REVIEW

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The neuroanatomy of sleep. Considerations on the role of the thalamus in sleep and a proposal for a caudorostral organization

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SUMMARY

This review synthetizes the most important historical contributions in sleep anatomy and the pioneer discoveries in sleep medicine in the light of our clinical observations in Fatal Familial Insomnia (FFI), a genetic prion disease. Together with Morvan's chorea and Delirium Tremens, FFI is characterized by inability to sleep with severe loss of sleep spindles and delta sleep, with preserved presleep behaviour and abnormal REM sleep, associated with motor and autonomic overactivation. We labelled this pattern as Agrypnia Excitata (AE). AE is due to dysfunction in thalamolimbic circuits, which emphasizes the key role of the thalamus in sleep physiology and indicates that the anatomo-functional substrate of stage 1 non-REM sleep differs from that generating slow-wave-sleep (SWS, spindle and delta activity). Accordingly, the sleep-wake cycle in man should be conceptualized as consisting of 5 different behavioural and electrophysiological distinct states: active wakefulness, quiet wakefulness, drowsiness (or stage 1 non-REM), SWS (which incorporates spindle and delta sleep) and REM sleep. An intricate neuronal network extending from the caudal brainstem to the forebrain controls these different wake and sleep behaviours with several, at least three distinct generators.

Key words: Fatal familial insomnia – Morvan's chorea – Delirium tremens – Agrypnia excitata – Thalamus – Sleep-wake cycle

INTRODUCTION

Sleep is a state of being which is currently viewed as comprising two clearly distinct types, REM and non-REM sleep, which have different neurophysiological characteristics, subserve different functions, and are organized in different regions of the brain and by different neural networks.

Clinical experience, however, in Fatal familial insomnia (FFI), a genetic prion disease, in Morvan's chorea (MC), an autoimmune limbic encephalitis, and in Delirium Tremens (DT), the alcohol withdrawal syndrome, has indicated that all these conditions share a similar pattern: an inability to sleep associated with motor and autonomic overactivation (Lugaresi et al., 1986; Liguori et al., 2001; Plazzi et al., 2002; Montagna and Lugaresi, 2002). Detailed neurophysiological analysis of these different clinicopathological conditions has shown that the inability to sleep really consists of a severe lack or disappearance of "spindle" and delta sleep, with preserved presleep behaviour and abnormal REM sleep. This generalized overactivity syndrome has been termed Agrypnia Excitata and has been linked to a functional imbalance within the thalamolimbic formations (Lugaresi and Provini, 2001; Montagna and Lugaresi, 2002).

It has been argued that Agrypnia Excitata represents a pathological condition that is relevant not only in the clinical setting, but is also a concept that has important repercussions on how we conceptualize the neurophysiological organization of sleep (Montagna and Lugaresi, 2002).

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Here we review how these anatomoclinical observations have generated new hypotheses and have led to a reappraisal of the mechanisms underlying sleep and wakefulness. A proposal is put forward for a new conceptualization of sleep as consisting of 3 different behavioural states, organized at different levels in a caudorostral pattern along the neuraxis.

I. Historical contributions: diencephalon versus brainstem

The pioneering contributions to sleep anatomy date back to the early years of the last century. Claparède first suggested that sleep was an instinctive behaviour preventing exhaustion or intoxication (Claparède, 1905). Some outstanding sleep physiologists, such as Hess and Moruzzi, shared this hypothesis (Hess, 1944; Moruzzi, 1969). In the years following Claparède's suggestion, Piéron, a French neurobiologist, proposed that chemical substances (which he called hypnotoxins) would become accumulated during wakefulness, reducing cerebral excitability and hence leading to sleep (Piéron, 1913). Sleep ensured the clearance of these substances so that the brain could then stay awake. Piéron's theory lacked convincing experimental evidence until the last two decades of the twentieth century, when his claim was substantially confirmed. Pavlov, studying conditioned reflexes, deduced that sleep was a sort of inhibition arising in the cerebral cortex and then spreading throughout the brain (Pavlov, 1923). Shortly before his death, he admitted that his theory was untenable (Pavlov in Kleitman, 1963). However, he denied that sleep might depend on a localized sleep centre, as hypothesized by von Economo.

Studying several cases of epidemic encephalitis (also called the Spanish 'flu), Von Economo, a neurologist who worked in Habsburg and post-Habsburg Vienna, documented that in patients who appeared clinically agitated and insomniac the anatomical lesion was located in the anterior hypothalamus and basal forebrain (von Economo, 1923). By contrast, if patients were hypersomnolent or stuporous, the predominant lesion was in the posterior hypothalamus and rostral midbrain. He concluded that the anterior hypothalamus contained the "schlafzentrum" (sleep centre) and the posterior hypothalamus the "wachzentrum" (wake centre). Some years later, Hess, a Swiss physiologist, using electric impulses to stimulate different brain regions, confirmed that the anterior region of the hypothalamus contains deactivating (trophotropic) structures while the posterior hypothalamus houses activating (ergotropic) structures (Hess, 1944). However, true sleep appeared with a short latency only upon stimulating the anteromedian region of the thalamus. Hess therefore believed that it was the thalamus and not the hypothalamus that contained the true sleep centre.

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The discovery of the bioelectrical activity of the brain (Berger, 1930) launched the era of electrophysiology. Using the new technique (electroencephalography - EEG), the Belgian physiologist Bremer documented that slicing the brain along the line between the medulla and spinal cord (so-called "encephale isolé" preparation) did not impair the animal's ability to stay awake (Bremer, 1935). By contrast, if the slice was made along the line joining the mesencephalon and diencephalon ("cerveau isolé" preparation), the animal no longer presented EEG signs of wakefulness (Bremer, 1935). He concluded that sleep was a passive phenomenon due to a loss of peripheral (visceral and somatic) stimuli reaching the cerebral cortex through the brainstem. Although incorrectly interpreted, Bremer's experimental findings were historically important because they shifted physiologists' attention away from the diencephalon to the brain stem. Studying the brainstem reticular formation, Moruzzi, first with Magoun and then with his collaborators, discovered that the upper brainstem contains an arousing (desynchronizing) system whereas the dearousing (synchronizing) structures are located in the lower brainstem (Moruzzi and Magoun, 1949; Batini et al., 1958).

II. The discovery of Rem sleep

Between 1953 and 1957, Kleitman's laboratory in Chicago made a discovery which was to revolutionize sleep physiology and which gave birth to sleep medicine. Kleitman and his co-workers discovered that there are two types of sleep: one identified by EEG tracings alone since the thirties and characterized by high amplitude EEG waves (sleep spindles and slow or delta waves), the other identified by recording eye movements that had been ignored until this time because its EEG features (low amplitude fast EEG activity) could not be distinguished from those characterizing active wakefulness and drowsiness (Aserinsky and Kleitman, 1953). Sleep associated with eye movements and vivid dream activity was called REM sleep (sleep with Rapid Eye Movements).

Between 1958 and 1962, Michel Jouvet, a French physiologist, demonstrated that the executive mechanisms responsible for REM sleep are located in the rostral part of the pontine reticular formation (Jouvet et al., 1959; Jouvet, 1962; Gutiérrez-Rivas et al., 1978). Jouvet called REM sleep "paradoxical sleep" (PS) because it represented a strange neuropsychological situation: a

waking (dreaming) brain in a "sleeping" body (skeletal muscles were functionally blocked during REM sleep).

III. Sleep in humans and in the cat: arbitrary decisions and misunderstandings

In 1957, Dement and Kleitman published the first study on sleep in humans recorded from falling asleep to physiological awakening (Dement and Kleitman, 1957). They called stage 1 the transition from wakefulness to sleep. This stage starts with the disappearance of alpha rhythm, characterizing quiet wakefulness, and ends with the appearance of sleep spindles characterizing stage 2, which is the true onset of sleep. Sleep stages 3 and 4, also called deep sleep, are characterized by a progressive increase in delta (high amplitude slow wave) EEG activities.

Awakened from stage 1, all subjects examined by Dement invariably stated they were not asleep. By contrast, awakened from stage 2, all subjects invariably claimed they had been sleeping. Stage 1 therefore represents pre-sleep behaviour, while "true sleep" starts only when sleep spindles appear. This is what Dement and Kleitman wrote in their historical paper. Some years later, Retchshaffen and Kales, proposing a standardization of sleep terminology, classified stage 1 as the lightest phase of non-REM sleep, considering stages 2,3 and 4 as a progressive deepening of this type of sleep (Rechtschaffen and Kales, 1968). The arbitrary decision to incorporate stage 1 into non-REM sleep has given rise to a series of misunderstandings ever since.

Non-REM sleep is currently divided into light (stages 1 and 2) and deep (stages 3 and 4) or slow wave sleep (SWS) in humans, whereas in the experimental animal (the cat) non-REM sleep and SWS are used as synonyms (Fig. 1). More importantly, in the cat stage 1 non-REM has never been described and it seems that the animal passes from quiet wakefulness directly to spindle sleep (Stage 2 non-REM) (Fig. 1). This premise is necessary because the point in discussion here is that the anatomofunctional substrate of stage 1 non-REM sleep differs completely from that generating SWS (spindles and delta activities). Indeed, sleep in the cat cannot be compared on a one-to-one basis with sleep in humans.

IV. An unsolved question: the role of the thalamus in sleep physiology

In 1989, Barbara Jones summarized the neurophysiological concepts of sleep shared at the time by the large majority of physiologists (Jones, 1989). Activating, wake promoting and deactivating sleep-inducing structures are dispersed and partially intermingled in a widespread neuronal network extending from the lower brain stem to the basal forebrain. Sleep initiates when deactivating systems prevail over activating systems. REM sleep is phasically activated by a neuronal pool localized in the upper pons as shown by Jouvet and others (Jouvet et al., 1959; Jouvet, 1962). The thalamus, which Hess thought to be the true sleep centre, was left unmentioned.

The reasons why the contribution of the thalamus to sleep physiology was underestimated or ignored at the time are well known. Bremer strongly criticized the technical procedures used by Hess and hence the results he had obtained. Bremer's view seemed to be confirmed when Naquet and others (1965) showed that the athalamic cat (a cat in which both thalami have been ablated) was unable to generate sleep spindling, but continued to present a normal behavioural sleep. Some years later, however, Villablanca and co-workers published convincing evidence that the athalamic cat does become severely and persistently insomniac, both behaviourally and electrophysiologically (Villablanca and Salinas-Zeballos, 1972). Also, the diencephalic cat (in which the cerebral cortex was ablated) presented the same sleep disorders as the athalamic cat (Villablanca and Marcus, 1972). Villablanca therefore assumed that a sleep-enhancing system was located in the corticothalamic circuits (Villablanca, 1994).

Meanwhile, Steriade and others had documented that sleep spindles are generated by the reticular nucleus of the thalamus and that the delta activites characterizing deep sleep originate in the thalamus and/or in the thalamo-cortical circuits (Steriade and Llinas, 1988; Steriade et al., 1993). Despite these experimental observations, the role of the thalamus in sleep physiology has been and remains underestimated. The thalamus is currently conceived more as a structure involved in the transmission of stimuli from the hypothalamus and the brainstem rather than in sleep generation.

V. Fatal Familial Insomnia and Agrypnia Excitata: the thalamus intervenes in sleep physiology

In 1986, we observed a hereditary disease we called Fatal Familial Insomnia (FFI) in which selective thalamic degeneration causes an inability to generate SWS. In fact, sleep spindles and delta activity progressively subside and then disappear completely in FFI patients (Lugaresi et al., 1986).

A drowsy condition, resembling physiological stage 1 non-REM predominates during day and night. Short atypical REM sleep episodes appear in clusters associated with hallucinations or dream enactment. Sleep loss is associated with motor and autonomic overactivation: motor

hyperactivity persists day and night for weeks or even months until death (Plazzi et al., 1997) and body temperature, heart rate and systemic arterial pressure, and cortisol and catecholamine secretion show persistently elevated values (Montagna et al., 1995).

This peculiar clinical condition results from selective atrophy of two thalamic formations: the anteroventral (AV) and mediodorsal (MD) nuclei (Gambetti et al., 1995). In fact, these two thalamic nuclei are those consistently and severely affected in all FFI patients. The MD and AV thalamic nuclei, having strong interconnections with the orbitofrontal and cingulate gyrus, on the one hand, and the ventral striatum, hypothalamus and brainstem, on the other, form the visceral or limbic part of the thalamus. Their degeneration disconnects the limbic cortex from subcortical limbic structures and leads to a functional imbalance within the circuits that regulate body homeostasis and orchestrate wake and sleep behaviours (Lugaresi et al., 1998).

Loss of sleep, motor and autonomic overactivation, and even the attenuation of visceral circadian oscillations reflect this functional imbalance within the limbic system. Sleep spindling, the EEG feature most characteristic of sleep onset, arises in the reticular nucleus (RN) of the thalamus and diffuses to extrathalamic formations via other thalamic nuclei, since the RN has virtually no extrathalamic efferents (Steriade et al., 1997). Thus, because the MD nucleus but not the AV nucleus, has robust connections with the RN, it is probably the degeneration of the MD nucleus that hinders the extrathalamic diffusion of sleep spindles, impairing sleep onset and continuity.

That the MD nucleus occupies a strategic position in the sleep machinery has been confirmed in recent findings by Velayos and Gritti and their co-workers, who demonstrated the strong interconnection between the MD nucleus (its magnocellular part) and sleep-promoting structures in the anterior hypothalamus and basal forebrain (Gritti et al., 1998; Velayos et al., 1998). Further evidence of the strategic importance of the MD nucleus in sleep physiology emerged from the work of Mancia and colleagues, who showed that bilateral lesions of the MD nuclei in the rat impair sleep, whereas bilateral lesions of the anterior nuclei do not disturb sleep physiology (Mancia and Marini, 1996). Clinical evidence in humans concurs with this experimental evidence: Guilleminault and Bassetti and coworkers showed that bilateral paramedian thalamic stroke syndromes, in which MD nuclei are lesioned, are characterized by behavioural and EEG features similar to those observed in FFI (Guilleminault et al., 1993; Bassetti et al., 1996).

At least two other neurological conditions were shown to share some behavioural and polysomnographic features of FFI: *delirium tremens* (DT), the alcohol or benzodiazepine withdrawal syndrome, and *Morvan's chorea* (MC), a rare autoimmune disease in which neuromyotonia is associated with severe or even complete loss of sleep (agrypnia) and other features of limbic encephalitis (Liguori et al., 2001; Plazzi et al., 2002). Like FFI, these conditions are characterized by a loss of SWS associated with drowsiness (stage 1 non-REM) or stupor with hallucinations and dream enactment and by motor and autonomic activation. FFI, MC and DT thus cause a similar generalized overactivation syndrome that we termed Agrypnia Excitata (Lugaresi and Provini, 2001; Montagna and Lugaresi, 2002). Agrypnia Excitata is probably brought about through different etiopathogenic mechanisms: 1. The thalamocorticolimbic disconnection due to the neurodegeneration in FFI; 2. the accumulation of antibodies within the thalamolimbic system in MC; 3. a transient prevalence of activating over deactivating synapses downregulated by chronic alcohol abuse within limbic structures in DT. All such mechanisms result in an imbalance in the thalamo-limbic circuitry. Thalamolimbic dysfunction thus leads to a generalized activation of body functions and to loss of SWS but, more importantly, it does not impair drowsiness (stage 1 non-REM). Therefore, it was hypothesized that stage 1 non-REM, really representing a pre-sleep behaviour, arises from an anatomo-functional system different from those generating SWS (Montagna and Lugaresi, 2002). Actually, the theta activities characterizing stage 1 non-REM may appear irrespective of thalamic integrity. If all this is true, non-REM sleep is a misleading term when applied to stage 1, and should not be used as a synonym for SWS.

Brain PET mapping of the different wake and sleep stages in humans have independently confirmed that the patterns of regional cerebral blood flow are different in light sleep as compared to slow-wave sleep (Kajimura et al., 1999). While light sleep is attended by the deactivation of, among other structures, the anterior cingulate and the inferomedial frontal gyri, deep sleep is additionally associated to pons, midbrain and thalamic deactivation (Kajimura et al., 1999).

VI. Old experiments and new insights into sleep anatomy

The fact that rest activity and presleep behaviour (stage 1 non-REM) have an anatomic location and a functional mechanism different from that controlling and organizing SWS is also confirmed by some experimental data in animals. In 1986, Siegel et al. showed that medullary and mid-pontine animal preparations periodically alternate rest and active behaviours, but are not able to organize sleep and presleep behaviours (Siegel et al., 1986). On the other hand, Villa-

blanca reported that the midbrain-transected cat alternated three behavioural conditions: the first corresponding to wakefulness; the second one to REM sleep (Villablanca, 1966), and the third a behavioural condition consisting of episodes of slow eye movements and fluctuating myosis arising during postural rest. These somatic sleep behaviours were not accompanied by any sleep EEG figures (spindles and delta activity). Villablanca had already documented that the "cerveau isolé" preparation was able to alternate EEG patterns of wakefulness and SWS (Villablanca, 1965). From his experiments, he concluded that non-REM sleep has a dual mechanism: a telencephalic mechanism organizing the sleep of the brain, and a brainstem mechanism organizing the sleep of the body.

Recently, Villablanca and co-workers emphasized that this sleep of the body in midbrain-transected cats is more similar to drowsiness than true sleep (Villablanca et al., 2001). All these experimental results indicate that the decerebrated cat is able to organize pre-sleep behaviour but not SWS.

In 1989, Sallanon and co-workers documented that organic insomnia caused by experimental lesions of the pre-optic area may be prevented by pharmacological inactivation of wake-promoting neurons in the posterior hypothalamus (Sallanon et al., 1989). These experiments confirmed Hess' original suggestion that the hypothalamus contains activating (ergotropic) and deactivating (trophotropic) systems, whereas the true generators of SWS are located elsewhere.

VII. The hypothalamus contains a sleep-wake switch system only

The passage from wake to sleep and vice versa is regulated by homeostatic and circadian mechanisms, both located in the hypothalamus. Homeostatic regulation occurs suggested by Piéron at the turn of the last century (Pieron, 1913): some biochemical substances (such as adenosine, prostaglandin D2 and some cytokines) that accumulate in the brain during wakefulness stimulate sleep-promoting GABAergic neurons located in the pre-optic region. In turn, these GABAergic neurons inhibit the aminergic (wake-promoting) neurons located in the tubero-mammillary (histaminergic) nucleus, in the dorsal raphe (serotoninergic neurons) and locus coeruleus (noradrenergic neurons). Inhibition of the wake-promoting neurons leads to drowsiness and favours the onset of sleep. When adenosine, PGD_2 and other somnogenic substances decrease during sleep, aminergic neurons are released

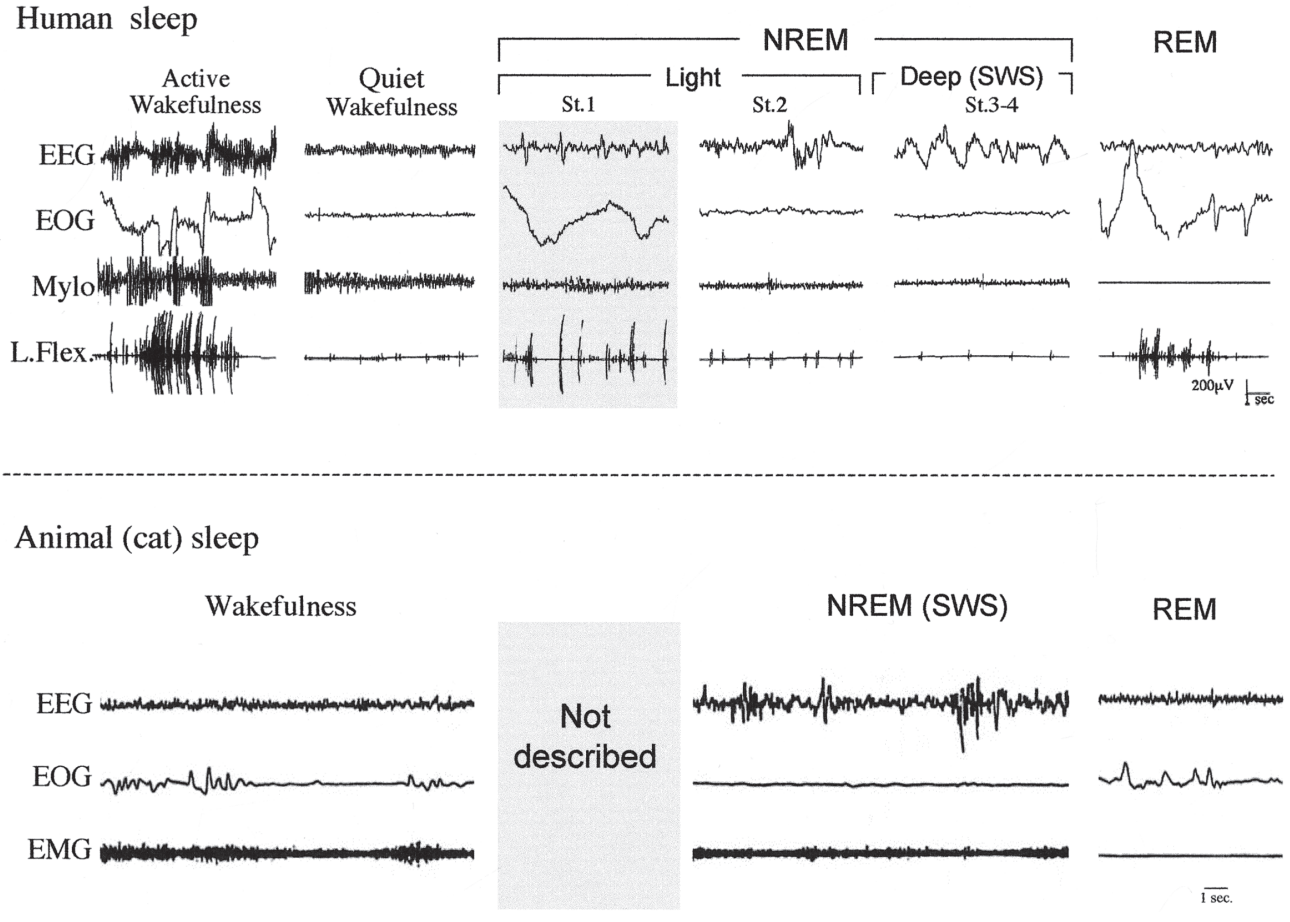

Fig. 1.- Correspondence between human and animal (cat) sleep.

from the inhibitory control of GABAergic neurons, thus favouring awakening (Mc Ginty and Szymusiak, 2000; Mc Ginty and Szymusiak, 2001).

A biological clock located in the suprachiasmatic nucleus dictates the times of falling asleep and awakening through complex molecular genetic mechanisms. Thus, a homeostatic and a circadian mechanism contribute synergistically to wake-sleep cycle regulation. A cholinergic system located in the laterodorsal and pediculopontine tegmentum also intervenes in sleep-wake regulation. This system contains two neuronal subpopulations: one promoting wakefulness, the other one triggering REM sleep (so-called REM-on cells).

Finally, recent studies on narcolepsy (a human and animal disease characterized by chronic drowsiness and abnormal intrusions of REM sleep in wakefulness) have clarified that a small pool of orexinergic neurons located in the lateroposterior hypothalamus also intervenes in wake-sleep regulation (Scammel, 2003). This orexinergic system promotes wakefulness by projecting activating impulses to aminergic neurons. In turn, the aminergic neurons inhibit the REM-on cells in the pontine tegmentum. Thus, orexinergic system deactivation or lesions, as in narcolepsy, have a dual effect: firstly they decrease the activity of aminergic neurons (favouring drowsiness and sleep onset) and, as a consequence of aminergic deactivation, they contribute to REM-on cell dysinhibition causing, as in narcolepsy, an abnormal REM sleep intrusion into wakefulness. REM sleep starts when aminergic neurons cease to fire. Summing up, the hypothalamus and the brainstem contain reciprocally interrelated arousing and dearousing systems that adjust the physiology of sleep and wakefulness through a mechanism similar to an electronic flip-flop switch (Saper et al., 2001). However, neither REM, SWS nor pre-sleep behaviours are permanently lost upon lesioning of the hypothalamus, and functional imbalances may be recovered by appropriate manipulations even within the hypothalamus itself (Sallanon et al., 1989).

VIII. Phylo-ontogenesis of sleep

Phylogeny of sleep

In 1983, Meddis, a British ethologist, defined the behavioural characteristics of sleep as follows: a prolonged period of inactivity arising one or more times every 24 hours; a raised response threshold; and a choice of a specific site and posture (Meddis, 1983). If these criteria are adopted, all animals living on our planet from insects to primates and man sleep. However, Irene Tobler, who documented the homeostatic regulation of rest-activity cycles in insects, defined rest behaviour as a state from which sleep evolved (Tobler, 2000). This implies that sleep is a condition in which some behavioural aspects or electrophysiological changes are different from a simple state of rest. Sleep emerges in vertebrates in the course of phylogenetic evolution.

The amphioxus, an animal which precedes vertebrates on the zoological scale, has a purely segmentary sensory-motor organization. It has also a small pool of neurons in its rostral pole representing a primordial rudimentary rhomboencephalon. If this rostral formation is damaged, each segment of the animal becomes more reactive. Thus, the rudimentary rhomboencephalon of the amphioxus exerts inhibitory control over the whole body. Fish and amphibians alternate rest and activity cycles throughout the 24 hours. Neither their behaviour nor physiological changes clearly distinguish sleep from rest in these animals. By contrast, a behavioural condition that seems distinguishable from rest is present in reptiles. During rest, some reptiles present phasic eyelid closure and fluctuating myosis associated with a raised threshold response. Sharp waves, either isolated or in clusters, similar to those characterizing stage 1 “sleep” in man are seen on the EEG during this type of behavioural situation. These somatic and electrophysiological events recall the characteristics of human drowsiness. Therefore, at least the most evolved poikilothermic animals present behavioural and electrophysiological changes mimicking drowsiness or the pre-sleep behaviour of humans. However, the two typical aspects of true sleep, SWS and paradoxical sleep, can only be identified with certainty in birds and mammals (Rial et al., 1996; Kavanau, 1997). Thus, rest-activity cycles characterize all animals and plants living on our planet. The behavioural and electrophysiological features similar to that of presleep behaviour of humans appear with certainty in reptiles, the most evolved poikilothermic animals. Slow-wave and paradoxical sleep in their paradigmatic forms appear in birds and mammals, in parallel with homeothermy.

Ontogeny of sleep

According to Heckel’s law, ontogeny repeats phylogeny. However, sleep physiologists claim that the lack of vigilance associated with violent jerks phasically appearing in kittens at birth represents a foetal form of REM sleep, also named active or seismic sleep (Valatx et al., 1964). Ontogenetically, this foetal form of paradoxical sleep, which is also encountered in human newborns, would thus precede the appearance of slow-wave sleep and also of presleep behaviour. Currently, this concept is widely accepted. By contrast, however, Frank and Heller, in a series of studies on the rat, recently demonstrated that active or seismic sleep does not correspond to any mature form

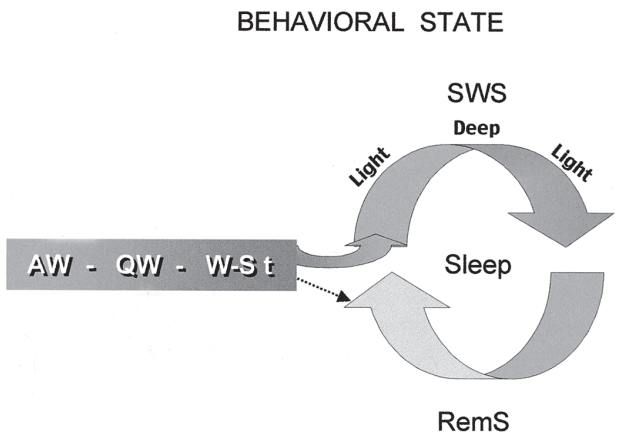

Fig. 2.- Schematic drawing of the principal behavioural states in humans (AW: active wakefulness; QW: quiet wakefulness; SWS: slow wave sleep; RemS: REM sleep; W-S t: wake-sleep transition).

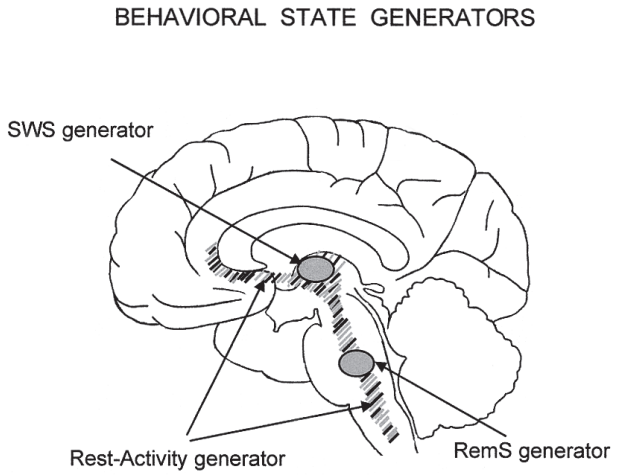

Fig. 3.- SWS and REM sleep generators placed within a more diffuse caudorostral rest-activity generator.

of REM sleep (Frank and Heller, 1997; 2003); in contrast, they viewed it as an undifferentiated behavioural state from which both slow-wave sleep and REM sleep develop simultaneously. Moreover, the notion that sleep associated with muscle jerking is always REM sleep is probably a common misconcept stemming from animal studies, and does not acknowledge the well documented evidence in humans that muscle jerking is at least as vigorous during stage 1 non-REM as during REM sleep (Dagnino et al., 1969; Montagna et al., 1988). Indeed, hypnic jerks are restricted to pre-sleep drowsiness in humans (Oswald, 1959). If Frank and Heller are right about the ontogenetic evolution of sleep, Heckel's law is confirmed: as in phylogenetic evolution a pre-sleep behaviour preceeds SWS and REM sleep.

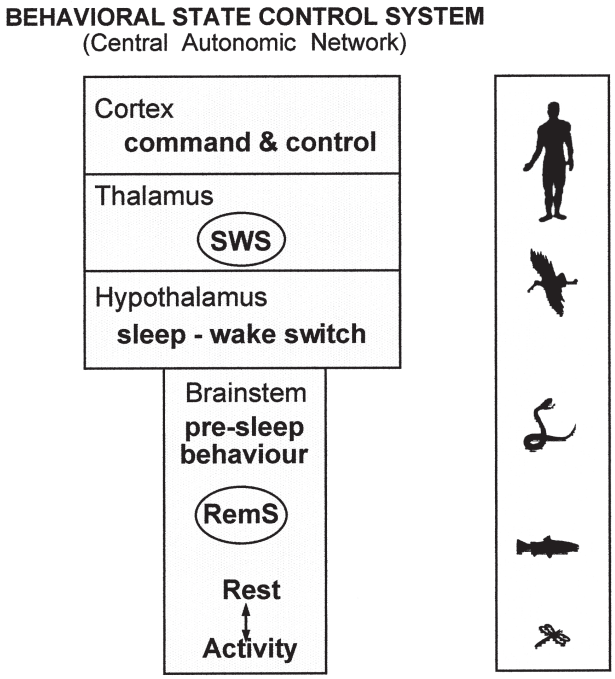

Fig. 4.- Parallel evolution of wake-sleep promoting structures, behaviours and phylogenesis.

IX. Conclusion: three different types of sleep with a caudo-rostral organization

At least in man, five different behavioural and electrophysiological states can be identified: active wakefulness, quiet wakefulness, drowsiness (or stage 1 non-REM), SWS (which incorporates spindle and delta sleep) and REM sleep (Fig. 2).

An intricate neuronal network extending from the caudal brainstem to the forebrain controls these different wake and sleep behaviours and at least three distinct generators are involved in sleep physiology. The first one, diffused from the medulla to the basal forebrain within the so-called extended reticular formation, controls and organizes the vigilance levels behaviourally expressed by three essential features: active wakefulness, quiet wakefulness and pre-sleep behaviour. Slow-wave sleep and REM sleep have two distinct and localized generators, respectively located at the telencephalic and rhombencephalic levels (Fig. 3). The central network controlling sleep and wakefulness can be conceived as having a caudorostral organization (Fig. 4). The caudalmost part of the network as shown by experimental medullary and midpontine preparations (Siegel et al., 1986) is still able to organize rest–activity cycles. Pre-sleep behaviour can be identified only if the whole brainstem is intact, as shown in midbrain-transected cats (Villablanca et al., 2001). The integrity of the rostral pons and the caudal midbrain is both necessary and sufficient to generate the basic aspects of REM sleep. Ablation of the thalami in experimental animals and degeneration of thala-

molimbic structures in humans not only abolish SWS, which is generated within the thalamus, but also impair REM sleep, thus favouring a persistent condition of motor and autonomic overactivation. It is likely that in addition to generating slow-wave sleep, the thalamolimbic circuits exert inhibitory control over activating-deactivating systems located in the hypothalamus and the brainstem.

The hypothalamus does contain important arousing and dearousing systems that reciprocally control and modulate the sleep-wake cycle (McGinty and Szymusiak, 2000; Saper et al., 2001). However, as claimed by Hess, the hypothalamus does not contain formations directly involved in sleep generation. Indeed, when both arousing and dearousing hypothalamic systems are blocked, sleep and wakefulness still continue to alternate (Sallanon et al., 1989) (Fig. 4).

All animals and plants living on earth are able to alternate rest-activity cycles (Fig.4). In its most primitive form, pre-sleep behaviour appeared in some poikilothermic animals, the reptiles, but both components of "true sleep" (SWS and REM) only developed and are present together in homeothermic animals. Why and how homeothermy produced two such different types of sleep, one generated within the core of archaic formations such as the pons and the caudal midbrain and the other by phylogenetically more recent systems, the thalamo-limbic circuits, will remain a mystery until we know the actual needs that REM and SWS satisfy.

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