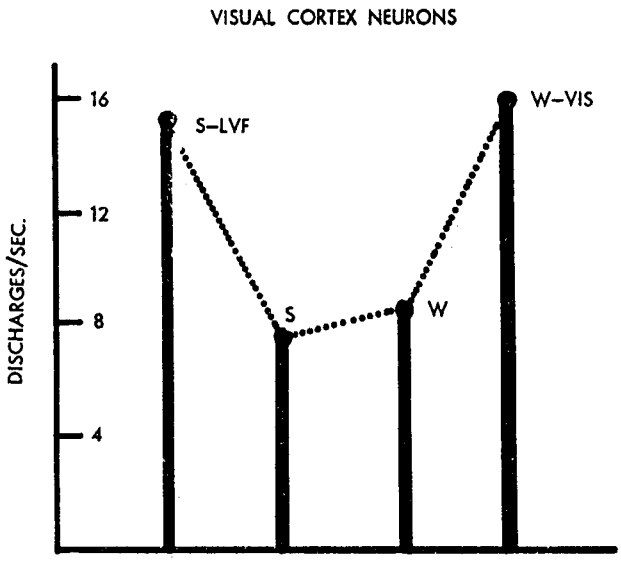


Fig. 4. Evarts (1965) recorded in cats single unit activity of the visual cortex during sleep–waking cycle. During paradoxical sleep (S-LVF) the firing was as strong as during waking when the animal was 'looking about at its surroundings' (W-VIS). During quiet waking (W) the firing was slightly higher than during slow wave sleep (S). Reprinted from CNRS, with permission.

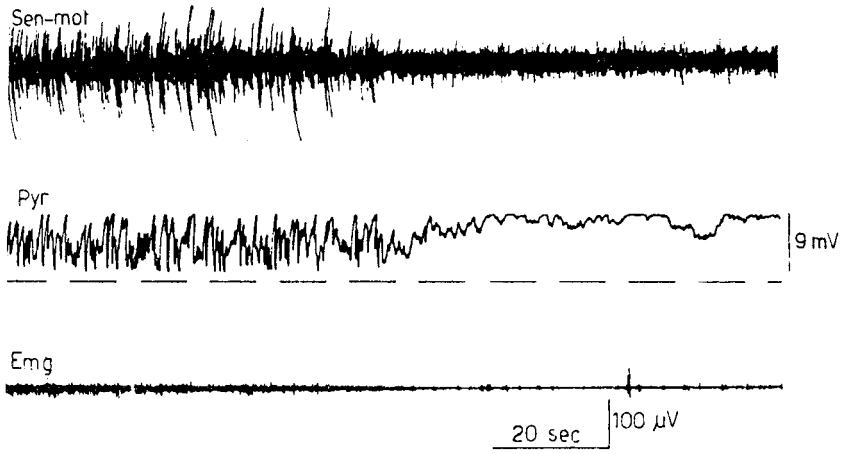


Fig. 5. Arduini et al. (1963) studied the cortex pyramidal cells during sleep by recording the integrated activity of the pyramidal tract. There was an increase of activity during paradoxical sleep. Abbreviations: Sen-mot, sensorimotor cortex; Pyr, pyramidal tract integrated activity. Reprinted from *Archives Italiennes de Biologie*, with permission.

discharge during spindles, and that there was an increase during the eye movements of paradoxical sleep.

Then began the area of responsiveness studies during sleep–waking cycle. Palestini et al. (1964) analyzed in cats the thalamocortical and cortical excitability of the primary visual system. The thalamocortical responsiveness tested by the positive fourth component amplitude was highest during paradoxical sleep, minimal during slow wave sleep and intermediate during waking (Fig. 6). Cordeau et al. (1965) found similar results. It was also the case for Favale et al. (1965) for the somesthetic system. Much later on, Arnaud et al. (1979) [see Gottesmann (1996) for review] found identical results in rats. In contrast, the results of the cortical response obtained by stimulation of cortical radiations show that cortical excitability is lowest during waking and highest or equal during slow wave sleep as compared to paradoxical sleep.

Another criterion of cortical activation during paradoxical sleep appeared with the study onto the influence of the ponto-geniculate-occipital waves (PGOs) (Jouvet et al., 1959; Mikiten et al., 1961; Michel et al., 1964). At cortical level they were carefully studied by Calvet et al. (1965) (who also observed some of these waves during waking). These surface-positive PGO waves induced cortical activation, as shown by unitary cell recordings. Some years later, this transient activation during PGOs was confirmed by Satoh (1971) who found an increase of cortical responsiveness during these waves. More recently, McCarley et al. (1983) recorded in humans occipital surface positive waves which begin a few milliseconds prior to eye movements in REM sleep. Similar waves were obtained for waking eye saccades (Fig. 7).

2.2. The Gamma Range Activity

Because of the more recent identification and the important functional implications of this activity, it is useful to analyze in some detail the initial findings in this field.

Although Rougeul et al. (1979) mentioned a fast synchronized cortical rhythm (mean 18 c/sec) during attention and immobility in the baboon and squirrel monkey, it was Bouyer et al. (1981), in the same group, who described for the first time a true gamma range activity (35–45 c/sec) in the cat during attentive behavioral arrest, that is, during high vigilance and immobility (Fig. 8). These bursts of synchronized waves were observed in two anterior zones focused at the cruciate sulcus (area 6) and the ansate sulcus (area 5). However, these rhythms were also recorded in the 'posterior group' of the thalamus, that is, between suprageniculate, mediate geniculate and lateralis posterior nuclei. Lesions at this thalamic level suppressed the synchronized waves in the posterior cortical area, and the authors hypothesised a thalamic pacemaker for these waves.

Similar fast EEG field activities centered on 30 Hz were recorded at the visual cortex level during conditioned responses in the monkey by Freeman and Van Dijk (1987). Ferster (1988), in cats, observed 45 c/sec activity in the visual cortex by presentation of bars across the receptive field of neurons.

Gray and Singer (1989) recorded simultaneously the field and unitary activities in the visual cortex of cats. They observed an increase in neuron firing during the EEG synchronization which was situated at 40 Hz. In the unanesthetized animal this gamma activity was induced by presentation of aligned light bars. To explain this field activity the authors postulated that "the interaction among a population of synaptically coupled neurons exhibiting both mutual excitation and recurrent inhibition is sufficient for the generation of oscillations" (p. 1702). Although possible behavioral functional implications are not discussed in their paper, these results show that these waves occur in neurons when "activated appropriately" (p. 1702). One year later, Singer (1990) showed that gamma range activity can be

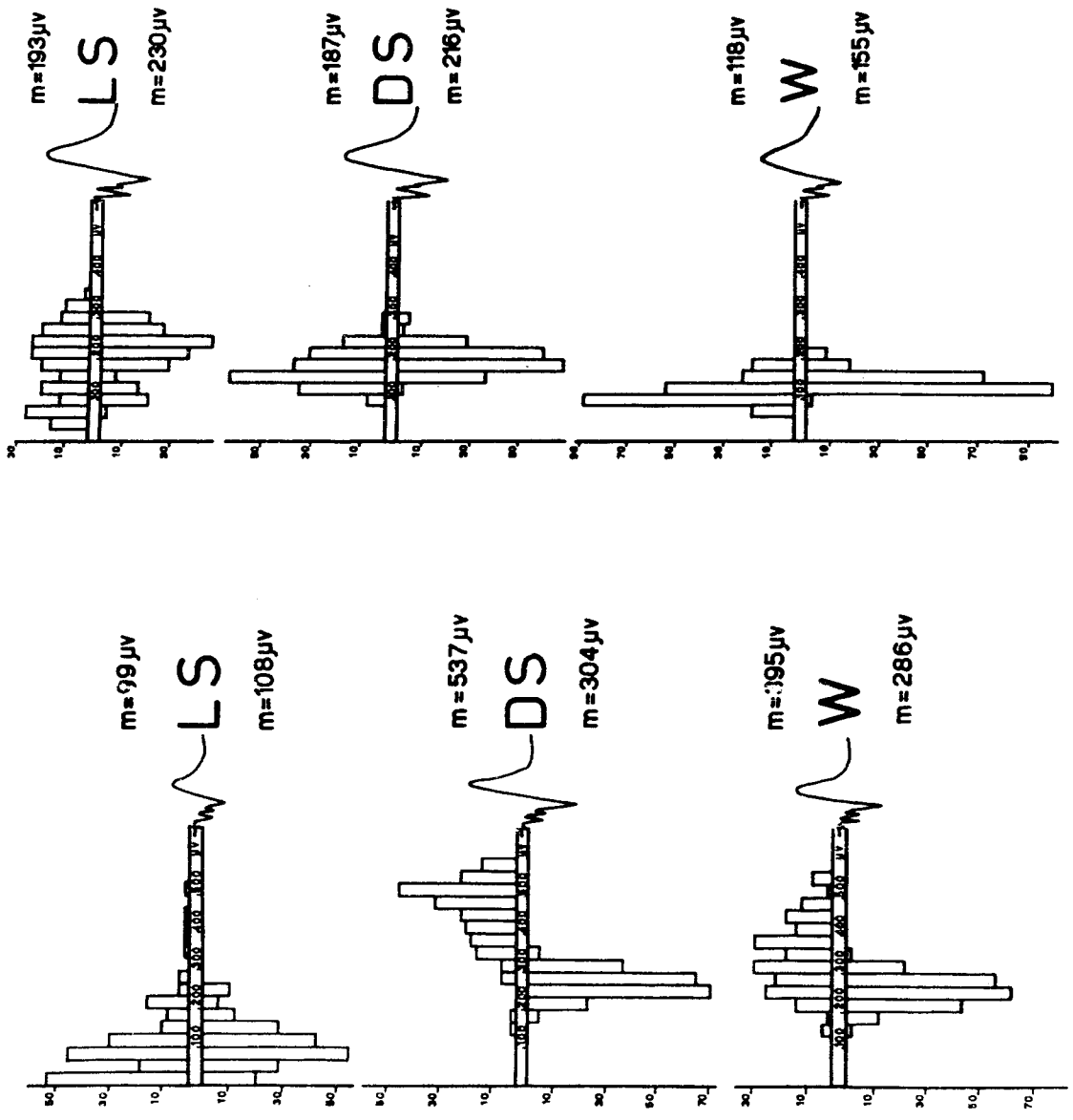


Fig. 6. Palestini et al. (1964) studied the forebrain responsiveness of the visual system. On the left, the thalamocortical excitability is maximal during paradoxical sleep (DS). It is slightly lower during waking (W) and much lower during slow wave sleep (LS). On the right, the cortical responsiveness studied by radiation stimulation is highest during slow wave sleep (LS) and lowest during waking (W). Reprinted from *Experimental Neurology*, with permission.

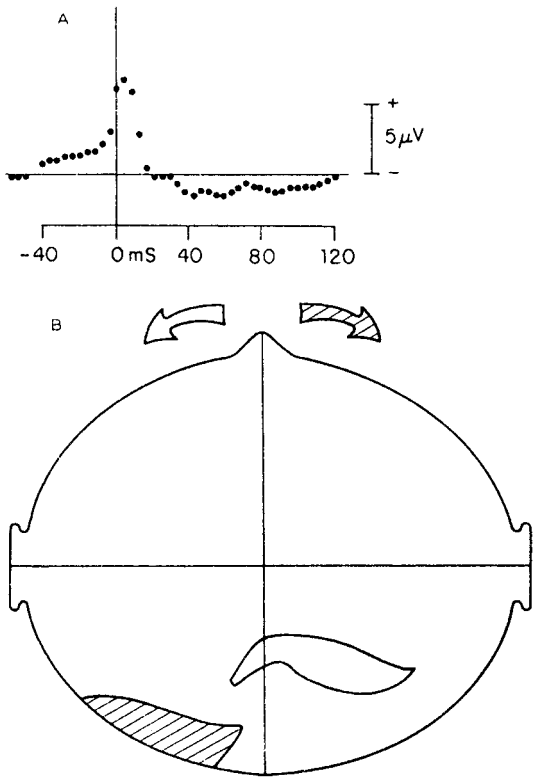


Fig. 7. McCarley et al. (1983) recorded in humans the cortical activity corresponding to ponto-geniculo-occipital waves during sleep and waking. In (A) it can be seen that the positive wave begins prior to the eye movement. In (B), the right-oriented eye movements during REM sleep are accompanied by maximal spikes on the left occiptal area (hatched). The right hemisphere is activated during left-oriented eye movements. Reprinted from *Brain Research*, with permission of Elsevier.

enhanced by stimulation of the midbrain reticular formation.

In 1991, Llinas et al. (1991) recorded *in vitro* the single neuron and field activities of the frontal cortex in guinea-pigs. Among the subthreshold oscillations they detected one close to 35–50 Hz in layer IV which contains interneurons. The authors suggested that these interneurons "elicit inhibitory postsynaptic potentials (IPSP) in other cortical neurons, including the pyramidal cells of layer VI. Rebound potentials triggered by these IPSPs generate rhythmic firing at 40 Hz" (p. 901). The authors hypothesized a cortico-thalamo-cortical loop for these gamma oscillations. Indeed, "this descending 40 Hz rhythmic volley, by activating thalamic projection neurons and the thalamic reticularis neurons, would result in the generation of 40 Hz excitatory postsynaptic potential–IPSP sequence in the thalamus" (p. 901). During waking, the regular neuron firing of the thalamic reticular nucleus, which contrasts with the bursting mode of discharge during slow wave sleep, "is more likely to generate the short-lasting inhibitory synaptic potentials, conducive to 40 Hz bursting in thalamic projection neurons" (p. 901).

The same year, Steriade et al. (1991) confirmed in anesthetized cats the ability to record gamma range activities in thalamocortical neurons (Bouyer et al., 1981). The authors found that the stimulation of the mesopontine cholinergic nuclei (mimicking waking processes) potentiated the 40 Hz activity in the thalamocortical neurons, even after forebrain nucleus basalis lesion. Like the previous authors, Steriade et al. (1991) hypothesized the favoring role of the regular firing of the thalamic reticular nucleus (sustained by the mesopontine nuclei) in the generation of gamma activity and suggested a thalamo-cortico-thalamic loop.

Among the results obtained in humans the paper of Ribary et al. (1991) has to be given special emphasis. Indeed, using magnetic field tomography, the authors showed that gamma range activity can be observed over the entire cortex, that it is independent of the stimulus presentation rate (in this case there were auditory stimulations) and that "it was clearly phase-locked over cortical areas" (p. 11039). The latency of gamma wave occurrence was shorter in the thalamus. In Alzheimer disease this activity was of lower amplitude and the waveform distorted (Fig. 9).

The neurophysiological background of the gamma range activity was further studied by Pinault and Deschênes (1992) in rats. They recorded the thalamic reticular nucleus neurons of urethane-anesthetized rats. Indeed, "on the basis of its connectivity, the thalamic reticular nucleus can be considered as an inhibitory system that could regulate in a state-dependent manner the coupling between thalamic and cortical activities" (p. 215). The results "indicate that the neurons of the thalamic reticular nucleus are endowed with voltage-dependent pacemaker properties allowing them to oscillate at 40 Hz, and that their resultant 40 Hz discharges induce an inhibitory modulation of similar frequency in thalamic relay cells. The regular firing of reticular cells was not driven by presynaptic elements firing at 40 Hz" (p. 254). They concluded that this thalamic reticular nucleus "might play a key role in the genesis of 40 Hz field potentials that are associated with states of focused arousal in behaving animals" (p. 256).

Similar synchronized high frequency field and related unitary activities were observed by Murphy and Fetz (1992) in the sensorimotor cortex of head fixed monkeys. "The oscillations occurred preferentially during demanding sensorimotor tasks, such as retrieving raisins from unseen sites, and occurred much less often during relatively automatic motor activity, such as overtrained alternating wrist movements" (p. 5673). "These coherent oscillations are particularly involved in neural interactions underlying attention to fine sensorimotor control" (p. 5674)[4].

[4]The reader can find more basic neurophysiological data on gamma range activity in the following papers: Munk et al. (1996), Steriade et al. (1996a) confirming Singer's finding (1990) of its induction or enhancement by midbrain reticular stimulation, also those of Steriade and Amzica (1996) and Steriade et al. (1996b) showing that this activity, not reversed in the deep layers of the cortex, is synchronized in the cortex and thalamus.

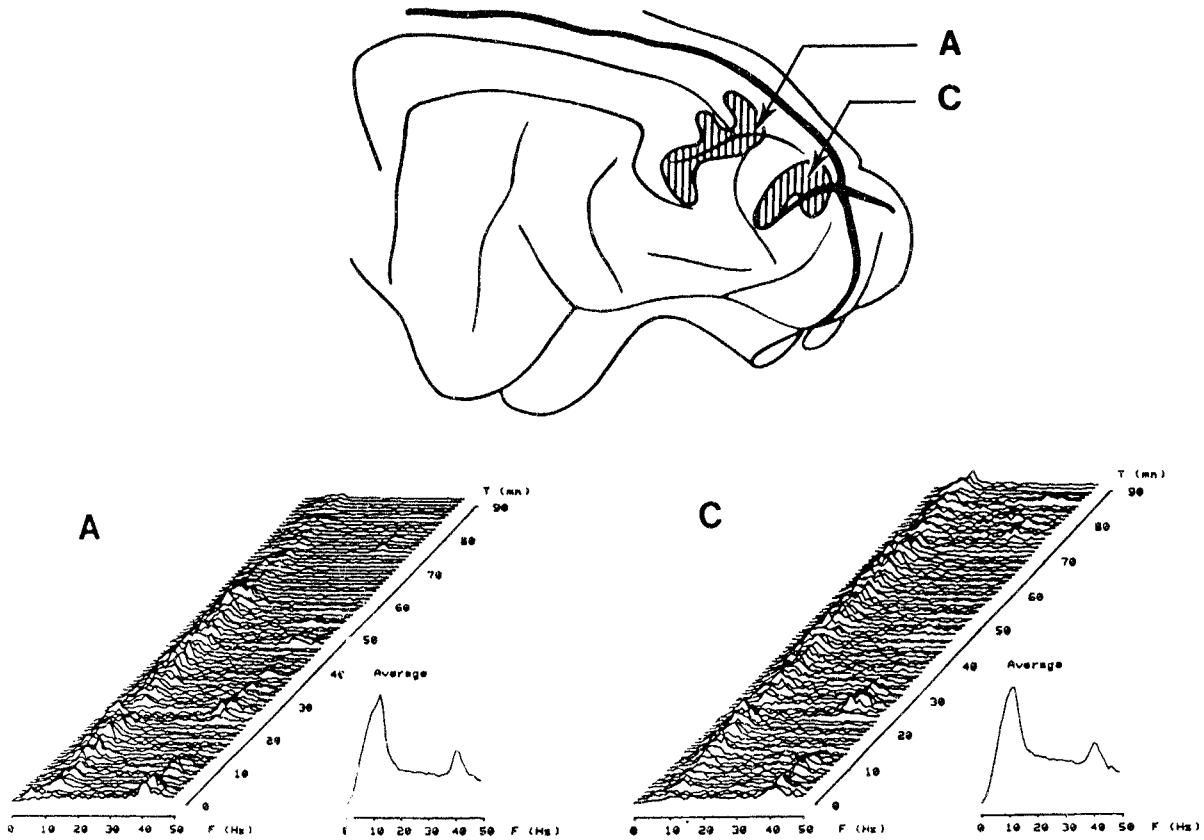


Fig. 8. Bouyer et al. (1981) recorded for the first time gamma range activity (ca 40 Hz) in two cortical areas of the cat; this high frequency rhythm occurred during high level of vigilance in the motionless animal. On the right of the two spectra can be seen the averaged spectrum. Reprinted from *Electroencephalography and Clinical Neurophysiology*, with permission of Elsevier.

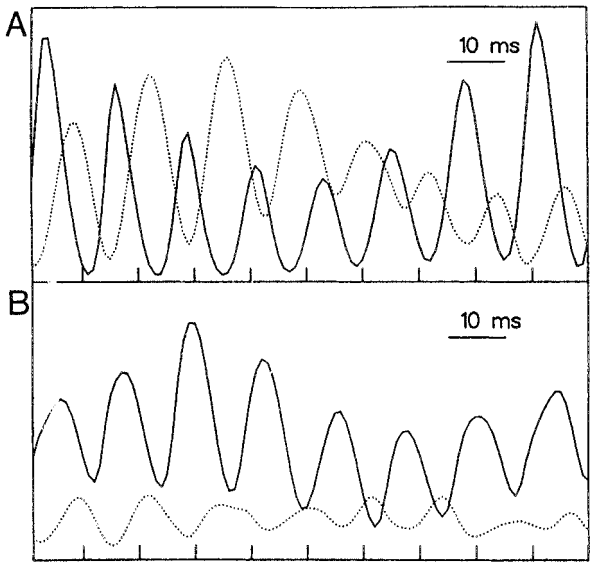


Fig. 9. Ribary et al. (1991) recorded for the first time gamma range activity in humans. (A) Thalamic (———) and cortical (· · ·) recording. (B) Same record in Alzheimer disease: the cortical activity is significantly reduced. Reprinted from *Proceedings of National Academy of Sciences*.

Consequently, all data available at this time showed that in mammals during attention, that is, during vigilance, there is a specific high frequency field activity in the cortex and thalamus.

The next major finding was the discovery by Llinas and Ribary (1993) that gamma range activity occurs in humans during REM sleep (Fig. 10). Indeed, magnetic recording showed "the presence of well-defined 40 Hz oscillation during wakefulness and dreaming and a marked reduction during delta sleep" (deep slow wave sleep, p. 2079). This field activity could be induced by auditory stimuli during wakefulness but not during deep slow wave sleep and REM sleep. The authors insisted on the fact that "these findings indicated that, while the awake and REM sleep states are similar electrically with respect to the presence of 40 Hz oscillations, the central difference between these states is the lack of sensory reset of the REM 40 Hz activity. By contrast, during delta sleep, the amplitude of these oscillations differs from that of wakefulness and REM sleep, but as in REM sleep there are no 40 Hz sensory responses" (p. 2080). And the authors insist "In addition to the finding that the electrical activity during waking and oneiric states is quite similar, a second significant finding was that during the dreaming state, 40 Hz oscillations are not reset by sensory input, although evoked potential responses indicate that the thalamocortical system is similarly accessible to sensory input in both states... It indicates that we do not perceive the external world during REM sleep... We may consider the dreaming condition a state of hyperattentiveness in which sensory input cannot address the machinery that generates conscious experience" (p. 2081). The authors suggest that the intralaminar thalamus, the specific and thalamic reticular nuclei possibly participate in the conscious experience: "the specific system would provide the content and the nonspecific system would provide the temporal binding of such content into a single cognitive experience evoked either by external stimuli or, intrinsically, during dreaming" (p. 2081). Moreover, "It is the dialogue between the thalamus and the cortex that generates subjectivity" (Llinas and Paré, 1991, p. 532)[5].

Subsequent papers on humans (Tiitinen et al., 1993; Joliot et al., 1994; Desmedt and Tomberg, 1994) confirmed the relationship of gamma range activity, brain activation and conscious experience during waking.

In animals, it was recently shown that this kind of activity also occurs in rats during paradoxical sleep (Franken et al., 1994; Maloney et al., 1997) and that it is particularly abundant during hippocampal theta rhythm, that is, during active waking and paradoxical sleep (Maloney et al., 1997). This is also the case during waking in the hippocampus (Bragin et al., 1995) and in the entorhinal cortex (Chrobak and Buzsaki, 1998), major structures of the integrative limbic system involved in memory processes (Grastyan et al., 1959; Landfield et al., 1970; Winson, 1978). Moreover, this rhythm can be conditioned in cats and is increased after daily training (Amzica et al., 1997). Finally, recently, Cape and Jones (1998) showed in rats the importance of the forebrain basalis nucleus in also generating cortical gamma range activity, since it is increased by local infusion of noradrenaline, while it is decreased by serotonin (5-HT) which does not modify the slow wave sleep amount.

[5]Recent findings of Portas et al. (1998) confirm the importance of the thalamus in support of cognitive processes. It may "represent the functional interface between the arousal and the attentional systems" (p. 8988).

2.3. Positron Emission Tomography Findings

Recently, a new field of research into cerebral blood flow variations during sleep–waking stages has been initiated using positron emission tomography. Firstly, Madsen et al. (1991) compared the cortical blood flow during waking and REM sleep, the eleven healthy subjects being awakened from this sleep stage. All subjects reported visual dreams. The authors observed an increase ($P < 0.01$) of blood flow in the associative visual area during REM sleep while there was a decrease in the inferior frontal cortex ($P < 0.01$). They concluded that the activation of visual associative cortex suggests complex processing of visual dream experiences. In contrast, the decrease in the frontal cortex might reflect "the poor temporal organization and bizareness often experienced in dreams" (p. 502). Slow wave sleep was not studied. Maquet et al. (1996) studying 30 young right handed male subjects receiving $H_2\,^{15}O$ infusions found an increase of cerebral blood flow during REM sleep "in the anterior cingulate cortex (mainly Brodmann's area, BA, 24), the posterior part of the right operculum (anterior part of BA 40), the right amygdala and surrounding entorhinal cortex, and in a region encompassing the left amygdala and surrounding entorhinal cortex, the thalamic nuclei... Local maxima of blood flow were located in the left amygdala, left thalamus... Significant negative correlations between regional cerebral blood flow and REM sleep were found in precuneus and posterior cingulate cortex (BA 31) and bilaterally, in a large area of dorsolateral prefrontal cortex (mainly BA 10, but also 46, 9, 8 and the lateral part of BA 11) and in parietal cortex (supramarginal gyrus, BA 40)" (p. 164). The authors suggest that "the amygdalo cingulate coactivation could account for the emotional and affective aspects of dreams. Other formal characteristics of dreams (temporal distorsions, weakening of self reflective control, amnesia on awakening) might be related to the relative prefrontal deactivation" (pp. 165–166). This last result could partly explain the silent locus coeruleus during para-

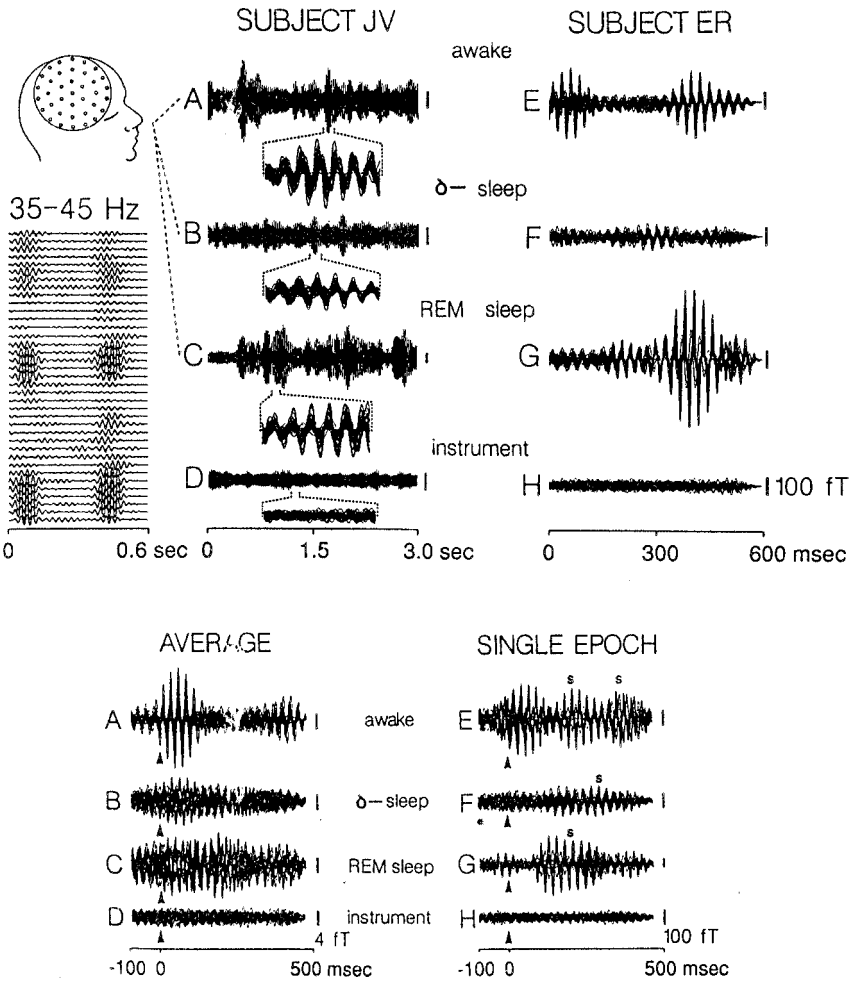


Fig. 10. Llinas and Ribary (1993) recorded the gamma range activity during sleep–waking stages in humans. Top, in the two subjects the rhythm was substantially lower during slow wave sleep (delta sleep stage 4), but it appeared during REM sleep. Bottom, during delta sleep and REM sleep there was no reset following auditory stimulation. Reprinted from *Proceedings of National Academy of Sciences.*

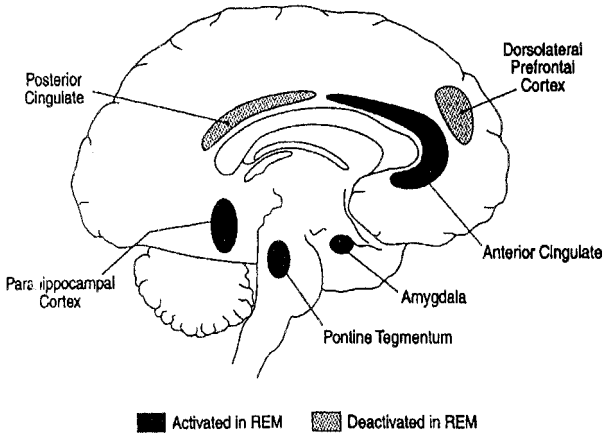


Fig. 11. Positron emission tomography studies show that when compared to waking, the limbic areas of the anterior cingulate, the amygdala and parahippocampal cortices are activated during REM sleep. In contrast, the dorsolateral prefrontal cortex and the posterior cingulate are deactivated. It is noteworthy that the state of the dorsolateral prefrontal cortex is slightly ambiguous (see discussion). Reprinted from *NeuroReport*, with permission of Lippincott-Raven.

doxical sleep since the prefrontal cortex strongly activates its noradrenergic neurons (Jodo et al., 1998). Braun et al. (1998) using the same methodological approach as Maquet et al. (1996) also found during REM sleep a decrease of activation in the dorsolateral prefrontal cortex. Interestingly, he also found an increase of activation of the visual extra striate cortex and the ventral processing stream—as compared to slow wave sleep—while there was an attenuation of activity in the primary visual cortex which could account for the results obtained by Llinas and Ribary (1993) who observed an absence of reset of gamma activity under sensory stimuli during REM sleep (see above). Limbic and paralimbic areas were also activated (Fig. 11). It is noteworthy that Nofzinger et al. (1997) also previously observed limbic activation during REM sleep although they detected an increase of glucose utilization in the dorsolateral prefrontal cortex when compared to waking. Here there seem to be a small discrepancy with Maquet et al. (1996) and Braun et al. (1998) results[6].

Comparison of cortical correlates of waking and paradoxical sleep occurring eye movements were established by positron emission tomography. Hong et al. (1995) observed that the eye movement saccades of paradoxical sleep are associated with an activation of the right hemisphere in the saccadic eye movement system (frontal eye field), dorsolateral prefrontal cortex, the midline attentional system (cingulate and medial frontal cortex, precuneus) and the parietal visual spatial attentional system (bilateral superior parietal lobules, right inferior parietal lobule). These eye saccades were negatively correlated with the glucose metabolic rate in the left inferior parietal lobule. The same areas were activated during waking eye saccades except in the inferior parietal lobule. The REMs of paradoxical sleep could be "saccadic scans of targets in the dream scene" (p. 570).

Cerebral regional blood flow (rCBF) during slow wave sleep was more specifically studied by Jones's group (Hofle et al., 1997) and Maquet et al. (1997). The former (Hofle et al., 1997) observed that "thalamic rCBF decreases dramatically as a function of δ (delta waves of advanced slow wave sleep) and spindle activity, reflecting the disfacilitation and active inhibition of thalamocortical neurons that occur during slow wave sleep and possibly underlie the loss of consciousness and sensory awareness characteristic of that state. Despite this closing of the afferent gateway to the cerebral cortex, certain areas, including the visual and secondary auditory cortex, appear relatively more active, thus revealing a possible substrate for dream-like mentation during slow wave sleep" (pp. 4806–4807) (Fig. 12). "Negative covariation of normalized rCBF and δ was seen in frontal regions of the cortex (anterior cingulate and orbitofrontal cortex" (p. 4806). Maquet et al. (1997) also found a decrease of rCBF in the anterior cingulate and orbitofrontal cortex, and a massive decrease of subcortical structures (pons, mesencephalon, thalamic nuclei and basal forebrain).

Consequently, all above described data show that the cortex is activated during paradoxical sleep as during waking. Although this is not directly the topic of the present paper, it can be recalled that the reticular formation, particularly of the midbrain, is to a great extent responsible for waking processes [Moruzzi and Magoun (1949), recently Steriade (1996)] (Fig. 13). Indeed, sensory afferent influences (Bremer, 1935, 1936, 1937) are not required for such activities (Batini et al., 1959a, 1959b, 1959c). These influences ascend through the thalamus, with complex regulating mechanisms (Steriade and McCarley, 1990), and the basal forebrain [Buzsaki et al. (1988); Steriade and Buzsaki (1990), see also Dringenberg and Vanderwolf (1998)]. This last brain level has apparently an important role, since although acute cerveau isolé preparations show continuous cortical

[6]The REM sleep positive slope of the DC potential (Marshall et al., 1998) also could be related to an increase of cortex excitability in deep layers.

slow wave sleep activities, corresponding chronic preparations recover cortical activations processes (Batsel, 1960, 1964; Villablanca, 1965; Belardetti et al., 1977; Zernicki et al., 1984). Moreover, a thalamectomy does not suppress the possiblity of cortical appearance of low voltage activity in cats (Naquet et al., 1965) Villablanca (1974) even observed an increase of waking EEG and a decrease of slow wave sleep and paradoxical sleep, as compared to normal control cats. Also in cats, the specific electrolytic lesion of the thalamic mediodorsal nucleus does not prevent cortical low voltage activity such as combined lesion of ventralis anterior, anterior ventralis, ventralis lateralis nuclei (Marini et al., 1988). In rats, large but incomplete thalamic lesions (Buzsaki et al., 1988) do not prevent cortical activation activities, a result confirmed by kainate massive lesions (Vanderwolf and Stewart, 1988). These brain stem ascending activating influences progressively decrease during slow wave sleep and disappear transiently just prior to paradoxical sleep (Gottesmann, 1964, 1967, 1996). During paradoxical sleep, the crucial ascending influences responsible for cortical activating activities emanate from pontine (Jouvet, 1962; George et al., 1964; Sakai, 1988; Onoe and Sakai, 1995) and mesopontine levels (Leonard and Llinas, 1990; Steriade and McCarley, 1990).

2.3.1. *Cortical Inhibitory–disinhibitory Balance*

As already mentioned by Creutzfeldt et al. (1956) and Krnjevic et al. (1966a), cortical inhibitory processes had already been addressed by Bubnoff and Heidenhain (1881) and Pavlov (from 1903). The two first authors showed in the morphin-narcotized dog that low-intensity peripheral or cortical stimulation is able to inhibit cortical stimulation-induced motor activities. They hypothesized that cortical inhibitory influences are induced alongside activating ones (p. 190)[7]. For Pavlov (1962), the cortex was first of all considered as essential for conditioned reflexes, and the connection between conditioned and unconditioned stimuli arose from excitatory processes of their respective receptive field which are surrounded by inhibitory areas. The differentiation processes involved concentration of activation, also because of surrounding cortical inhibitory processes (p. 218).

Thereafter, Hess (1931, 1949) was the first to propose that sleep involves cerebral inhibition: ''the essential mechanism of sleep cannot be explained differently as by active inhibition of some functions of the organism'' (Hess, 1931, p. 1553).

In the later studies on cortical inhibitory processes related to sleep, Evarts et al. (1960) initiated this field of approach with the electrophysiological analysis of the recovery cycle of responsiveness. Stimulating the lateral geniculate radiations, they showed that there was, for the positive wave 4 and the negative wave 5 of the evoked potential, a more substantial recovery during slow wave sleep than during waking. This means that there were more important cortical inhibitory processes during waking. Rossi et al. (1965) found the same results but, in addition, observed that the recovery was still slightly more rapid for paradoxical sleep (Fig. 14). A shortened recovery time during slow wave sleep and paradoxical sleep was also found by Allison (1968) in the sensorymotor cortex. All these studies performed in cats clearly show a cortical disinhibitory process during sleep and particularly during paradoxical sleep.

However, in those days, the most detailed study related to the forebrain inhibitory processes during sleep–waking cycle was produced by Demetrescu et al. (1966) in cats. Using four consecutive stimuli applied to the geniculate nucleus in two successive couples, with short interval (*ca* 7 msec), the third stimulus being delivered at longer interval (from 50 msec), they were able to dissociate facilitatory and inhibitory influences induced at cortical level, by the amplitude and recovery cycle of the evoked potentials (Fig. 15). Attentive waking was characterized by a high level of activating and inhibitory influences (high amplitude of the first response and long recovery). Both influences were decreased during relaxed waking. The activating influences decreased significantly during slow wave sleep while inhibitory ones were maintained at a higher level, identical to the level of relaxed waking. Just prior to onset of paradoxical sleep both types of influences were at their lowest level. Finally, during paradoxical sleep, the activating influences were increased whereas there was a strong disinhibition. These interesting results, particularly the concomitant significant activation and inhibition during waking opposed to the activation and disinhibition during paradoxical sleep led us, at that time, to draw up psychophysiological hypotheses about dreaming neurophysiological support (Gottesmann, 1967, 1970, 1971).

The intimate processes related to cortical inhibition were extensively studied by the team of Krnjevic et al. (1966a, 1966b, 1966c). Indeed, although Creutzfeldt et al. (1956) observed at cellular level true inhibition resulting from direct cortical and transcallosal stimulation, Krnjevic et al. (1966a) observed an inhibition of extracellular recorded cortical neurons, particularly in neurons preliminary activated by local application of glutamate or acetylcholine (Fig. 16). This inhibition could be induced by cortical, transcallosal, thalamic and peripheral stimulations. It could last up to 300 msec but was often preceded and followed by phases of increased excitability. Only the antidromic stimulation of the cortical pyramidal cells was much less effective in evoking inhibition of Betz cells. This inhibitory process at cortical level is a general phenomenon, since the authors observed it in cats, rabbits and monkeys. In the following paper, Krnjevic et al. (1966b) established definitively that this inhibition is intracortical, since it was observed in isolated cortical labs. Its inhibitory nature could be overcome by

[7]These experiments were based on the previous data of Fritsch and Hitzig (1870) who showed in dogs: 1, that the cortex (generally brain tissue) is excitable; 2, the localization of the motor cortex; 3, that there is a somatotopy (p. 311). This pioneer work was also at point of departure of the original but questionable clinical observations of human cortex stimulation by Bartholow (1874), who showed the localization of the motor and somesthetic cortex, and that brain tissue is insensitive to pain.

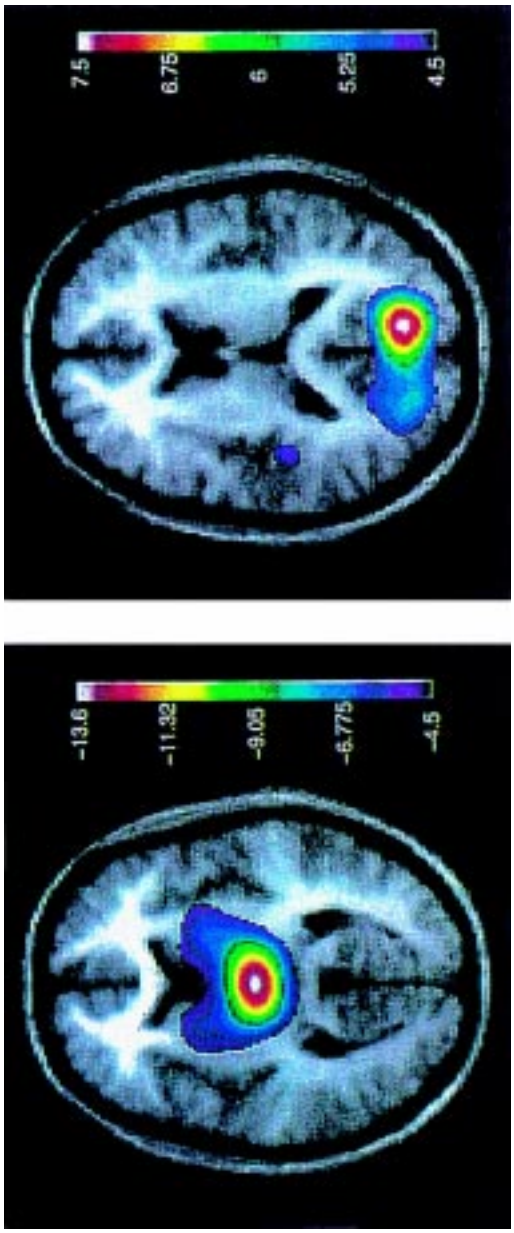
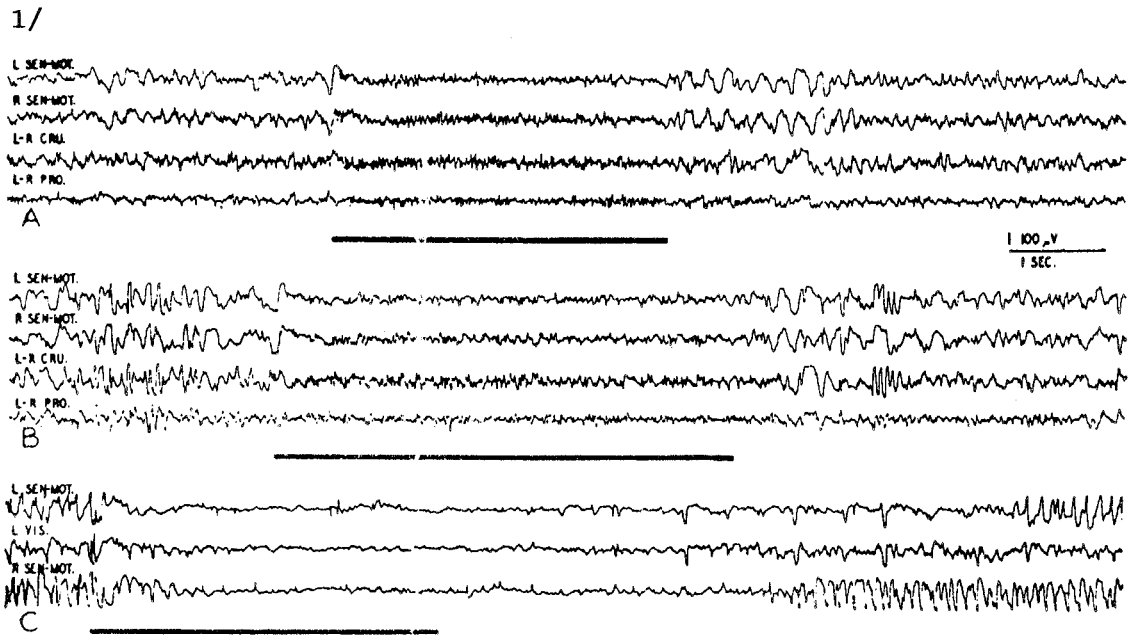


Fig. 12. Hofle et al. (1997) studied the cerebral blood flow during slow wave sleep. They found a decrease in the thalamus (left), an increase in the visual cortex and a light increase in the secondary auditory cortex (right) when spindles and delta waves occurred. Reprinted from the *Journal of Neuroscience*, with permission.



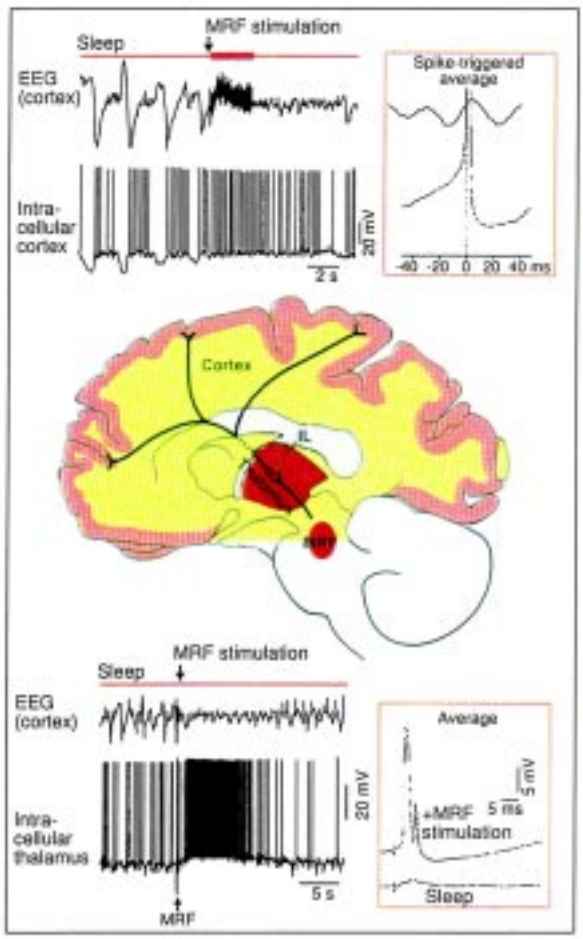


Fig. 13. (*Caption opposite*).

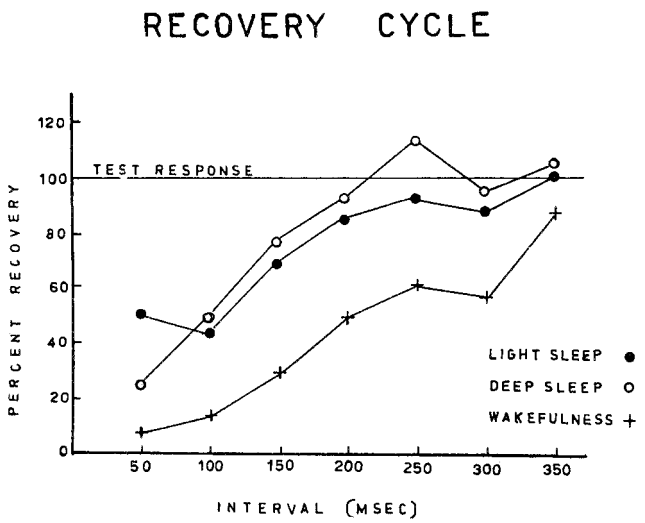


Fig. 14. Rossi et al. (1965) showed that the cortical recovery cycle of the visual cortex tested by radiation stimulation is shorter during slow wave sleep than during waking and still slightly shorter during paradoxical sleep. Reprinted from CNRS edited with permission.

higher doses of glutamate. In addition, true inhibitory postsynaptic potentials (IPSP) could be recorded by intracellular recordings. The authors postulated that this inhibition results from activation of interneurons influencing other cortical neurons. In the third paper (Krnjevic et al., 1966c), although several drugs were tested to try to identify the neurochemical support of this cortical inhibition, without true success, a note added in proof described "a remarkable similarity between the action of GABA (gamma aminobutyric acid) and of inhibition" (p. 102).

In 1973 and 1974, Steriade's team published three papers (Steriade and Deschênes, 1973, 1974; Steriade et al., 1974) on the inhibitory processes of the cortex which were studied in monkeys. Unfortunately, the research was devoted to variations during arousal, steady waking, slow wave sleep but not paradoxical sleep. The main results were that fast pyramidal neurons stopped firing and slow pyramidal neurons increased their firing during arousal from slow wave sleep, the activity of both being increased during steady waking. In contrast, interneurons, characterized by a high firing rate, increased their discharges during slow wave sleep. Finally, the inhibition of pyramidal tract neurons which followed pes pedunculi stimulation, lasted much longer during slow wave sleep than during waking. The authors concluded that "if one consider that inhibitory mechanisms subserve a fine control of corticofugal responses to incoming messages and knowing that receptive fields shrink during cortical inhibition, thus enhancing contrast, the deep and short feedback and feedforward inhibition seen during steady waking shows that this state provides neuronal organization leading to accuracy in the analysis of excitatory inputs and to ability in following rapidly recurring activity" (Steriade and Deschênes, 1974, p. 1112). In a following paper, Steriade et al. (1979) studied in cats the antidromic response induced in neurons of the associative parietal cortex by stimulation of different subcortical structures. The excitatory–inhibitory process which followed stimulation was very similar during waking and paradoxical sleep and differed from that of slow wave sleep during which the firing was lower and the inhibitory rebound of longer duration.

From all above results, it can be concluded that, during paradoxical sleep, like during waking, there are strong activating influences allowing cortical functioning but also that the inhibitory processes

Fig. 13. 1, Moruzzi and Magoun (1949) activated the cortex of light-anesthetized cat by stimulation of the brain stem reticular formation A and B: encéphale isolé cats. C, Intact animal. Reprinted from *Electroencephalography and Clinical Neurophysiology*, with permission of Elsevier. 2, Steriade (1996), using the intracellular data currently available, confirms that stimulation of the midbrain reticular formation activates cortical EEG field activity and increases the firing of cortical (top) and intralaminar thalamic (bottom) neurons. Upper inset, 'enlarged view of the intracellular recorded action potentials and 30 Hz EEG waves during midbrain reticular stimulation (spike-triggered average)'. Bottom inset, 'averaged intracellular responses show increased probability of responses, resulting in cell firing, during the activated period (top) and subthreshold responses during the sleep period'. Abbreviations: IL, intralaminar thalamus; MRF, midbrain reticular formation. Reprinted from *Science*. Nevertheless, it has to be emphasized that the lesion of cell bodies in the midbrain reticular formation does not suppress waking (Denoyer et al., 1991).

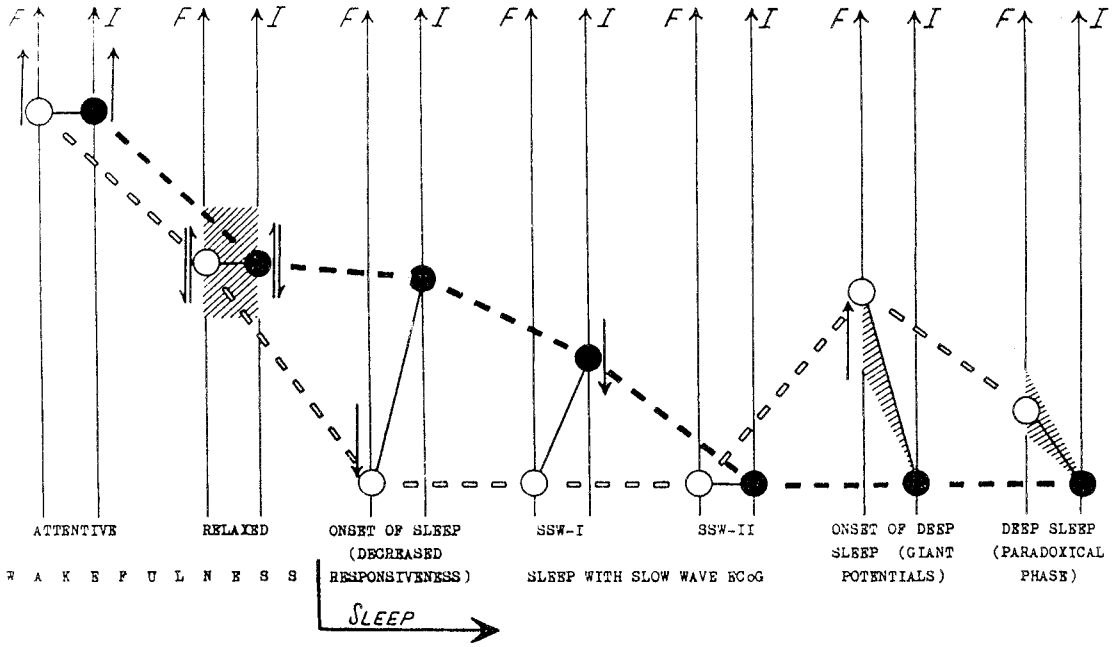


Fig. 15. Demetrescu et al. (1966) distinguished facilitatory and inhibitory influences acting at cortical level during sleep–waking cycle in cats. Their conclusion was issued on the variation of amplitude of four consecutive thalamocortical evoked potentials induced in the visual cortex by geniculate nucleus stimulation. Reprinted from *Electroencephalography and Clinical Neurophysiology*, with Elsevier's permission.

possibly regulating this cortical functioning appear to be decreased during paradoxical sleep.

2.4. Neurochemical Approach

There were three successive, but now complementary, historical steps in the development of neurosciences: the anatomo-functional approach which really began with the discovery by Broca (1861) of true cerebral localizations, then the electrophysiological approach and now the major neurochemical field. These three approaches have the same aim: to identify the intimate functioning and responsibility of the structures implicated, in our topic, in sleep–waking processes.

2.4.1. *Acetylcholine*

The first neurotransmitter studied in the neurochemical approach, the 'wet' neurophysiology (Schmitt, 1962; Jouvet, 1972), was acetylcholine. The first paper devoted to cortical activating processes seems to be that of Bonnet and Bremer (1937). In encéphale isolé cats injection of acetylcholine into the carotid (at very low dose: 0.1–0.2 γ) induced an activation of the EEG. The effect was short-lasting (2–4 min). Bremer and Chatonnet (1949) further studied the influence of eserine and prostigmine (anticholinesterase compounds) which induced similar effects but with longer latency and longer duration. In contrast, atropine (a muscarinic receptor blocker) had an antagonist effect, high doses significantly slowing down the EEG. A much more frequently quoted paper, probably because being in English, is that of Wikler (1952), performed on chronic dogs without anesthesia. After subcutaneous injection of atropine, he observed EEG slow wave sleep patterns in the dog 'excited' behaviorally (Fig. 17). He concluded "that the spontaneous electrical activity of the cerebral cortex reflects the activity of neuronal systems which, in part at least, are independent of those neuronal systems that subserve behavior in general" (pp. 264–265). In these three pioneer papers it was clearly shown that acetylcholine activates the EEG, although the mode of action (direct or indirect) was not elucidated. Several authors later confirmed these conclusions [see Vanderwolf (1988), Szymusiak et al. (1990) for more recent results and references)] However, at cellular level in monkeys, acetylcholine excites and inhibits almost the same number of neurons, the "inhibitory responses to acetylcholine having shorter latency and faster recovery than the excitatory responses"...The threshold of both inhibitory and excitatory responses were almost the same. In some cases the "responses to acetylcholine reversed from excitatory to inhibitory with increasing dose" (Nelson et al., 1973, p. 123)[8].

The following papers showed a release of acetylcholine at cortical level. Mitchell (1963) made an extensive study in several mammals and was able to quantify the release level which was increased during cortical and somesthetic stimulation. Kinai and Szerb (1965) found similar cortical increase of

[8]Recent research shows that pyramidal cells are excited by acetylcholine directly applied either at dendrite or at soma level (Mednikova et al., 1998).

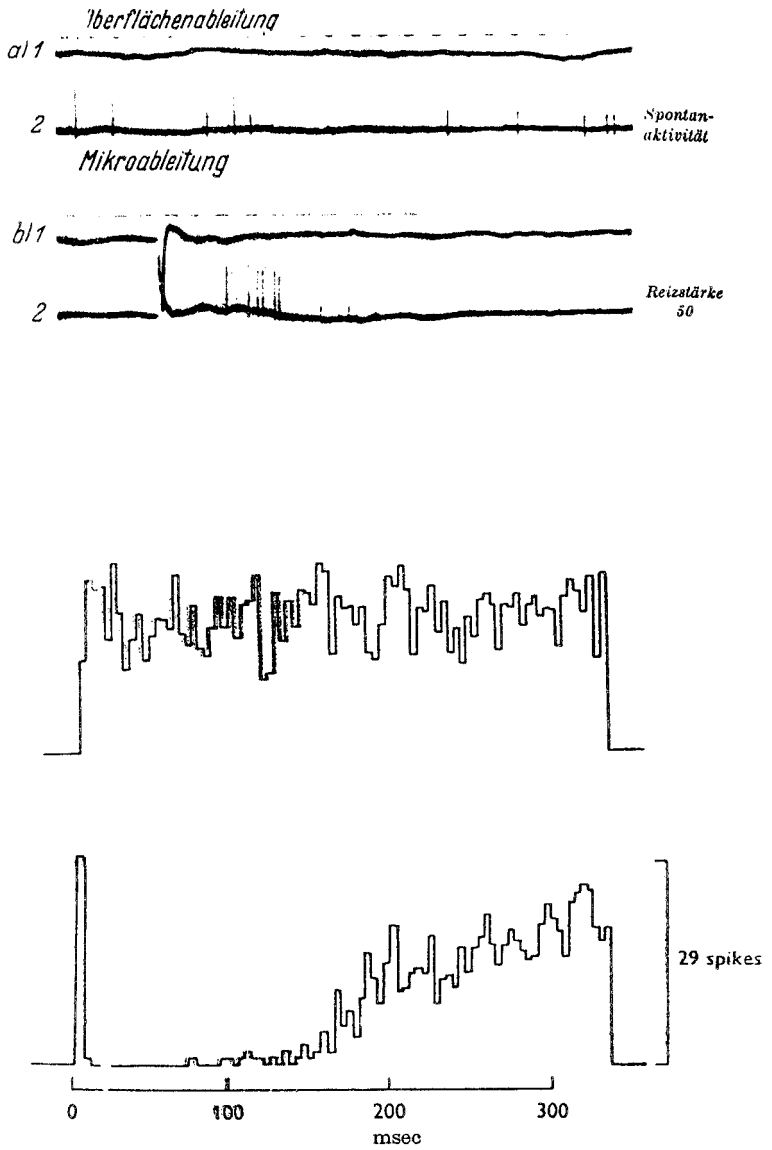


Fig. 16. Top, Creutzfeldt et al. (1956) identified cortical inhibitory processes in the visual cortex. (A) 1, Superficial recording; 2, spontaneous neuron activity. (B) Neuron activity after cortical stimulation at 1–3 mm of the microelectrode. There is first an inhibition of firing followed by a rebound of activity. From *Archiv für Psychiatrie und NervenKranheiten*, with permission from Springer Verlag. Bottom, Krnjevic et al. (1966a) recorded cortical neurons activated by glutamate. Their control firing (top) was inhibited by a stimulation produced at 3 mm distance (bottom). From *Journal of Physiology*, with permission.

acetylcholine release during activation induced by stimulation of mesencephalic reticular formation and Phillis and Chong (1965) confirmed the link of cortical release of acetylcholine and EEG activation. All these up to those days data were confirmed by Celesia and Jasper (1966), Szerb (1967), Cuculic et al. (1968) and Pepeu and Bartolini (1968) (Fig. 18). Then, began the already mentioned studies of the basal forebrain, involved in cortical activating processes. They showed that there are cholinergic projections from this area to the entire cortex (Divac, 1975; Lehmann et al., 1980; Bigl et al., 1982) and that basal forebrain electrical stimulation favors acetylcholine release in the cortex (Kurosawa et al., 1989) (Fig. 19), release which was increased by amphetamine and inhibited by GABA agonists (Casamenti et al., 1986). Moreover, basal forebrain neurons firing is increased five-fold during cortical activation (Détari and Vanderwolf, 1987). The implication of cholinergic basal forebrain in cortical activation was clearly identified by several researches, the more extensive being those of Buzsaki et al. (1988) and Buzsaki and Gage (1989), performed in rats. This study showed that nucleus basalis lesion induces cortical slow waves. It also confirmed that the firing of the nucleus basalis

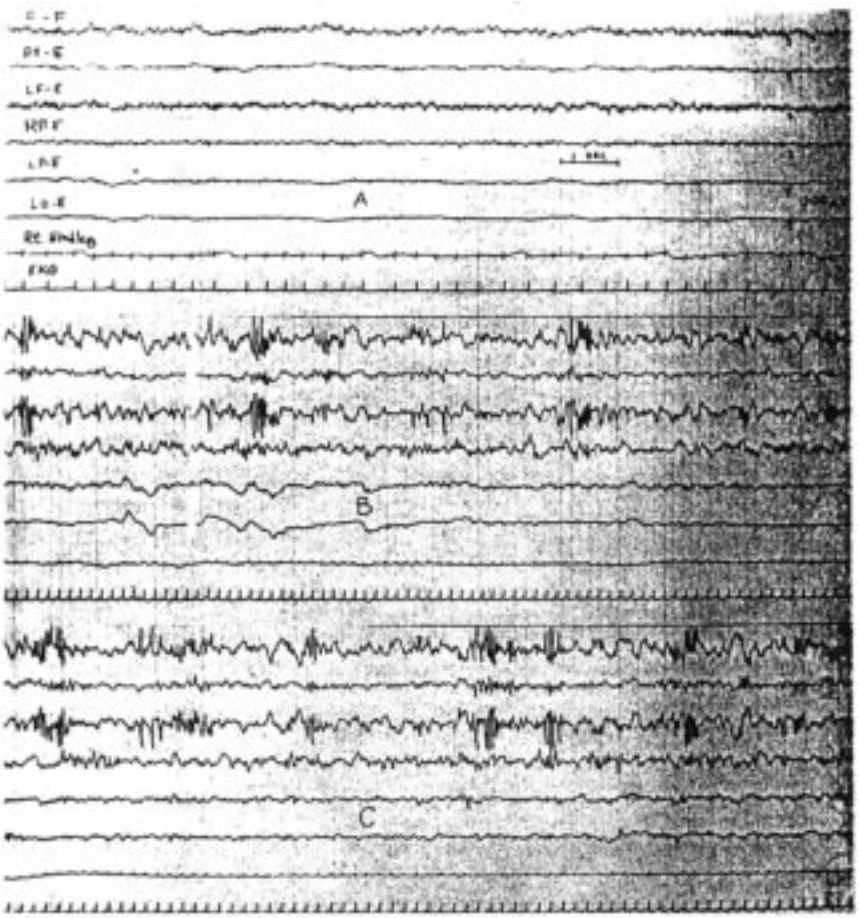


Fig. 17. Wikler (1952) studied the effect of atropine (a muscarinic receptor blocker) on the cortical EEG activity. (A) Waking control; (B) 23 min after subcutaneous injection of atropine. (C) 31 min after injection. Under atropine, the behaviorally waking dog shows cortical slow waves and spindles. Reprinted from *Proceedings of Society for Experimental Biolgy and Medicine*, with permission of Blakwell Science.

increases during EEG activation[9] and that it inhibits the GABAergic neurons of the thalamic reticular nucleus which is responsible for thalamocortical spindles, by inducing a burst firing mode (Steriade et al., 1985, 1987, 1993), and slow waves (Nunez et al., 1992). Once again, in spite of the inhibition of some cortical neurons by acetylcholine (Nelson et al., 1973) the importance of this basal forebrain structure in cortical waking mechanisms, was emphasized by the fact that its activation induces cortical low voltage activity (see above).

Ray and Jackson (1991) confirmed that basal forebrain lesions induce cortical slow waves and reduce cortical choline acetyltransferase activity, these effects being inverted by intracortical grafts of embryogenic basal forebrain tissue in kainic acid lesioned basal forebrain of rats (Vanderwolf et al. (1990). However, other cholinergic processes also favor EEG activation, since cholinergic agonists, given systemically, induce cortical actiavtion in the rat with kainic lesions of the basal forebrain. These influences are probably mediated by thalamic projections of pedunculopontine and dorsolateral tegmental cholinergic nuclei (Vanderwolf et al., 1993). The importance of these muscarinic activating influences were further studied by Metherate and Ashe (1991), Metherate et al. (1992), and McCormick (1992). This latter wrote a major review on this topic. The important point is that very few of acetylcholine cortical terminals give rise to synaptic junctions. This is the case for only 14% of terminals which concerns $< 3\%$ of the total surface of varicosities [see Descarries et al. (1997) for review]. This mean that cortical release of acetylcholine is largely responsible for diffuse transmission processes, the transmitter acting on a large population of neurons. It could explain influences such as the cortical sensory reorganization after nucleus basalis stimulation (Kilgard and Merzenich, 1998), the cortical release of acetylcholine being increased by sensory stimulations (Inglis and Fibiger, 1995). This increase is reduced by α_2 noradrenergic agonists and α_1 antag-

[9]Later on, Nunez (1996) dissociated tonic and bursting neurons in the nucleus basalis. The second ones fired in bursts during synchronized EEG, and tonically during EEG activation.

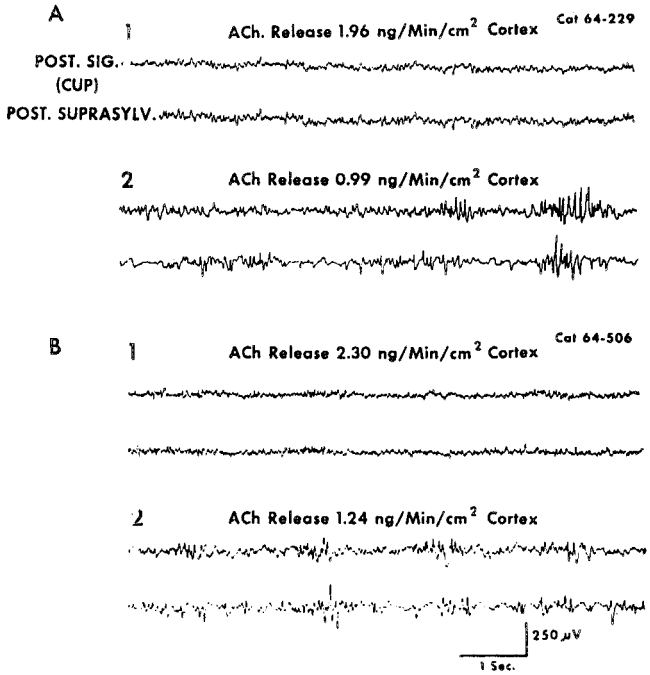


Fig. 18. Celesia and Jasper (1966) demontrated that the cortical release of acetylcholine in cats A and B is higher during activated EEG (1) than during slow wave sleep (2). Reprinted from *Neurology*, with permission of Lippincott-Raven publishers.

onists, while the basal release of acetylcholine is not affected (Acquas et al., 1998).

To conclude on acetylcholine influences on the cortex, in spite of the fact that they are functionally crucial, as shown by animal experiments (Muir et al., 1994) and Alzheimer's syndrome (Iversen, 1998; Ladner and Lee, 1998)[10], this transmitter release does not show significant differences between waking and paradoxical sleep liable to explain a dissociation of psychophysiological functioning. Indeed, as shown (as early as 1971) by Jasper and Tessier (1971), acetylcholine release at cortical level is slightly higher during paradoxical sleep (2.2 ng/min) than during waking (2.1 ng/min) and significantly lower during slow wave sleep (1.2 ng/min). This result has been recently confirmed (Marrosu et al., 1995). Consequently, acetylcholine on the cortex is essentially linked to EEG activation[11].

2.4.2. *Dopamine*

The cortical influences of dopamine offer an interesting area of investigation since dopaminergic neurons do not show significant variations of firing during the different sleep–waking stages in rats (Miller et al., 1983) and cats (Trulson and Preussler, 1984) (Fig. 20).

Although Dahlström and Fuxe (1964) identified dopaminergic neurons in the mesencephalon and diencephalon using the formaldehyde fluorescent method of Falck et al. (1962), it was Thierry et al.

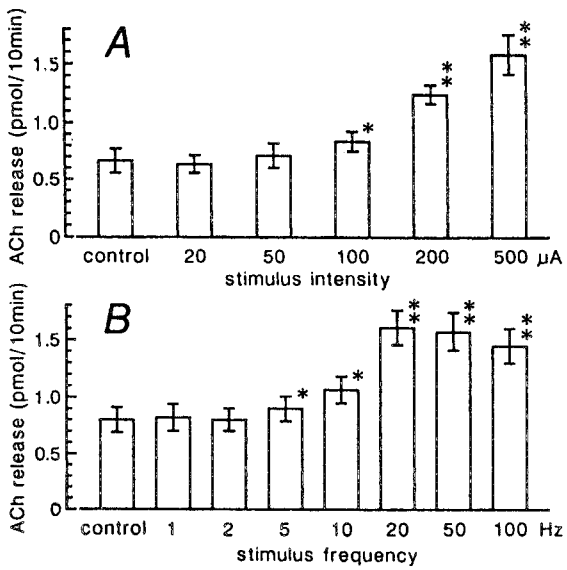


Fig. 19. Kurosawa et al. (1989) increased cortical release of acetylcholine by stimulation of forebrain nucleus basalis (Meynert nucleus in humans) which is responsible for the main cholinergic input of the cortex. This increase varied with frequency and intensity of stimulation. Reprinted from *Neuroscience Letters*, with permission of Elsevier.

[10]It is noteworthy that the role of acetylcholine in Alzheimer's disease is questioned by some researchers. Indeed, some patients have no neuronal loss in the Meynert nucleus and in the olivopontocerebellar atrophy with very limited dementia, there is considerable loss of neurons in this nucleus (Smith, 1998).

[11]For general implications of acetylcholine in sleep mechanisms, the reader can consult Jouvet (1975), Jones (1991) and Baghdoyan (1997).

(1973) who first described the presence of dopamine in the cortex by dosage amount. However, they could not clearly dissociate between axon terminals and cell bodies, since they made slightly too lateral lesions of the ventral tegmental area A_{10} which did not reduce cortical content. Hökfelt et al. (1974) described dopamine nerve terminals in the limbic and "basal parts of frontal" cortex and established the relationship with schizophrenia. Fuxe et al. (1974) first showed the existence of mesolimbic and mesocortical dopaminergic systems stemming of area A_{10} (and as described in those days, medial A_9 area). Although in the rat, the dopaminergic neurons innervate only the prefrontal neocortex, in primates they project to all cortical areas [Berger et al. (1991) see their Table 1 for summary]. As shown by Smiley and Goldman-Rakic (1993), the neuron terminals in the prefrontal cortex of monkeys "indicates a relatively high incidence of synapses per varicosity. In addition to identifiable synapses on 39% of surveyed varicosities, we often noted subtle membrane specializations that were suggestive of synapses...It is possible that the most or all dopamine varicosities form synapses. This interpretation does not exclude nonsynaptic dopamine effects; in fact, there is a growing body of literature that indicates that neurotransmitters do act via diffusion over a distance" (Smiley and Goldman-Rakic, 1993; p. 229). "The majority of dopamine synapses are on pyramidal cells (and) there was also a significant fraction on apparent nonpyramidal cells" (p. 232)..."probably belonging to GABAergic interneurons" (p. 234). The authors mention that in human cortex, the varicosities are of larger size like all dendrites receiving dopamine synapses. Moreover, "dopamine synapses are about evenly divided between spines and shafts in all layers" (p. 236).

As shown by Krnjevic and Phillis (1963) (thus, prior to demonstration of dopamine existence at cortical level) this transmitter inhibits cortical neurons activated by glutamate or sensory stimulation. "This inhibition is mediated, at least in part, by a calcium-dependent process" (Yarbrough et al., 1974). This long latency and long-lasting inhibition, blocks acetylcholine excitatory effects (Reader et al., 1979) (Fig. 21). More recent findings have shown that dopamine has a double inhibitory influence at cortical level, by favoring GABA release from spontaneous firing interneurons by an action on D_2 receptors (Rétaux et al., 1991; Pirot et al., 1992; Grobin and Deutch, 1998) and also inducing direct inhibition of pyramidal cell apical dendrite (Pirot et al., 1992). Today results demonstrate that dopamine changes the cortical long-term potentiation (LTP) induced by glutamate in long-term depression (LTD) and probably "acutely modifies signal/noise relation...Dopamine may generally filter dendritic transmission but it may amplify the signal at soma...With this mechanism, dopamine may gate to select significant events to transmit further within

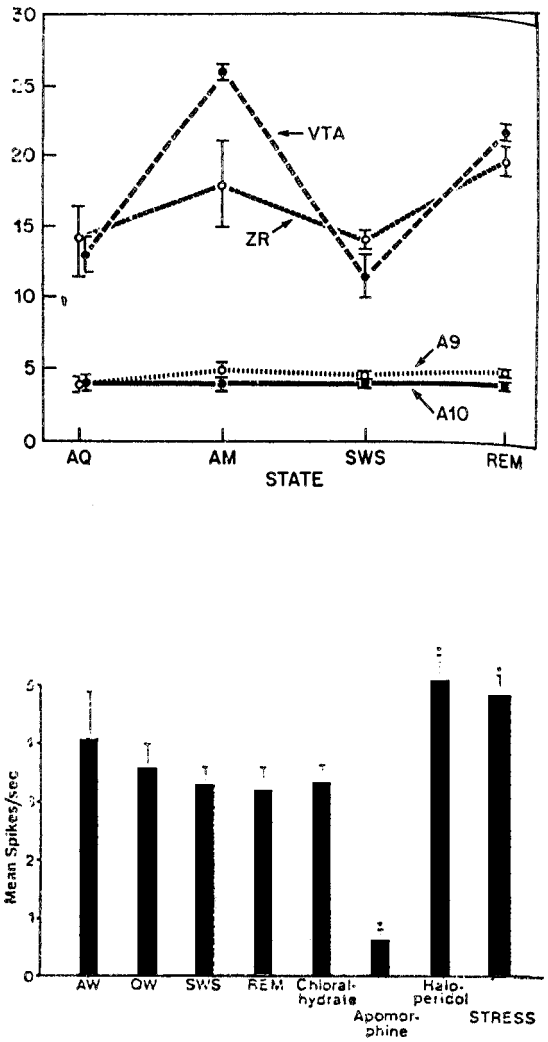


Fig. 20. Top, Miller et al. (1983) showed in rats that the dopaminergic neurons of areas 9 (substantia nigra) and 10 (ventral tegmental area at the origin of mesolimbic and mesocortical projections) slowly fire similarly during all sleep–waking stages (lower curves). Non dopaminergic neurons fired differently (upper curves). Abbreviations: VTA, ventral tegmental area; Zr, zona reticulata of substantia nigra. Reprinted from *Brain Research*, with Elsevier's permission. Bottom, Trulson and Preussler (1984) confirmed in cats the similar mode of firing of dopaminergic neurons in area 10 during the sleep–waking cycle. Abbreviations: AW, active waking; QW, quiet waking; SWS, slow wave sleep; REM, paradoxical sleep. Reprinted from *Experimental Neurology*, with permission.

and from the prefrontal cortex" (Otani et al., 1998, p. 675)[12]. From an intregated standpoint, Luciana et al. (1998) also state that dopamine "with respect to cognitive functions (induces) signal-to-noise enhancement. Dopamine enhances the incoming neural signal to background noise or interference" (p. 218). These results have been shown principally in rats where there are only dopaminergic cortical terminals in the prefrontal cortex. They probably concern other areas in humans (Smiley and Goldman-Rakic, 1993).

[12]It was recently shown that, in some cases, dopamine can depolarize prefrontal pyramidal cells *in vitro*, may be by a nonspecific mechanism (Shi et al., 1997).

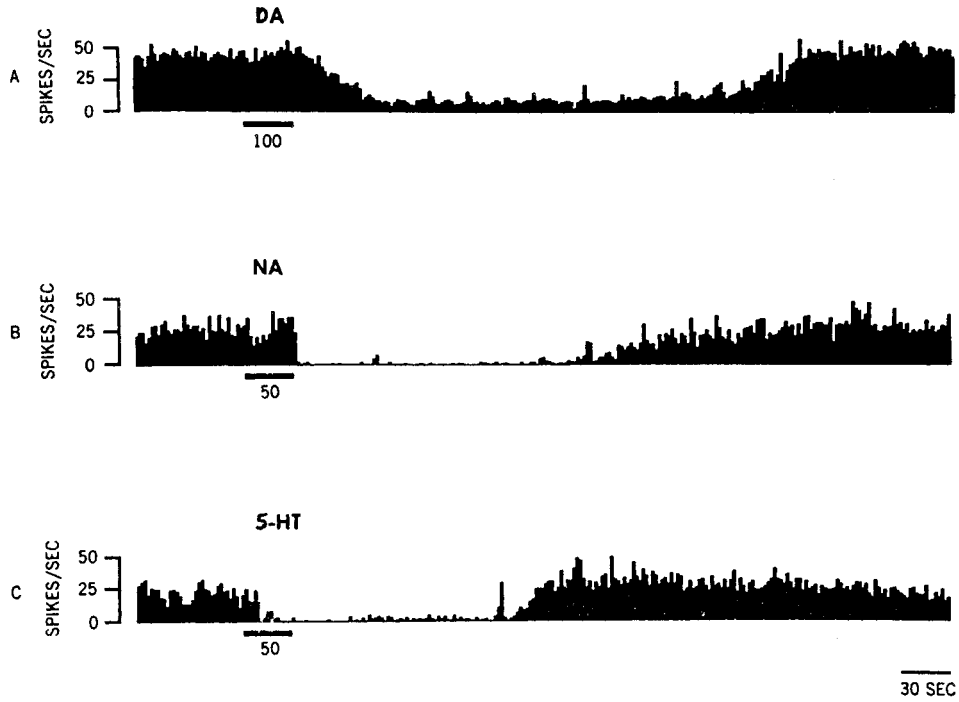


Fig. 21. Reader et al. (1979) confirmed that microiontophoretic application of dopamine (DA), noradrenaline (NA) and 5-HT inhibits cortical neurons activated by acetylcholine. Reprinted from *Brain Research* with permission of Elsevier.

It is not the aim of this paper to analyze in details the integrative functions of dopamine at cortical level. However, dopamine implication in cognitive processes has long been established in monkeys (Brozovski et al., 1979) and rats (Simon et al., 1980), and schizophrenia which involves forebrain dopaminergic disturbances, induces cognitive and attention troubles. The role of dopaminergic terminals is crucial in working memory (delayed responses and delayed alternation), the D_1 receptors being particularly implicated. Indeed, oculomotor delayed response is impaired in monkeys by D_1 receptor antagonists (Sawaguchi and Goldman-Rakic, 1991), which could result from an excessive receptor blockade possibly preventing facilitatory glutamatergic *N*-methyl-D-aspartate (NMDA) processes (Williams and Goldman-Rakic, 1995). Furthermore, "Recently, it has been suggested that the beneficial effect of the atypical neuroleptic, clozapine, on the negative symptoms of schizophrenia may be due to its action on dopamine D_4 receptors, a property not shared by typical neuroleptics" (Iversen, 1998, p. 213). In this short and incomplete summary of cortical dopaminergic functions, it can be added that dopamine could intervene in Alzheimer's disease, since the D_2 receptor band distribution (principally in layers III and IV) which appears in the temporal cortex of the normal human (Goldsmith and Joyce, 1996) disappears in this syndrom, which could "contribute to the disturbances in information processing (and) promote the cognitive and non-cognitive impairments" (Joyce et al., 1998, p. 7). Finally, ontogenetic growing of cortical dopaminergic terminals was shown to be function of environment (Winterfeld et al., 1998).

The effects of dopamine on sleep–waking behavior have revealed that apomorphine and other agonists, at low dose, have sedative and slow wave sleep inducing properties, by acting at autoreceptor level. In contrast, at high doses, they induce waking activities by an action at postsynaptic level (Di Chiara et al., 1976; Kafi and Gaillard, 1976; Gessa et al., 1985; Bagetta et al., 1988; Monti et al., 1989; Kroft and Kuschinsky, 1991). This double mode of action was first demonstrated by Carlsson (1975). The D_2 receptor type situated either at pre- or postsynaptic could be particularly involved in this dual behavioral effect (Bagetta et al., 1988; Monti et al., 1989; Kroft and Kuschinsky, 1991).

To conclude, in relation to the topic of this paper, the dopamine influence on cortical activity seems to be sustained since the neuron firing is not significantly changed during sleep–waking cycle. Moreover, dopamine plays an original role since it involves few interferences with other transmitters. Indeed, it has probably only facilitating influences on cortical acetylcholine release by an action on the basal forebrain neurons (Day and Fibiger, 1992).

2.4.3. *Noradrenaline*

Noradrenaline has important functions. Its impact on waking processes has long been identified and recent findings have revealed that molecules which increase waking (Lin et al., 1992), without disturbing attentional performances (Stivalet et al., 1998), could be partly related to a Gabaergic disinhibition of noradrenergic neurons (Fuxe et al., 1996).

Moreover, locus coeruleus stimulation induces "well-being" and "improved clarity of...thinking" (Libet and Gleason, 1994, p. 179).

After a brief mention (Fuxe, 1965), a full description was given of noradrenaline in cortical nerve terminals with varicosities in all areas (Fuxe et al., 1968). Prior to this, Krnjevic and Phillis (1963) had already tested the effect of cortical applied neurotransmitters. In a three words sentence they indicated that noradrenaline had a weaker inhibitory effect on neurons than dopamine and adrenaline. Soon afterwards, Frederickson et al. (1971) showed that inhibition was maximal at pH 4 in the spontaneous as well as in the glutamate-fired cells. Two years later, Phillis et al. (1973) confirmed that "noradrenaline had only depressant actions on rat cortical neurons" (p. 466) and that this effect is abolished by calcium antagonists, as with the other monoamines [see also Yarbrough et al. (1974)] (see Fig. 21). Similar inhibitory influences were shown by Nelson et al. (1973) in monkeys which are not mediated by cyclic adenosine monophosphate (cAMP) (Lake et al., 1972, 1973). In fact "all noradrenaline sensitive pyramidal tract cells are depressed by noradrenaline, and it is only when attention is transfered to non-pyramidal tract cells that excitant responses can be found, although the number seen here was much less" (Stone, 1973, p. 342). Nelson et al. (1973) also observed that only "5 neurons (out of 77 examined) accelerated their firing rate during application of noradrenaline" (p. 121). Histological studies progressed in the same decade. Descarries and Lapierre (1973) showed that, besides varicosities at noradrenergic nerve terminals, there are true synaptic contacts between axons and postsynaptic dendrites. In 1977, Descarries et al. (1977), also in rats, determined that "widely dispersed unmyelinated axons of very fine caliber" give rise to varicosities with highly concentrated noradrenaline with a "very low proportion...of genuine synaptic relationships...It seems probable that noradrenergic afferents might exert a diffuse...and tonic influence on vast neuronal assemblies, and thus modulate integrative and/or specific cortical functions" (p. 198). At the same time, Levit and Moore (1978) showed that the cortex is ipsilaterally innervated by the locus coeruleus, the more intense branching being in the molecular layer (Fig. 22).

Consequently, in the late 1970s, it was already established that noradrenaline has a predominantly inhibitory influence on the neuronal activity of the cortex. In 1975, Foote et al. (1975) recorded in monkeys neurones of the auditory cortex during spontaneous activity and during vocalization-evoked discharges. Local iontophoretic infusion of noradrenaline decreased both firings, the spontaneous decrease being larger. While "GABA may cause brief inhibitory pauses observed in auditory responses (such pauses appear to result from active inhibition), noradrenaline may provide a tonic, low-level inhibition accounting for observed spontaneous IPSPs, and the resulting low spontaneous activity levels in these cells. Such tonic inhibition...would enhance the difference between background and stimulus-bound activity" (p. 241). Later on, this phenomena was termed "increase in the signal to noise ratio" (Aston-Jones and Bloom, 1981b). Waterhouse et al. (1990) arrived to similar conclusions with noradrenaline for visual stimuli and Warren and Dykes (1996) for somatosensory ones. Finally, the increase of cortical noradrenaline release induced by qualitative changes of naturalistic environmental stimuli in the rat seems to promote such a process (Dalley and Stanford, 1995). As stated by Berlucchi (1997), quoting other authors, "the direct actions of acetylcholine and noradrenaline on cortical neurons have been described as increasing the signal/to/noise ratio of the response of these neurons to their specific stimuli. The effect on the signal/to/noise ratio by acetylcholine seems to be due to signal enhancement relative to an unchanged noise, while that from noradrenaline seems to be due to a noise reduction relative to an unchanged signal" (p. 8).

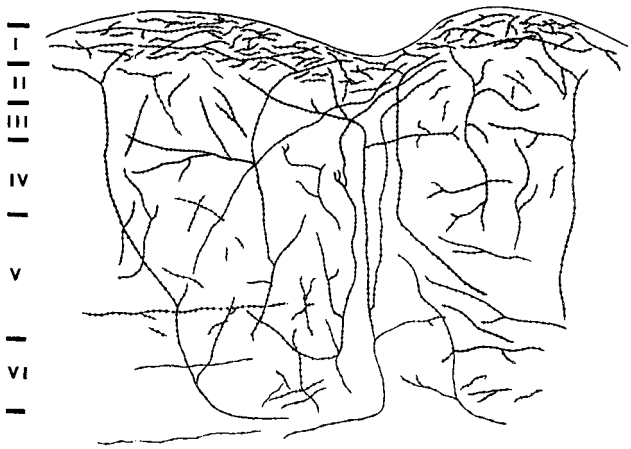


Fig. 22. Levit and Moore (1978) confirmed that noradrenaline cortical terminals which end in all cortical layers, but preferentially in the upper ones, comprise large number of varicosities as is the case for other aminergic terminals. Reprinted from *Brain Research*, with permission of Elsevier.

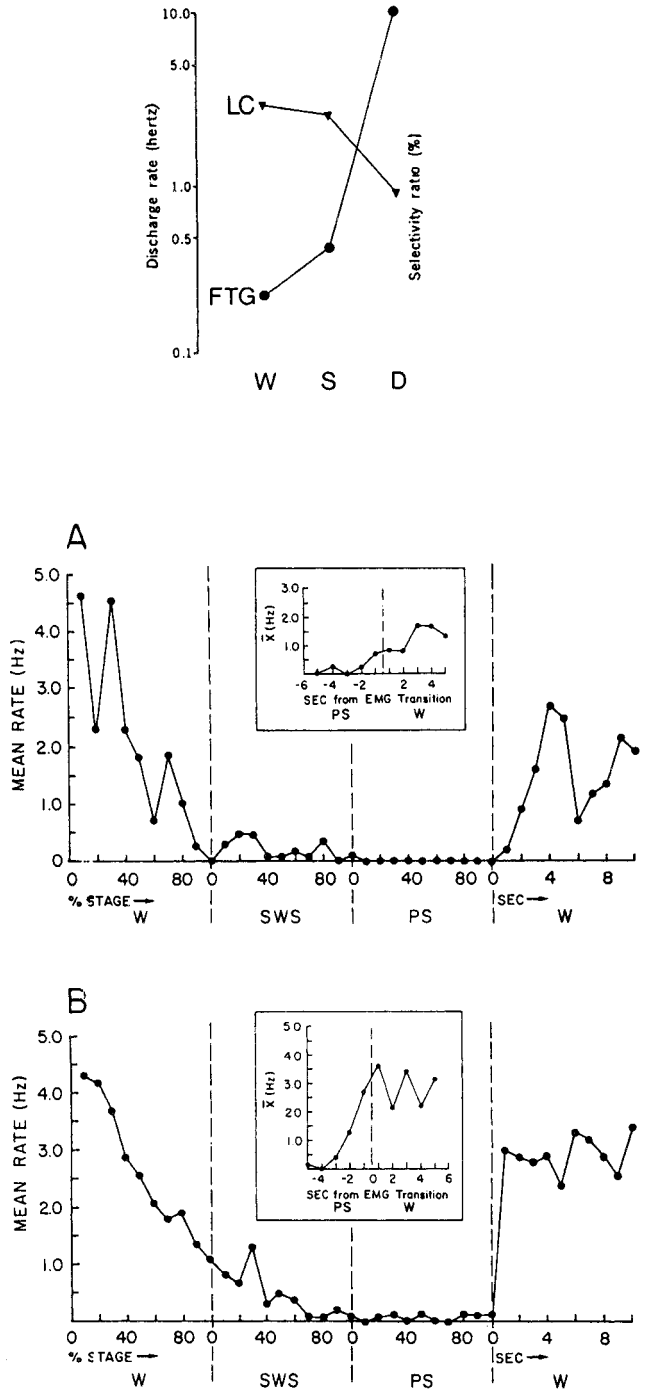


Fig. 23. Top, Hobson et al. (1975) showed in cats that the locus coeruleus neurons which innervate the cortex decrease their firing rate during slow wave sleep and become nearly silent during paradoxical sleep. Abbreviations: LC, locus coeruleus; FTG, gigantocellular tegmental field; W, waking; S, slow wave sleep; D, paradoxical sleep. Reprinted from *Science*, with permission. Bottom, Aston-Jones and Bloom (1981a) showed in rats [by single (A) and multiunit (B) recordings] that the noradrenergic neurons of locus coeruleus become silent during paradoxical sleep. As shown in the insets these neurons anticipate the reappearance of dorsal neck muscle activity of waking. Reprinted from *Journal of Neuroscience*, with permission.

The same year the results were published of a major study for paradoxical sleep mechanisms, and for the specific topic of the present paper. Hobson et al. (1975) showed in cats that the neurons of the locus coeruleus have their maximal firing during waking, that the firing decreases during slow wave sleep and becomes silent or nearly silent during paradoxical sleep. This result was confirmed in rats by Aston-Jones and Bloom (1981a) (Fig. 23). This means that cortical inhibitory processes decrease when compared to waking, but also compared to slow wave sleep, that is, that there is a cortical disinhibition and, consequently, less control of cortical functioning, at least in the sensory input field. It should be stressed that, as stated by McCormick (1992) and more recently confirmed [see for example Manunta and Edeline (1998)], noradrenaline has some excitatory effects [often preceded by transient inhibition: Warren and Dykes (1996)], particularly on the deep (subcortical output) layers of the cortex. Thus, it could be argued that there is also a decrease of facilitating processes during paradoxical sleep. However, these influences seem to be insignificant when compared to the excitatory processes, such as those supported by acetylcholine. The absence of noradrenaline, and the consequent probable reduction of the signal/to/noise ratio could account for the absence of gamma rhythm reset by peripheral stimuli during paradoxical sleep (Llinas and Ribary, 1993). Finally, in spite of strong cortical activation during paradoxical sleep, there should be a lower level of available metabolic energizing molecules since noradrenaline, which acts synergically with intestinal peptide (VIP), favors cAMP synthesis (Magistretti and Schorderet, 1984).

One other field of research still remains open: the interaction of different neurotransmitters at cortical level. Grenhoff et al. (1993) showed in rats that single-pulse locus coeruleus stimulation induces an activation (1–136 msec) followed by an inhibition (145–336 msec) of the neurons of the tegmental ventral area (dopaminergic A_{10} area) which should have cortical consequences on dopamine release. The activation would imply postsynaptic α_1 receptors, while the inhibitory response could imply GABAergic interneurons. The authors postulate that the locus coeruleus noradrenergic activation (which occurs particularly during immediate attention) of dopaminergic neurons could be important "in behavioral situations involving novelty and reward" (p. 11). Fink and Göthert (1993) showed that the cortical release of noradrenaline is increased by excitatory amino acids (EAA) acting at NMDA receptors. However, this release is negatively controlled by α_2 receptors, possibly to protect the noradrenergic neurons from neurotoxic effects of excessive glutamatergic influence. Recently, Gobert et al. (1998) using microdialysis studied the cortical release of several neurotransmitters under specific agonists and antagonists given systematically. They showed that in the brain stem, α_1 postsynaptic receptors facilitate activation of dorsal raphe neurons which project to the cortex. At cortical level, first of all, α_{2A} autoreceptors control noradrenaline release. Moreover, noradrenaline release inhibits dopamine and 5-HT release by an action on α_2 heteroreceptors situated on corresponding axon terminals [which have been shown to have possible important implications for 5-HT in the mechanism of action of antidepressant drugs: Mongeau et al. (1994)]. In addition, activation of α_1 receptors decreases dopaminergic D_1 transmission (Gioanni et al., 1998), an effect which disappears during paradoxical sleep. Finally, some 5-HT reuptake inhibitors favor noradrenaline release (Hughes and Stanford, 1996).

To summarize, the cortical neurophysiological influence of noradrenaline is highly important, its main original influence being the locally induced inhibitory processes. Indeed, although this transmitter induces some excitatory effects, they are certainly of lower functional importance than those, massive, induced for example by acetylcholine. The fact that these noradrenergic neurons are fire less during slow wave sleep and become nearly silent during paradoxical sleep implies progressive disinhibitory processes, with a large decrease of signal to noise ratio which could explain that sensory stimuli, unlike waking, are not able to reset gamma range activity.

2.4.4. *Serotonin*

Serotonin is an essential transmitter which has given rise to many studies in the brain functioning field. It is involved in cortical maturation processes (Cases et al., 1996; Lavdas et al., 1997; Roerig and Katz, 1997; Roerig et al., 1997; Turlelski et al., 1997; Mansour-Robaey et al., 1998) and is implicated at least in anxiety (Eison and Eison, 1994) depression and schizophrenia (Saito et al., 1996). Moreover, the neurons of the ascending raphe nuclei (dorsal and medial) decrase their firing rate during slow wave sleep and become silent during paradoxical sleep (McGinty et al., 1974; Rasmussen et al., 1984) (Fig. 24). Their influence on cortical neuron functioning is thus of great interest.

From the neurohistological point of view, Although Fuxe (1965) and Anden et al. (1967) first mentioned serotoninergic terminals of fine unmyelinated axons in the cortex of rats, Nelson et al. (1973) again in monkeys, confirmed "fine unmyelinated axons" which showed "characteristic varicosities throughout the cortex" (p. 115). Two years later, Descarries et al. (1975) confirmed these findings in rats and observed that only "a very small fraction of 5-HT varicosities exhibited the membrane differentiations of typical synaptic terminals". These "varicosities were found to be present within all cortical layers except layer VI…The intralaminar density of 5-HT innervation increased progressively from layer V to layer I, in a distribution pattern of unspecific afferents…5-HT nerve endings may be considered as capable of exerting a rather widespread influence in the neocortex" (p. 301) (Beaudet and Descarries, 1976). Bobillier et al. (1975) began to differentiate the ascending projections of dorsal and median raphe nuclei, but the differences of the two nuclei afferents at cortical level were shown by Kosofsky and Molliver (1987): "axons which arise in the dorsal raphe nucleus (type D) have heterogenous, pleomorphic varicosities: they range from extremely fine, granular to spindle-shaped, fusiform varicosities (1–3 mm diameter).

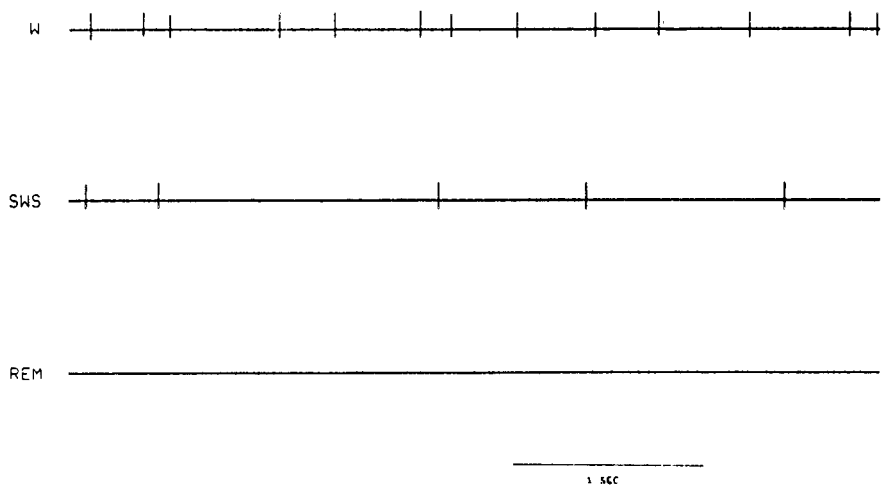


Fig. 24. McGinty and Harper (1976) recorded in cats the neurons of the dorsal raphe nucleus during sleep–waking cycle. Their firing decreased during slow wave sleep and was suppressed during paradoxial sleep. Reprinted from *Brain Research*, with permission of Elsevier.

Axons arising from the median raphe nucleus (type M) have highly distinctive, large spherical varicosities (3–5 mm diameter)'' (p. 166). One important point was stressed more recently by Smiley and Goldman-Rakic (1996). They showed that serotoninergic terminals in the prefrontal cortex of monkey predominantly synapse on interneurons. However, they recall that many terminals comprise varicosities without clearcut synaptic structures, thus allowing diffuse release of neurotransmitters which can act as a neurohormone. Indeed, ''only 23 of 213 varicosities formed identifiable synapses even though these varicosities contained synaptic vesicles'' (p. 434).

Serotonin exerts a powerful inhibitory influence on the majority of cortical neurons (Krnjevic and Phillis, 1963; Nelson et al., 1973; Reader et al., 1979) (see Fig. 21). In some cases, 5-HT acting at 5-HT_2 receptor level can activate GABAergic interneurons which results in a hyperpolarization of pyramidal cells (Sheldon and Aghajanian, 1990). Araneda and Andrade (1991) also described the ''very high prevalent'' hyperpolarization of rat prefrontal pyramidal neurons by 5-HT. However, some depolarization effects of this transmitter ''reduced the afterhyperpolarization that normally follows a burst of spikes (and) elicited a marked decrease in spike frequency accommodation...resulting in an increase in the number of spikes triggered by the depolarizing current pulse'' (p. 401). The hyperpolarizations were related to 5-HT_{1A} receptors and the depolarizating effects to 5-HT_2 receptors, these two kinds of receptors being possibly situated on the same pyramidal cell. The authors suggest that these receptors could be impinged by different serotoninergic terminals (dorsal and median raphe nuclei). The modulated action of these two kinds of receptor could give rise, as hypothesized by McCormick (1992), ''to an increase in the so-called signal to noise ration of the neuron'' (p. 373), depending the level of their respective activation.

The serotoninergic interactions take place first at brain stem level, where 5-HT inhibits dopaminergic neurons, as shown by raphe nuclei lesion (Nicolaou et al., 1979), by an action on 5-HT_2 receptors (Ugedo et al., 1989) and possibly on 5-HT_{1C} receptors (Prisco et al., 1994). In the same way, 5-HT inhibits the noradrenergic neurons of the locus coeruleus (McRae-Degueurce et al., 1982) also by an action at 5-HT_2 receptor level (Gorea and Adrien, 1988). At cortical level, several authors found presynaptic interactions. First, Chen et al. (1992) using microdialysis described how 5-HT_3 heteroreceptors located on dopaminergic terminals seem to favor dopamine release in the prefrontal cortex of rats. Tanda et al. (1995) showed that 5-HT reuptake blocker increases dopamine release at the same prefrontal level in the same species. Iyer and Bradberry (1996), also by microdialysis, found that locally applied 5-HT increases dopamine release at the same level. An apparent contradictory result was obtained by Pehek (1996) who observed an increase of dopamine release after a 5-HT_2 receptor antagonist. It is specially interesting that the established inhibitory influence of 5-HT on ventral tegmental dopaminergic neurons can be accompanied by a facilitatory influence on cortical dopamine release. Up to now the only logical divergence concerned a reduced 5-HT release at cortical level accompanied by an increase of release at nerve cell level during sleep, because of activation of the body cell located 5-HT_{1A} receptors (Cespuglio et al., 1992).

As described by Saito et al. (1996) there are few data relative to serotoninergic presynaptic modulation of noradrenaline release at cortical level. However, Schlicker et al. (1994) showed that 5-HT_3 receptor agonists increase noradrenaline release by blockade of α_2 receptors. In the same way, 5-HT in rats favors acetylcholine release by acting on 5-HT_4 receptors (Yamaguchi et al., 1997), while in human cortex, 5-HT_3 receptors also situated on cholinergic

terminals inhibit its release (Maura et al. (1992). This last result is in accordance with older data (Barnes et al., 1989).

Finally, 5-HT influences cortical glutamatergic neurons. "Activation of serotonergic afferents to the cerebral cortex could enhance excitatory synaptic transmission by increasing activation of NMDA receptor ionophore complex" (Reynolds et al., 1988, p. 291) by 5-HT_{2A} heteroreceptors (Neuman and Rahman, 1996) and is underlied by Ca^{2+} (Rahman and Neuman, 1996). Conversely, NMDA receptors located on serotoninergic terminals favor 5-HT release (Fink et al., 1996).

To summarize, 5-HT principally inhibits cortical neurons. This effect is important during waking and disappears during paradoxical sleep since corresponding neurons become silent. Consequently, serotoninergic neurons inhibition of dopaminergic and noradrenergic neurons disappears during paradoxical sleep, potentially affecting only dopaminergic neurons which maintain their firing during paradoxical sleep. Moreover, cortical release of glutamate should be lower during slow wave sleep and paradoxical sleep. Finally, although 5-HT was shown to participate in cortical EEG activation (Vanderwolf, 1988), its role seems secondary since cortical low voltage fast activity persists during paradoxical sleep.

2.4.5. *Histamine*

Histamine, like noradrenaline and 5-HT, is a transmitter of peculiar interest for a comparative study of cortex functioning during waking and sleep, for a possible explaination for differences of mind functioning. Indeed, the histaminergic body cells localized in the posterior hypothalamus (Steinbusch and Mulder, 1984; Watanabe et al., 1984; Yamatodani et al., 1991), which show all electrophysiological properties of aminergic neurons (Reiner and McGeer, 1987), are active during waking and become silent as slow wave sleep deepens and remain silent during paradoxical sleep (Vanni-Mercier et al., 1984) (Fig. 25). Moreover, it has long been established that lesions at this level at this level induce somnolence and/or hypersomnia in humans (von Economo, 1928), monkeys (Ranson, 1939), cats (Swett and Hobson, 1968) and rats (Nauta, 1946; McGinty, 1969).

The waking favoring influences of histamine were already shown by Monnier and Hatt (1969) in rabbits, by injection in the third ventricle, and it is well known that classical histamine antagonists used against allergies have a sedative effect. At brain level, histamine reaches a maximum during the day rest period of rats while its turnover is highest during the night active period (Orr and Quay, 1975;

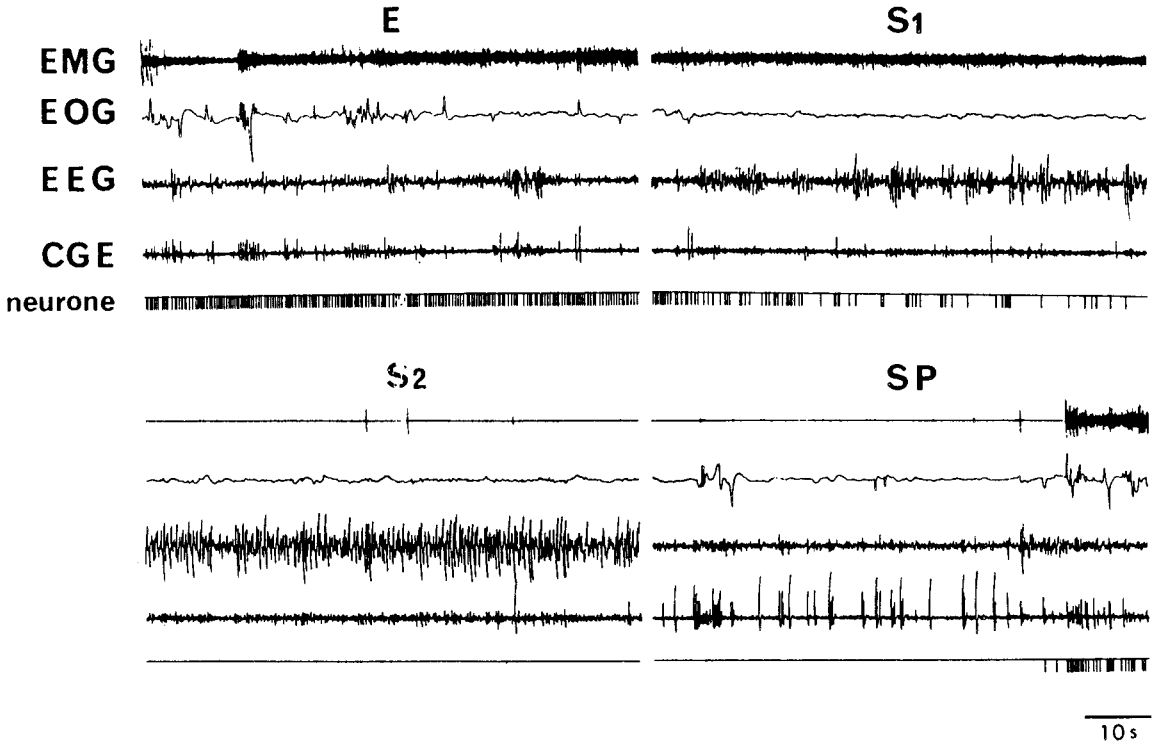


Fig. 25. Vanni-Mercier et al. (1984) recorded in cats the neurons of the posterior hypothalamus which show aminergic mode of firing. They were active during waking, became silent during the first stage of slow wave sleep and remained silent during paradoxical sleep. Abbreviations: E, waking; S_1, light slow wave sleep; S_2, deep slow wave sleep; SP, paradoxical sleep; EMG, electromyography; EOG, electrooculogram; EEG, cortical activity; CGE, geniculate nucleus. Reprinted from *Comptes Rendus de l'Académie des Sciences*, with permission of Elsevier.

Tuomisto and Tuomisto, 1982). Its release is maximal, at least in the anterior hypothalamus, during the night (Mochizucki et al., 1992). Direct confirmation of its action on waking is provided by several experimental arguments:

1. Inhibition of its synthesizing enzyme decreases waking in cats (Lin et al., 1986, 1988) and in rats (Kiyono et al., 1985, 1991).
2. Agonists of the postsynaptic H_1 receptor increases waking (Kalivas, 1982; Monti et al., 1986; Monti et al., 1994; Lin et al., 1988) while antagonists induce slow wave increase (Tasaka et al., 1989).
3. Agonists of the presynaptic H_3 autoreceptor decrease waking in cats (Lin et al., 1990) and rats (Monti et al., 1991; Monti, 1993) while antagonists reduce cortical low frequency EEG activities (Valjakka et al., 1996).

It should be mentioned that an increase of waking by 72 hr paradoxical sleep deprivation did not increase histamine amount in the cortex, whereas the ratio tele-methylhistamine/histamine was increased in both anterior and posterior hypothalamus (Porkka-Heiskanen et al., 1994).

Among the numerous integrative and behavioral influences of histamine (de Almeida and Izquierdo, 1986; White and Rumbold, 1988; Schwartz et al., 1991; Onodera et al., 1994; Prast et al., 1996; Frisch et al., 1998; Panula et al., 1998), those specifically favoring waking processes could be accounted for a threefold action: first a direct or indirect inhibition of the hypothalamic preoptic area neurons (Lin et al., 1994) which are involved in waking antagonistic influences (von Economo, 1928; Nauta, 1946; Manceau and Jorda, 1948; Maire and Patton, 1954; Sterman and Clemente, 1962). Second, by descending activating influences on the mesopontine cholinergic nuclei which themselves favor basal forebrain activity (Lin et al., 1996) and activate thalamic relay nucleus neurons, by transforming *in vitro* the bursting mode of functioning characteristic of slow wave sleep into the continuous firing of waking, thus "promoting the accurate transmission and processing of sensory information and cognition" (McCormick and Williamson, 1991, p. 3188). Third, direct histaminergic facilitation of the intralaminar thalamus and basal forebrain projections toward the cortex (Lin et al., 1996). Indeed, basal forebrain neurons are activated by histamine (Khateb et al., 1995) which, when infused at this level, increases cortical acetylcholine release (Cecchi et al., 1998). Finally, since Watanabe et al. (1984) identified histaminergic terminals in the solitary tract nucleus, it could be possible that as falling asleep progressive disinhibition of its neurons favors sleep inducing influences (Magnes et al., 1961; Bonvallet and Allen, 1963; Padel and Dell, 1965) since histaminergic neurons are active during waking and become silent during light slow wave sleep (Vanni-Mercier et al., 1984).

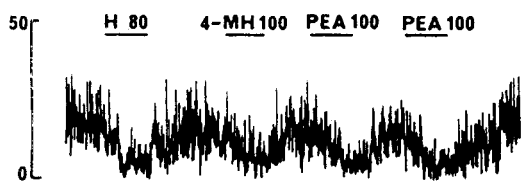


Fig. 26. Sastry and Phillis (1976) inhibited corticospinal neurons with histamine, 4-methylhistamine (4-MH), a H_2 receptor agonist and 2-pyridylethylamine (PEA), a H_1 agonist. It was later shown that excitatory effects are obtained by H_1 receptor activation. Reprinted from *European Journal of Pharmacology*, with permission of Elsevier.

At cortical level, histamine was first identified by Kwiatkowski (1943) then by Adam and Hye (1966). The hypothalamic afferents ascend along the medial forebrain bundle (Schwartz, 1975) and significantly innervate the neocortex (Inagaki et al., 1988), all cortical layers being concerned, but particularly layer 1, and the nerve terminals comprising varicose and nonvaricose endings (Panula et al., 1990; Schwartz et al., 1991; Manning et al., 1996). Histamine was first shown to inhibit cortical neurons (Sastry and Phillis, 1976; Haas and Wolf, 1977) by an action at H_1 and H_2 receptor level (Sastry and Phillis, 1976) (Fig. 26). However, it was later most often observed that histamine acting at H_1 receptor level has excitatory effects (Haas, 1985; Schwartz et al., 1991).

Histamine interferes with several transmitters; it inhibits K^+ induced acetylcholine and noradrenaline release by an action on H_3 receptors (Blandina et al., 1996; Schlicker et al., 1989; Tim et al., 1998). This effect could be indirect since possibly mediated by GABAergic interneurons (Giorgetti et al., 1997). In the same way, 5-HT release at cortical level is also inhibited by an action on H_3 receptors (Schlicker et al., 1988). Moreover, histamine "potentiates NMDA receptor-mediated ion currents in a subpopulation of primary cultured rat cortical neurones...by regulating the desensitization properties of the NMDA receptor" (Zwart et al., 1996, p. 2210). This effect could implicate two distinct mechanisms: an activation of H_1 receptors and a direct action on NMDA receptors (Zwart et al., 1996; Payne and Neuman, 1997).

Finally, also related to cortical influences of histamine, pharmacological evidence has suggested that it may not play a crucial role in cortical activation during waking behavior (Servos et al., 1994). This conclusion is strengthened by the fact that there is cortical activation during paradoxical sleep in spite of silent histaminergic neurons (Vanni-Mercier et al., 1984). Moreover, destruction of posterior hypothalamic neurons do not suppress waking (Denoyer et al., 1991).

To conclude, although EEG activation can occur without histaminergic intervention, at least during paradoxical sleep, its influence to sustain waking is crucial as shown by numerous pharmacological studies. At cortical level, since hypothalamic neuron firing becoming silent during slow wave sleep and paradoxical sleep, it may possibly reduce activating influences, but undoubtedly induces a disinhibitory process.

Other avenues remain to be explored, for example the influence of nitric oxide (NO). Indeed, acetylcholine has a specific biphasic influence on cortical NO, increasing NO synthetase activity at low dose,

decreasing it at high doses (Borda et al., 1998). Moreover, NO is very often colocalized with several transmitters, particularly 5-HT (Wang et al., 1995) and its cortical release is slightly decreased during slow wave sleep (−6%) as compared to waking and still more during paradoxical sleep (−9%) (Burlet and Cespuglio, 1997).

3. DISCUSSION

3.1. Synthesis Of Neurophysiological Data Relative To Cortical State During Waking And Sleep

3.1.1. *Waking*

Spontaneous EEG field activity (Berger, 1929; Bremer, 1935; Bremer, 1936, 1937; Loomis et al., 1935a, 1935b, 1937) and recent gamma range activity (Bouyer et al., 1981; Freeman and Van Dijk, 1987; Gray and Singer, 1989; Singer, 1990; Llinas et al., 1991) as well as cell firing studies (Arduini et al., 1963; Evarts, 1965) and brain stem induced activities (Moruzzi and Magoun, 1949; Singer, 1990; Steriade, 1996) show that the cortex low amplitude activity corresponds to an activated state. This activation is confirmed by recent positron emission tomography (Madsen et al., 1991; Maquet et al., 1996; Nofzinger et al., 1997; Braun et al., 1998). Several transmitter release probably contributes to this cortical activation but acetylcholine seems to be the more important, as shown by pharmacological approach (Wikler, 1952; Vanderwolf, 1988; Szymusiak et al., 1990) and release amount which is increased during waking (Mitchell, 1963; Phillis and Chong, 1965; Celesia and Jasper, 1966; Szerb, 1967; Cuculic et al., 1968; Pepeu and Bartolini, 1968).

However, in addition to these subcortical influences which induce a cortical activated state, there are also inhibitory processes involved in cortex functioning (Bubnoff and Heidenhain, 1881, Creutzfeldt et al., 1956; Krnjevic et al., 1966a, 1966b, 1966c). The research of Demetrescu et al. (1966), which was specifically related to sleep–waking mechanisms, was the first to describe in detail the coexistence of cortical acting activating and inhibitory influences during waking. However, our specific knowledge has been substantially extended by more recent neurochemical advances which have shown that dopamine (Krnjevic and Phillis, 1963; Reader et al., 1979; Rétaux et al., 1991; Pirot et al., 1992; Grobin and Deutch, 1998), noradrenaline (Foote et al., 1975; Waterhouse et al., 1990; Warren and Dykes, 1996), 5-HT (Krnjevic and Phillis, 1963; Nelson et al., 1973; Sheldon and Aghajanian, 1990; Araneda and Andrade, 1991) and histamine (Sastry and Phillis, 1976; Haas and Wolf, 1977) have predominant a direct or indirect inhibitory influences on cortical main neurons. And this action is probably of great importance on account of its massive scale since corresponding afferent neuron terminals end in majority with varicosities, implying diffuse release acting on numerous neurons, like neurohormones. One of the functions of these released neurotransmitters would be to increase the signal to noise ratio of incoming information as shown for acetylcholine (Berlucchi, 1997), noradrenaline (Foote et al., 1975; Aston-Jones and Bloom, 1981b) and 5-HT (McCormick, 1992).

3.1.2. *Slow Wave Sleep*

All data relative to EEG spontaneous field (Bremer, 1936, 1937; Moruzzi and Magoun, 1949; Ribary et al., 1991) and unitary (Evarts, 1965) activities, like those related to positron emission tomography (Hofle et al., 1997; Maquet et al., 1997), show a decrease of cortical activated state. The only exception concerns the primary sensory evoked responses induced by cortical radiation stimulation which show a higher amplitude than during waking (Evarts, 1965; Palestini et al., 1964; Favale et al., 1965; Arnaud et al., 1979). This could perhaps explain the unexpected activation of visual and secondary auditory cortex during sigma spindles and delta activity of sleep (Hofle et al., 1997).

All transmitter data show a decrease (Jasper and Tessier, 1971; McGinty et al., 1974; Hobson et al., 1975; Aston-Jones and Bloom, 1981a; Rasmussen et al., 1984) or rapid suppression (Vanni-Mercier et al., 1984) of cortical release, except dopamine (Miller et al., 1983; Trulson and Preussler, 1984). Together, these data, obtained during slow wave sleep, suggest a decrease of cortical activation and the maintainance of a decreased cortical inhibition.

3.1.3. *Paradoxical Sleep*

Cortical classical EEG field activity is generally difficult to distinguish from waking patterns (Loomis et al., 1937; Klaue, 1937; Aserinski and Kleitman, 1953; Aserinski and Kleitman, 1955; Dement, 1958), and gamma range activity occurs in humans (Llinas and Ribary, 1993) and in animals (Franken et al., 1994; Maloney et al., 1997). However, although gamma range activity is present, there is not reset by peripheral information (Llinas and Ribary, 1993) and the late components of the field evoked responses (which partly correspond to what is nowadays called event related potentials and reflects cortical treatment and integration of sensory information) are suppressed (Williams et al., 1964; Velasco et al., 1980). Moreover, there should be a large decrease of signal to noise ratio for residual sensory information (Foote et al., 1975; Aston-Jones and Bloom, 1981b; McCormick, 1992; Luciana et al., 1998).

However, the major feature of paradoxical sleep is presence of the disinhibition processes in the cortex. Demetrescu et al. (1966) were the first to show the coexistence of cortical activation and disinhibition state during this sleep stage. This conclusion was definitively confirmed by neurochemical findings. Indeed, noradrenaline (Hobson et al., 1975; Aston-Jones and Bloom, 1981a), 5-HT (McGinty et al., 1974; Rasmussen et al., 1984) histamine (Vanni-Mercier et al., 1984) containing neurons, which principally inhibit cortical neurons, become or remain (histamine) silent. The only remaining influences are those of dopamine, the release of which should be favored by the suppression of brain stem serotoninergic inhibitory processes acting on A_{10} area (Nicolaou et al., 1979; Ugedo et al., 1989; Prisco et al., 1994; Gobert et al., 1998).

Finally, prefrontal deactivation could accentuate the original cortical state during paradoxical sleep. However, it is noteworthy that the condition of the dorsolateral prefrontal cortex has given rise to condradictory results, since two teams found a decrease of activation (Maquet et al., 1996; Braun et al., 1998) while two found an increase [Hong et al. (1995) during eye movements, and Nofzinger et al. (1997)].

3.1.4. *Intermediate Stage*

A particular feature of the lapse of time just prior to induction of paradoxical sleep needs to be highlighted because of described specific psychological content (Lairy, 1966; Lairy et al., 1968). In the rat (Gottesmann, 1964, 1967; Bjorvatn et al., 1998) cat (Gottesmann et al., 1984) and mouse (Glin et al., 1991) slow wave sleep is characterized by slow waves interspersed with spindles which increase in number and amplitude as sleep deepens to become maximal just prior to entrance paradoxical sleep. During these last maximal amplitude spindles, low frequency theta rhythm occurs in the hippocampus (Gottesmann, 1964; Weiss and Adey, 1965; Depoortere and Loew, 1973; Gaillard et al., 1977; Gottesmann et al., 1984; Glin et al., 1991; Kleinlogel, 1990; Neckelmann and Ursin, 1993; Benington et al., 1994; Lancel et al., 1996). During this "intermediate stage" (Gottesmann, 1967, 1972, 1996) the thalamocortical and thalamic responsiveness, which is controlled by brain stem ascending activating influences (Dumont and Dell, 1958; Steriade, 1970), is the lowest of all sleep–waking stages (Gandolfo et al., 1980). Moreover, low or medium doses of barbiturates, which in the rat suppress the pontine activation of paradoxical sleep (Gottesmann, 1967, 1969), and benzodiazepines (Gandolfo et al., 1994), induce long-lasting intermediate stage (up to several minutes) at the expense of paradoxical sleep which is suppressed. As the hypnotics are progressiveley metabolized, the sustained intermediate stage diminishes and the cortical activation of paradoxical sleep reappears while the theta rhythm frequency increases. Finally, acute intercollicular transection, in rats and cats, induces long-lasting (several hours), cortical and hippocampal activities of the intermediate stage (Gottesmann et al., 1980, 1984). Consequently, this short-lasting stage (few seconds) seems to occur when brain stem ascending activating influences of waking, which progressively decrease during slow wave sleep, are at their lowest level, or suppressed, while pontine (George et al., 1964; Gottesmann, 1967, 1969; McCarley and Hobson, 1971; Vertes, 1977; Sakai, 1988; Onoe and Sakai, 1995) and/or mesopontine (Steriade and McCarley, 1990) activating influences are still absent or probably at too low level (McCarley and Hobson, 1970) to influence cortical spontaneous and evoked field activities. The intermediate stage seems to correspond to a transient physiological cerveau isolé stage (Bremer, 1935). This stage occurs in the rat in 75% of cases at paradoxical sleep onset. It also appears in 15% of cases at this stage ending before awakening by suppression of pontine paradoxical sleep influences during short-lasting absence of activating influences of waking [for more details see Gottesmann (1996)].

Interestingly, Demetrescu et al. (1966) already described at this particular sleep hinge step the lowest amount of facilitatory and inhibitory influences acting on the cortex. Recent neurochemical data show that noradrenergic (Hobson et al., 1975; Aston-Jones and Bloom, 1981a) and serotoninergic (McGinty et al., 1974; Rasmussen et al., 1984) neurons which preferentially inhibit cortical neurons, become already silent just prior to paradoxical sleep entrance while histaminergic neurons which also inhibit numerous cortical neurons are already silent by sleep onset (Vanni-Mercier et al., 1984).

To summarize, during waking, ascending activating influences allow cortex functioning while inhibitory processes potentially modulate them. During slow wave sleep both kinds of influence decrease until their transient disappearance just prior to onset of paradoxical sleep. During this last sleep stage, the cortex is again subjected to activating influences while largely disinhibited (only the dopaminergic inhibitory influences persist). Consequently, the major differences of cortical state observed during sleep–waking cycle should have differential influences on mental functioning.

3.2. Correlative Mental Functioning

A quelque moment de mon sommeil que je me sois éveillé ou fait éveiller, j'ai toujours eu l'impression d'un rêve interrompu (Hervey de Saint Denys, 1867, p. 235)[13].

3.2.1. *Slow Wave Sleep*

Falling asleep is marked by "hypnagogic hallucinations"[14]. First so called by Baillarger (1845), they were extensively studied by Maury (1861). They are most often described as erratic sensory stimulations, "floating sensations, flashing lights, lantern slide phenomena, fleeting progressions of thoughts and images" [Foulkes (1962), p. 22, see also Vogel et al. (1966) for their psychological correlates]. With the development of EEG studies Foulkes (1962) first demonstrated[15] that there was high frequency of mental recall outside REM sleep, that is, during slow wave sleep. "The mean proportion of recall for all subjects was 0.74 in non-REM awakenings and 0.87 in REM sleep awakenings" (p. 18). Although Dement and Kleitman (1957b) thought that the rare dream recalls they obtained in slow wave sleep were delayed reports of REM sleep content, "the considerable and consistent qualitative differences" (Foulkes, 1962, p. 22)

[13] "At whatever moment of sleep I awakened or was awakened, I always had the feeling of an interrupted dream".

[14] *Upnos* = sleep, *agogos* = which leads.

[15] Foulkes mentions a previous extensive (but inaccessible) study of Teplitz (1953) who "found that reports of having dreamed were obtained in 63% of 78 spindle and delta awakenings" and concluded "that dreams may occur in association with any type of sleep potential pattern" (p. 24).

found between these two stage content show that this seems unlikely. Also, "the hypothesis that (slow wave sleep) recall is of hypnagogic material seems, on the basis of available evidence, to lack adequate empirical evidence... Despite broad similarities there were enough differences between the hypnagogic reports and reports from later spindle and delta awakenings to suggest that those later reports were not unretouched, or slightly faded, memories of hypnagogic material" (p. 22). The author also ruled out that the mental content emanated from hypnopompic hallucinations (occurring just prior to waking up). Slow wave sleep "reports were less often visual and had a higher degree of correspondence with reality" (p. 23). Consequently, the 'thought-like' content of slow wave sleep rather corresponds somewhat to Freud's "secondary process" (Freud, 1875, p. 324) involving the "principle of reality" (Freud, 1911, p. 219). As already stated by Rechschaffen et al. (1963) slow wave sleep mentation "has more of the secondary process characteristics which are assigned to preconscious mentation than does REM sleep mentation" (p. 546). Since the cortex continue to be subjected to diminished brain stem activating influences, it is, understandably, able to generate some mentation. The maintainance, albeit reduced, of inhibitory influences could in some way explain why the mode of mind functioning is often similar, although of low level, to that of waking. However, it has to be mentioned that Foulkes (1962) like Tracy and Tracy (1974), Cavallero et al. (1992), Bosinelli (1995) more recently, also found dream contents during slow wave sleep.

3.2.2. *Particular Features Of The Pre-REM Sleep Stage*

Lairy (1966) and Lairy et al. (1968) described an "intermediate phase" occurring prior to and sometimes at the end of REM sleep. This brief stage (a few seconds to a few minutes) has been characterized by the interspersed association of sigma spindles and K complexes (the index of slow wave sleep stage II preceding REM sleep) and low voltage EEG activity without eye movements (index of REM sleep). Lairy's team also considered also as intermediate phase the low voltage activity of 20 sec without eye movements occurring at the onset and outcome of REM sleep. In the normal subject, it seems to be difficult to establish a psychological contact with the subject behaviorally wakened from this stage. Verbal reports do not reveal visual contents but, instead a "feeling of indefinable discomfort, anxious perplexity and harrowing worry" (p. 279)*. In brief reactive psychosis illness, when patients were awakened from REM sleep they momentarily showed no pathological symptoms [which is consistent with ethological theory of Snyder (1968) which predicted clear perception and cognition following paradoxical sleep awakening: a "sentry" function of paradoxical sleep]. Psychiatric troubles only reappeared after minutes later when the waking state was definitively established. In contrast, the pathological symptoms were amplified when the patients were awakened from the intermediate phase. This transient sleep stage was found to be increased in brief reactive psychosis and absent in dementia. Koresco et al. (1963) also described such undetermined EEG patterns during and at the end of REM sleep in schizophrenia. The increase of this stage at the expense of REM sleep was also described in oligophrenia (Grubar, 1983).

The intermediate phase in humans occurs at the same time than the intermediate stage in rat, cat and mouse. This stage in animals seems to correspond to a functional cerveau isolé preparation during which all brain stem ascending influences are transiently suppressed. The particular mental content during the intermediate phase could suggest that the cortex without brain stem facilitatory and inhibitory ascending influences, which allow and modulate its noble functioning respectively, is generating poor and anguished mental content, because of its very unusual state. As claimed by Rechschaffen (1994) for mental content at all sleep stages, it could result during this stage from a particulary important "loss of volitional control over thought process" (p. 17).

3.2.3. *REM Sleep*

At all times dreaming has fascinated Man: "un rêve qu'on interprète pas, est comme une lettre qu'on ne lit pas"[16] [Talmud, in Fromm (1953)]. An important study of historical literature can be found in Freud (1900) (Chapter 1) and of the nineteenth century literature in Hobson (1988) (part 1). Apart from the rather rare episode of nocturnal awakening, memories of dreams essentially occur on waking in the morning, the end of what is generally the longuest phase of REM sleep. As carefully analyzed by Hobson et al. (1998), dreaming of REM sleep is characterized by "sensorimotor hallucinations, bizarre imagery, the delusional belief that one is awake, diminished self-reflective awareness, orientational instability, narrative structure, intensification of emotion, instinctual behaviors, attenuated volition and very poor memory" (p. R2)[17]. This highly original and unusual mode of mental functioning implicates a particular state of the structures involved in psychological generating activities. Above all, this concerns the cortex. Indeed, although it was once suggested that brain stem activation could in some way determine dream imagery (Hobson and McCarley, 1977), this hypothesis was rapidly discarded [Vogel (1978), see recently Mancia (1995)][18]. The brain stem supports cortical functioning but the psychological processes are generated in the most recent phylogenetic structures with, however, possible involvement of thalamocortical relations (Llinas and Paré, 1991). At all events, the absence of gamma range activity reset as well as the abolition of late components of peripheral evoked

*The finding is debatable (Foulkes, personal communication 1998).

[16]An uninterpreted dream is like an unreaded letter.

[17]The reader can consult another previous paper by the same team (Kahn et al., 1997).

[18]The interested reader can consult a contemporary paper by the same authors devoted to Freud's neurobiological hypotheses about dreaming mechanisms (McCarley and Hobson, 1977).

potentials are the objective facts which confirm that "REM sleep can be considered as modified state in which attention is turned away from the sensory input, toward memories" (Llinas and Paré, 1991, p. 525)[19]. However, the mental content does not concern memories alone. It involves true creative processes which for Freud (1900) represent wish symbolic fulfilment, the "manifest content" (Freud, 1900, p 277) being the disguised representation of previous "latent contents" which cannot gain access to consciousness as they create disturbing anguish.

The manifest content most often appears to be illogical, made up of apparently irrational event associations. This unusual mode of functioning could be related to the decrease in prefrontal dorsolateral cortex activation, as compared to waking, but more probably (because of contradictory present-day results) to the disappearance of noradrenergic, serotoninergic and histaminergic inputs to the cortex. These transmitters have predominantly diffuse inhibitory influences which could in some way control the cortical activation induced by mesopontine and pontine structures[20]. The sequence of ideas occurs often rapidly and although the intantaneous dream of Maury (1861)[21] is debatable, rapid jump of mental content could also be attributable to a decrease of cortical inhibitory control which supports the thoughtful mental functioning of waking.

In some cases, particularly after dramatic actual experiences, there are repetitive dreams. Here also, because of the diminishing or absence of cortical inhibitory processes, memories, or phantasy memories, could repeatedly enter the consciousness of the dreamer. This would result in an important load of the specific memory 'trace' (by analogy to a condensor) inducing a lowered threshold of evocation added to the decrease of inhibitory control which, particularly during waking, avoids its content entrance in consciousness. The substantial affective accompaniment of these dreams, as of all dreams, could be related to the activation of limbic areas observed during REM sleep.

The difficulty or impossibility experienced by individuals in recalling dreams, or as commonly occurs, the way they forget them shortly after waking could be the result of very different modalities of brain functioning during REM sleep and waking. The brutal reappearance of noradrenergic, serotoninergic and histaminergic influences—which partly shortly anticipate waking (Aston-Jones and Bloom, 1981a)—probably favors forgetting, apart very pregnant psychological contents. This could have teleological purpose: to reject useless and potentially disturbing contents for behavioral adaptative processes of waking. It could correspond to a kind of physiological counterpart of the psychological "censorship" (Freud, 1897[22], p 213; Freud, 1900). It could be somewhat in accordance and complement with the theory of Crick and Michison (1983) of REM sleep purpose which "is to remove certain indesirable modes of interaction in networks of cells in the cerebral cortex. We postulate that this is done in REM sleep by a reverse learning mechanism, so that the trace in the brain of the unconscious dream is weakened, rather than strenghthened by the dream" (p. 111). "We dream in order to forget" (p. 112). Consequently, REM sleep could be a complex functioning behavioral stage during which some memory traces tend to be suppressed and other reinforced [see Hennevin et al. (1995)] while genetic programming of behavior is reactivated (Jouvet, 1992); all these possible functions being increased during early childhood [Roffwarg et al. (1966) see also the discussion of Mimiran and Van Someren (1993)].

The possible function of the cortex in eye movements of REM sleep related to dreams gave rise to several studies. Dement and Wolpert (1958) followed by Berger and Oswald (1962) showed that active dreams are correlated with more numerous eye movements. Roffwarg et al. (1962) found a direct relationship between eye movement direction and ocular content of dreams, which was confirmed by the same group some years later (Herman et al., 1984). This direct correspondence was found neither by Moskowitz and Berger (1969) nor by Jacobs et al. (1972). Molinari and Foulkes (1969) distinguished the mental content during and outside eye movement burts of REM sleep and found that during phasic activities it was characterized by "primary visual experience" while outside of phasic activities it was correlated with what they called "secondary cognitive elaboration" which seems to correspond roughly to the secondary process of Freud. The primary visual experience linked to eye movement burts was "marginally" confirmed and extended to the EEG sawtouth waves which precede the eye movement bursts (Foulkes and Pope, 1973). The fact that eye movement bursts can be recorded during paradoxical sleep in pontine cats (Jouvet, 1962) show that they are triggered by lower brain stem structures (Vanni-Mercier et al., 1996).

[19]The relation between gamma range activity and consciousness was further analyzed by Paré and Llinas (1995).

[20]It is worth mentioning that, for paradoxical sleep inducing mechanisms, the activating processes (PS-on neuron activities) are more important than the level of inhibitory influences (PS-off-neurons), as hypothesized by Sakai (1988). Indeed, the serotoninergic dorsal raphe neurons fire six times more than in intact cats during paradoxical sleep without atonia (Trulson et al., 1981) and Gervasoni et al. (1998) have shown that locus coeruleus noradrenergic neurons fire during paradoxical sleep during local bicuculine ($GABA_A$ receptor antagonist) infusion without suppressing this sleep stage. For the quality of mental functioning, the inhibitory processes seem crucial.

[21]"I am dreaming about the (revolutionary) Terror; I witness scenes of carnage, I appear before the revolutionary tribunal, I see Robespierre, Marat, Fouquier-Tinville, all the ugly figures of that terrible epoch; I debate with them; finally, after numerous events, I remember unperfectly, I am convicted, sentenced to death, driven off in a cart, amist an countless throng, to the revolution square; I mount the scaffold; the hangman attaches me to the fatal board, operates it, the blade falls; I feel that my head is separated from my trunk, I awake in the most violent anguish, and I feel the bedpost which has come loose and fallen on my cervical vertebrae like the blade of the guillotine" (p. 161). This dream occurred 40 years before the narration of it. Maury (1861) was unwell and his mother was sitting at his bed side.

[22]The first mention of censorhip appeared for psychosis in a letter to W. Fliess.

However, the eye movements are also under cortical control since decortication of the occipital cortex decrease paradoxical sleep eye movements, while decortication of the frontal cortex increases eye movements (Mouret, 1964). Thus, it cannot be ruled out that mental content may induce eye movements since, during REM sleep, there is activation of the cortical right saccadic eye movement system–frontal eye field (Hong et al., 1995). Moreover, contrary to the primary visual cortex, the associative visual cortex is activated during REM sleep (Madsen et al., 1991; Braun et al., 1998).

Finally, the relation of dreaming with psychiatric mental functioning has long been emphasized. Freud (1900) (p. 90) mentions Kant (''the madman is a waking dreamer''), Schopenhauer (''Dreams are brief madness and madness a long dream'') etc...Maury (1861) says ''dream is a kind of delirium'' (p. 26). The possible deactivation of the dorsolateral prefrontal cortex, when confirmed, could be of importance. Indeed, following Jackson's theory, deactivation of this most recent phylogenetic brain area could create a deficit in psychological functioning by suppression of its specific potentialities (negative consequences) and could suppress control exerted on even slightly older cortical structures, thus explaining the rich distorted mental activity characteristic of dreams (positive consequences). It is of interest to recall that glucose uptake in the frontal cortex is reduced in schizophrenic patients without medication (Buschbaum et al., 1982) and that the prefrontal blood flow is not increased during cognitive activity in impaired schizophrenic patients (Breman et al., 1993).

However, there is another hypothesis. The original contribution of Ey's quotation (see Section 1) is that he says that madness and dreaming spring from the same sources. Indeed, all neurophysiological data show that the influences generating mental functioning are not induced but sustained by the brain stem, that is, rather old phylogenetic structures. Once again, the ascending facilitatory influences allow cortical functioning (as petrol propels an auto engine) while the inhibitory ones seem to control these activating processes. The major decrease in the inhibitory ascending influences could explain the unusual modalities of mental activities during REM sleep. It is our belief that, in addition to this cortical unusual state, the persistence of dopaminergic influences could play a crucial role in the often psychiatric-like mode of psychological functioning. Indeed, it is known that aside the nightmares induced by dopamine agonists (Thompson and Pierce 1999), an excess of dopamine release (Pehek 1999) leads to psychotic disorders (Buffenstein et al., 1999). Additionally, the neuroleptics used to alleviate schizophrenia reduce dopamine influence at cortical and limbic levels by acting on pre and/or postsynaptic receptors (Kinon and Lieberman, 1996). This influence of dopamine could be favored by the silence of serotoninergic neurons. Moreover, new atypical neuroleptics also increase noradrenaline release at cortical level (Nutt et al., 1997). Consequently, the specific release of dopamine and the silence of noradrenergic neurons could lead to phantasies and the generally irrational mental activities of dreaming, somewhat similar to those of psychotic diseases.

4. CONCLUSION

In spite of major progresses in our knowledge of brain mechanisms during sleep and waking, the mystery of psychological functioning still persists. It is a source of fascination that the highest integrated brain functions are not generated but sustained by lower brain rather old phylogenetic structures. Future researches certainly will shed still more light on the neurophysiological differences supporting the mental content during these behavioral states. However, it will probably provide no further enlightenment regarding the ultimate significance of psychological content of sleep.

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