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Methods and related results in animal sleep research – a historical review

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The experimental sciences mainly progress, if not only, by development of methods. This is particularly evidenced for what concern the neurobiological support of sleep-waking cycle. We will provide the main approaches used in sleep research, showing that already far centuries ago spontaneous observations of sleep rather well described peripheral characteristics of dreaming. Today identified as occurring in a specific sleep stage mainly called rapid eye movement (REM) sleep, but also paradoxical sleep, it will be shown that surgical operations, already from two previous centuries, brought significant results on sleep regulation, before the major contribution of electrophysiology and its derivative methods which opened the crucial complementary fields of pharmacology, neurochemistry and genetic study of this highly important biological rhythm on which all other behaviors are inserted.

Sleep studies performed prior to the appearance of electrophysiology

Summary. The first results mainly concerned observations of spontaneous behavioral components of sleep and the latter variations after surgical operations.

Already in classical times LUCRETIUS (circa 98-55 BC), in «De rerum natura» (LUCRECE, 1900) gave a wonderfully detailed description of dreaming and its behavioral activation correlates in animals as well as in humans. *«In truth you will see strong horses when their limbs lie at rest, yet sweat in their sleep, and go on panting, and strain every nerve as though for victory, or else as though the barriers were opened (struggle to start). And hunters' dogs often in their soft sleep yet suddenly toss their legs, and all at once give tongue, and again and again sniff the air with their nostrils, as if they had found and were following the tracks of wild beasts, yea, roused from slumber they often pursue empty images of stags, as though they saw them in eager flight, until they shake off the delusion and return to themselves. But the fawning brood of pups brought up in the house, in a moment shake their*

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body and lift it from the ground, just as if they beheld unknown forms and faces. And the wilder any breed may be, the more must it needs rage in its sleep. But the diverse tribes of birds fly off,and on a sudden in the night time trouble the peace of the groves of the gods with the whirr of wings, as if in their gentle sleep they have seen hawks, flying in pursuit, offer fight and battle. Moreover, the minds of men, which with mighty movements bring forth mighty deeds, often in sleep do and dare just the same; they storm kings, are captured, join battle, raise a loud cry,as though being murdered – all without moving. Many men fight hard, and utter groans through their pain, and, as though the teeth of a panther or savage lion bit them, fill all around them with loud cries. Many in their sleep discourse of high affairs, and very often have been witness to their own guilt. Many meet death; many as though they were falling headlong with all their body from high mountains to the earth, are beside themselves with fear, and, as though bereft of reason, scarcely recover themselves from sleep, quivering with the turmoil of their body. Likewise, a thirsty man sits down beside a stream or a pleasant spring, and gulps almost the whole river down his throat. Cleanly persons often, if bound fast in slumber they think they are lifting their dress at a latrine or a shallow pot, pour forth the filtered liquid from their whole body, and the Babylonian coverlets of rich beauty are soaked. Later on those, into the channel of whose life the vital seed is passing for the first time, when the ripeness of time has created it in their limbs, there come from without idols from every body, heralding a glorious face or beautiful colouring, which stir and rouse their members swelling with much seed, and often, as though all were over, they pour forth huge floods of moisture and soil their clothes» (lines 987-1036) (GOTTESMANN 2001).

Many centuries later, FONTANA (1765) (as quoted by numerous authors (RAEHLMANN and WITKOWSKI 1878, PIERON 1913, MORUZZI 1963) observed that shortly after sleep onset a cat «*begins to tremble as though it were in convulsion. I have observed this phenomenon more than once in heavily sleeping animals, and more especially in dogs*» (p 22). Moreover, he showed that the pupils were restricted during sleep.

Forelast century experiments showed in dogs that neodecortication performed under chloroform did not suppress behavioral sleep (GOLTZ 1892). In the same way, it was shown that long-term sleep deprivation in young dogs was fatal after 96 to 120 hour duration (MANACEINE DE 1894). The deprivation induced weight loss, a lowered of central temperature from the second day, and red blood cells were shown to decrease from 5 millions down to 2 millions per mm^3 after longer deprivation.

At the beginning of last century, LEGENDRE and PIERON (1908), also in dogs, found serious brain cell disturbances after much longer sleep deprivation (up to 240 h, but which were shown to have been

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incomplete (KLEITMAN (1927)), which however were reversible after sleep recovery. Moreover, these authors performed sucessful transferts of cerebrospinal fluid from sleep deprived dogs to control animals which induced sleep (LEGENDRE and PIERON 1910). The same experiment had been just previously made in Japan (ISHIMORI 1909) (see (KUBOTA 1989)). However, the true identication of an interspecies sleep factor was only much later identified (PAPPENHEIMER et al. 1975). These cerebral fluid transfert studies were later continued (SALLANON et al. 1982) after discovery of REM sleep stage.

Electrophysiology

Summary. The observation of brain functioning by help of electrical activity has led to major discoveries in sleep mechanisms: identification of stages, neuronal firing, brain responsiveness.

Spontaneous and induced electrical activity of the brain was recorded in rabbits and monkey as soon as 1875: «*When any part of the grey matter is in a state of functional activity, its electrical current usually exhibits negative variation*» (p 278) (*Caton* 1875). This finding was an extraordinary discovery given the methodology then available, a galvanometer. However, the true entrance in EEG area began with HANS BERGER who studied human cortical waves at scalp level in his son (electroencephalogram) and directly on the cortex in other subjects (electrocorticogram) (BERGER 1929). In animals, DERBYSHIRE et al. (1936) described sleep in cats, even showing periods of low voltage cortical activity during which there was twitching of the vibrissae (p (582) and, the year after, BLAKE and GERARD (1937) observed in humans similar low voltage waves with increased arousal threshold, and LOOMIS et al. (1937) found that dreams occurred during this rapid low voltage EEG. The same year, in cats, KLAUE (1937) observed a «tiefer Schlaf» characterized by low cortical activity which was termed «Beruhigung in Strombilde» with «eine völlige Entspannung der Muskulatur und häufige Zuckungen in einzelne Extremitäten» (p 514).

The next step was the true discovery of REM sleep which first occurred in humans (ASERINSKY and KLEITMAN 1953, DEMENT and KLEITMAN 1957a, DEMENT and KLEITMAN 1957b). The year after, DEMENT (1958) described in cats REM sleep recorded by needles inserted under the scalp and small wires placed on the dura. While the animals were asleep, «the EEG changed from slow wave, spindle patterns to low voltage, fast rhythms. Concomitant with the latter phase were considerable amounts of twitching movements of the legs, ears and vibrissae and occasional tail movements… There was also complete absence of muscle potentials, an excess of which characterized the record of the wakeful

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animals» (the electromyogram (EMG) was recorded as artefactual by needles inserted into the scalp). Moreover, «there was considerable movement of the eye balls» (p 293).

From 1959, this REM sleep stage, called by them as paradoxical sleep, was then the main topic of the explosion of researches on sleep performed by Jouvet's team on cats (JOUVET and MICHEL 1959, 1960a, b, c, JOUVET et al. 1959 a, b, 1960 a, b) **(Figure 1)**. A different method was used to record the EMG: electrodes were inserted in the dorsal neck muscles which confirmed the abolition of muscular activity, although short jerks observed by Dement were rediscovered. Cortical recordings were made by screws placed into the skull or small silver balls placed on the dura whereas brain deep structures were recorded by wires often sticking out a needle. The recordings were made monopolarly (active electrode compared to a neutral point, as bone), or bipolarly recordings, to record the activity between two active brain levels.

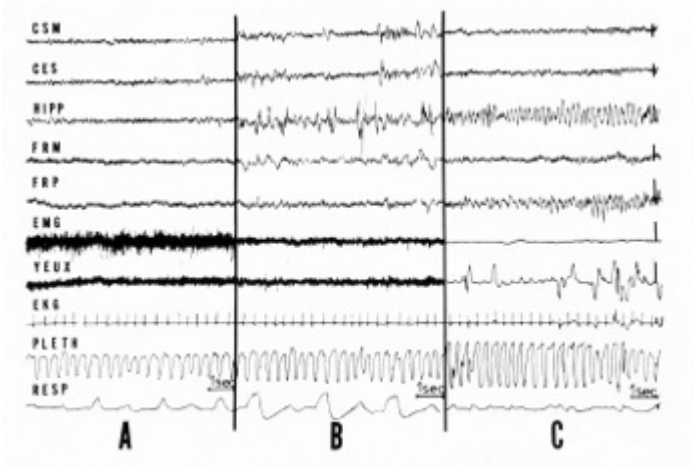

Fig. 1. One of the first EEG sleep-waking polygraphic recordings performed in the cat. It comprised REM sleep with all its main characteristics: rapid, low voltage cortical activity, hippocampal theta rhythm, pontine sharp waves, EMG abolition and eye movements. A: waking, B: NREM sleep, C: REM sleep. CMS: sensory-motor cortex, CES: ectosylvian cortex, FRM: midbrain reticular formation, FRP: pontine reticular formation, EMG: dorsal neck muscular activity, Yeux: eyes, EKG and Pleth: cardiac rhythm, Resp: respiration. (JOUVET 1962)

The above described method to record electrical field activity in the brain led to the much later major discovery of gamma rhythm. It was first in 1981, that was observed an unusual high frequency EEG rhythm in cats. Indeed, while up to then the EEG was generally studied up to nearly 25 c/s, the above frequencies being filtered to avoid artefacts, BOUYER et al. (1981) observed 35-45 c/s synchronized activity occurring in cats during attentive behavior and recorded it in the cortex as well as in the

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thalamus. This result was then confirmed in this species (FERSTER 1988, STERIADE et al. 1991), guinea-pigs (LLINAS et al. 1991), rats (FRANKEN et al. 1994, MALONEY et al. 1997) but also in monkeys (FREEMAN and VAN DIJK 1987). In humans, this rhythm mainly observed during waking and REM sleep (RIBARY et al. 1991, LLINAS and RIBARY1993), «was phase-looked over cortical areas» (p 11039) (RIBARY et al. 1991). In contrast, which was of particular interest, is that during REM sleep, the gamma rhythm becomes uncoupled over cortical and subcortical areas (PEREZ-GARCI et al. 2001, CANTERO et al. 2004). The occurrence of this rhythm during REM sleep, with its particularity of becoming uncoupled, which shows a functional disconnection between brain structures, gave rise to different hypotheses concerning abnormal dreaming mentation (GOTTESMANN 2006, 2010). It is worth mentioning that recently still higher frequency oscillations (80-200 Hz) have been recorded in cats (GRENIER et al. 2001) as well as in humans (SABA et al. 2004). Contrary to what had been observed in the cortex of cats (GRENIER et al. 2001), in the rat limbic accumbens nucleus the power of this high frequency activity (140-180 Hz) was significantly ($p= 0.03$) lower during NREM sleep than during REM sleep. There was nearly no difference between waking and REM sleep (HUNT et al. 2009). The meaning of such high frequency oscillations is open to discussion. However, pentobarbital, urethane and isoflurane, decreased this activity whereas ketamine (a N-methyl -D- aspartate antagonist) increased it. The fact that gamma activity in some cases occurs under anesthesia (VANDERWOLF 2000) calls for caution regarding its relation to consciousness.

Another step in the methods to study sleep was the recording brain activity with long time constant to study EEG steady potentials (D.C. currents). The first results were uncertain. Whereas Caspers (CASPERS and SCHULZE 1959, CASPERS, 1965) and WURTZ et al (1964) observed positive shifts during different stages of sleep, KAWAMURA and SAWYER (1964) in rabbits and then WURTZ (1965 a, b) definitively established in rats and cats that negative shifts occurred during waking and REM sleep, and positive variations during slow wave sleep (NREM sleep). It was, very indirectly, an unexpected confirmation of CATON's observation that activation of the brain leads to negative variations of the polarity!

The EEG field activity studied above allowed the identication and characterization of all tonic and phasic (ponto-geniculo-occipital – PGO- spike-waves: (MIKITEN et al. 1961, BIZZI and BROOKS 1963, JEANNEROD 1966) brain field processes during sleep and waking.

A new major step was the recording of neuron activity by unit or multi-unit way. Although CREUTZFELDT et al. (1956) were able to record single cortical neurons and could indentify inhibitory processes regulating cortical cell activity, it was HUTTENLOCHER (1961), then EVARTS (1962) who

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showed cell recordings during sleep with enhanced firing at midbrain and visual cortex levels, respectively, during REM sleep. However, the first complete sleep-waking detailed study was performed by EVARTS (1964) in the monkey visual cortex and pyramidal neurons The latter neurons discharged regularly and at high frequency, particulary during attentive waking, decreased their firing rate and became irregular during NREM sleep while during REM sleep, discharges of high frequency, in bursts, were interspersed with long silences. EVARTS postulated the disappearance of a cortical frequency-limiting control process involving inhibitory influences. At pontine level, multi-unit (GOTTESMANN 1967, 1969) **(Figure 2)** and unit (MCCARLEY and HOBSON 1971, VERTES 1977) recordings first showed high tonic reticular activation, nearly specific of REM sleep, underlying the highest involvement of this brain level in REM sleep basic processes. Later, it was shown that during REM sleep, serotonergic dorsal (MCGINTY et al. 1974) and medial (RASMUSSEN et al. 1984) brainstem raphe nuclei come silent or nearly silent as well as noradrenergic locus coeruleus neurons (HOBSON et al. 1975, ASTON-JONES and BLOOM 1981) **(Figure 3)**, leading to major theories concerning sleep-waking regulation, since this neurons mainly inhibit cortical neurons, thus leading to cortical significant disinhibition during REM sleep, in spite of strong activation. Thus, the brain level mainly involved in cognitive processes, would be less controlled during the dreaming sleep stage allowing appearance of a psychotic-like mentation (GOTTESMANN 2006). This conclusion was reinforced by dopaminergic functioning, the neurons of which continue to be active during REM sleep (MILLER et al. 1983), moreover firing by bursts (DAHAN et al. 2007) which is known to release a maximal level of transmitter (CHERGUI et al. 1994) **(Figure 4).**

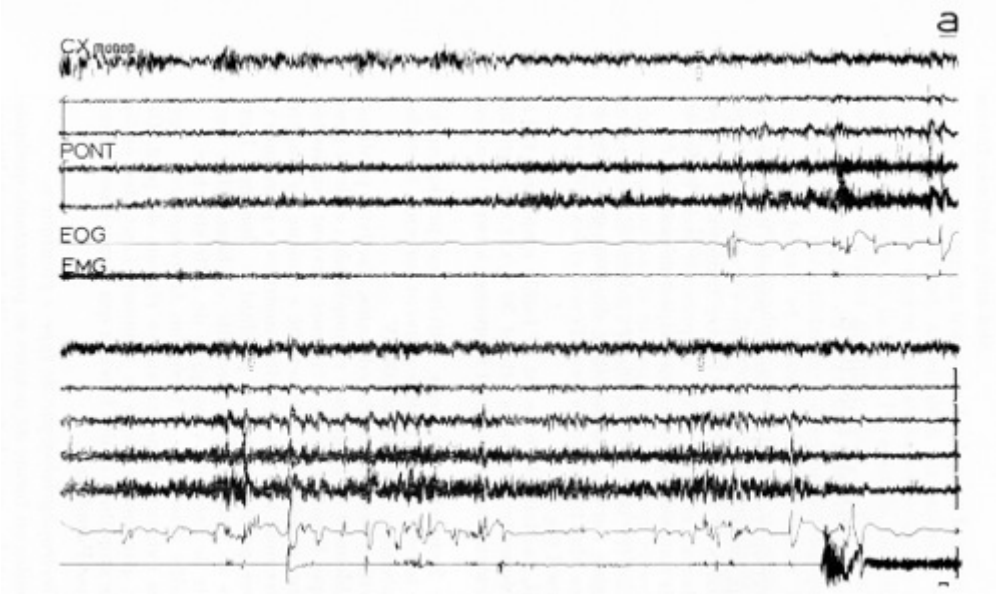

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Fig. 2. Pontine reticular activity during REM sleep in the rat. This poly-unit recording showed for the first time a pontine tonic activation nearly specific of REM sleep. CX monop: monopolarly recording of the cortex. PONT: pons, EOG: eye movements (GOTTESMANN 1967).

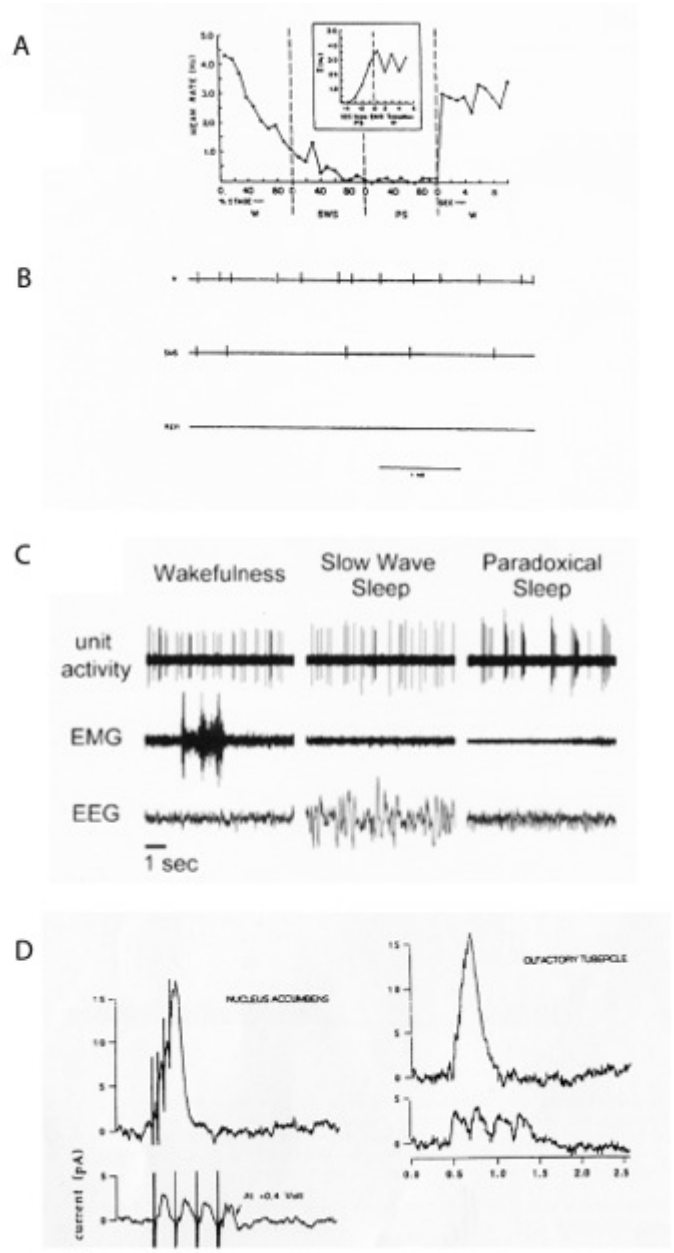

Fig. 3. REM sleep activity of monoamines activity. A. locus coeruleus recording during sleep-waking stages. The noradrenergic neurons become silent during REM sleep (ASTON-JONES and BLOOM 1981). Notice that the neurons again fire few seconds prior to behavioral arousal (insert) which is important for brain state at behavioral arousal and forgetting of dreams. B. Dorsal raphe nucleus. The serotonergic also become silent during REM sleep (MCGINTY and HARPER 1976). C. the ventral tegmental area. The dopaminergic neurons fire by bursts during REM sleep (DAHAN et al. 2007) D. It still increases transmitter release, when compared to low frequency spiking (CHERGUI et al. 1994).

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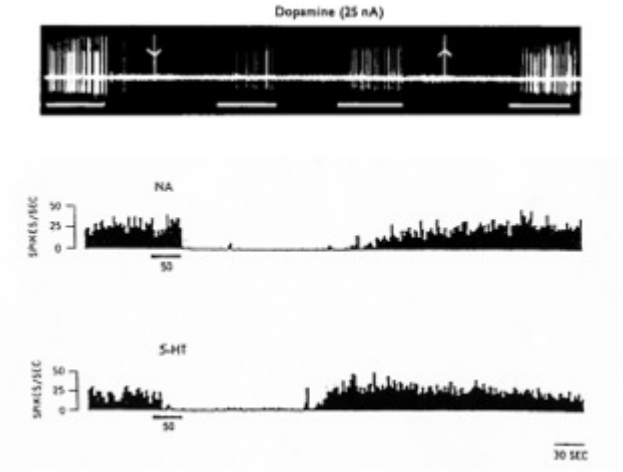

Fig. 4. Dopamine inhibits cortical neuron firing (arrow on and off), even during glutamate application (white line) (KRNJEVIC and PHILLIS 1963). Noradrenaline (NA) and serotonin (5-HT) also inhibit cortical neurons (see text) (READER el al. 1979).

Stimulation experiments.

Summary. The brain responsiveness study during sleep brought major information about the cerebral functional state.

Old fashioned results already brought high important findings. It was first the case of FRITSCH and HITZIG (1870) who showed that the brain is excitable, and that its stimulation could induced motor movements. Then, it was the case of BARTHLOW (1874) who, already aware of previous authors's result (!) stimulated the brain of a woman and observed that it induced sensory feeling, paroxystic behavior with stronger stimulations, and that even during these stimulations, major finding, the brain was insensitive to pain. In those days, it was also BUBNOFF and HEIDENHAIN (1881) who could inhibit peripheral movements by cortical stimulation, identifying for the first time inhibitory processes in the brain. Finally, HESS (1931) was able, by low voltage and low frequency pulses to induce physiological sleep in cats by stimulating the anterior hypothalamus (the cat was looking around for a place to lay down and fall asleep). It was the first result clearly showing that sleep results from active inhibitory processes and is not the only consequence of sensory deafferentation : for details about this on these days mainly retained theory see MORUZZI (1964).

With the appearance of electrophysiology, the stimulation method allowed major progresses in sleep–waking knowledge. After old days capacitor discharges, stimulation was first mainly made of alternative sinusoidal current, then constituted by rectanglar pulses, the duration of which in

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milliseconds, their amplitude in volts, and their frequency/s permitted a large choice of parameters. However, since being of similar polarity and become less efficient by the progressive polarization of the electrode, many later stimulateurs delivered constant intensity (micro- or tenth of milliampere) stimulations to avoid previous inconvenients.

One of the first results of central stimulation was the more precise identification of the midbrain reticular formation, since its stimulation at high frequency induced EEG arousal. This was observed first in an acute experiment (MORUZZI and MAGOUN 1949). It already can be underlined that subcortical high frequency stimulations have mainly arousal effects whereas low frequency stimulations rather favor sleep or at least NREM EEG patterns (FAVALE et al. 1961, MAGNES et al., 1961). Also, REM sleep could be elicited by brainstem (JOUVET et al. 1960b) and even by cortical (DI PAola et al. 1965) stimulation when the animal was in NREM sleep, with always a refractory period for a new elicitation. Finally, increased arousal threshold by central (BENOIT and BLOCH 1960) and peripheral (JOUVET et al. 1960b) stimulation was observed during REM sleep, when compared to NREM sleep.

Major results were obtained concerning brain responsivenes, thus, of its excitability by evoked potential studies (GOTTESMANN 1992) **(Figure 5)**. The first results showed that the cortical response induced by peripheral (FAVALE et al. 1962b), and thalamocortical (FAvale et al. 1962b, PISANO et al. 1962) somesthetic stimulations was of high amplitude during waking and became highest during REM sleep, being maximal during the eye movements bursts. Similar results were obtained for the visual system (PALESTINI et al. 1964). The analysis of responsiveness at thalamic relay nuclei level, revealed that during the PGO waves which are concomitant of REM sleep eye movement bursts even showed a presynaptic inhibition of thalamic afferents, as shown by the decrease of the t_1 component amplitude and a postsynaptic activation as evidenced by the enhancement of the postssynaptic r_1 component (SAKAKURA and IWAMA 1965). In contrast the radiatio-cortical response was highest during NREM sleep (FAVALE et al. 1962a).

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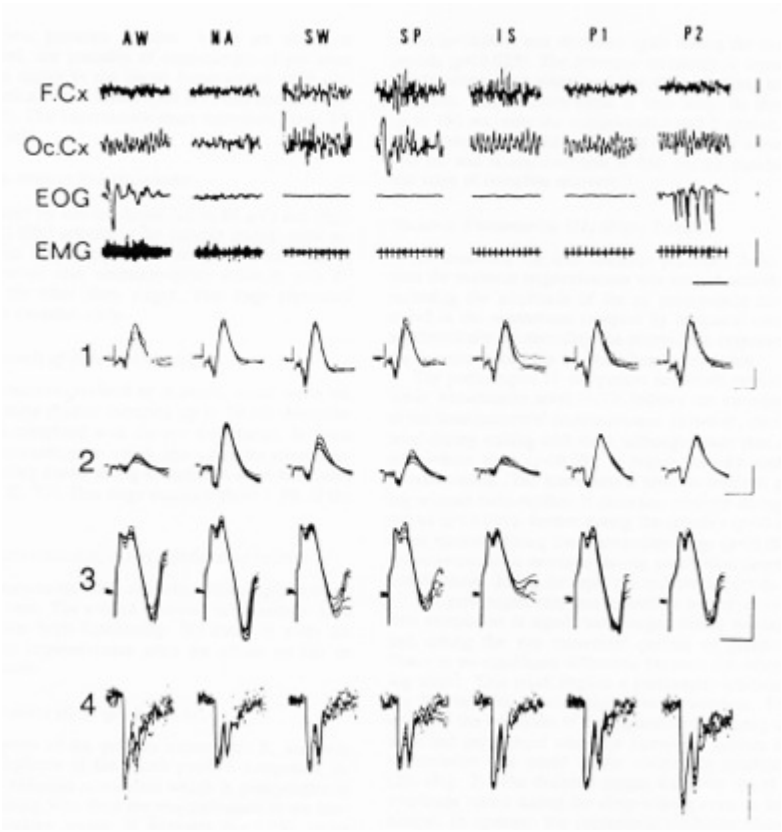

Fig. 5. Sleep-waking related central responsiveness in the rat. Top: The seven sleep-waking stages studied in the rat. AW: active waking, with rapid, low voltage activity in the frontal cortex (F.Cx) and hippocampal synchronized theta rhythm spreading on the occipital cortex (Oc.Cx); NA: non active (quiet) waking without theta activity; SW: cortical and subcortical slow wave stage; SP: Frontal cortex spindles which occur as sleep deepens; IS: intermediate stage occurring before onset and just after REM sleep episodes, and characterized by high amplitude cortical spindles and low frequency theta activity; P1: REM sleep without eye movements; P2: rapid eye movement periods. 1. Cortical responsiveness to thalamocortical radiation stimulation of the somesthetic system. The neuron excitability is always quantified by the amplitude of the positive component 4 (maximal downward wave). Note its low amplitude during active waking, and during REM sleep the responsiveness is not significantly different from that of NREM sleep stages (particularly SW). 2. The thalamocortical responsiveness also is low during active waking, decreases from NA to IS and strongly increases during REM sleep, but is slightly reduced during the eye movements. 3. The amplitude of the ventrobasal r_1 postsynaptic (second) wave shows that the thalamic relay transmission is significantly decreased during active waking when compared quiet waking and is increased during REM sleep, but slightly reduced during the eye movements. 4. Thalamic antidromic t_1 wave amplitude. The presynaptic inhibition is significantly highest during active waking and during REM sleep eye movement periods. This last experiment explained the results obtained for postsynaptic r1 component and more generally at cortical level (GOTTESMANN 1992).

However, a pulse generating the evoked potential only reflected the brain state at a moment, and although it generally evidenced activating processes, conclusions were sometimes discutable, for example at cortical level which, as shown by the EEG, is activated during REM sleep, although it is

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clearly not reflected by the cortical response obtained above by radiation stimulation. Therefore, the next step of responsiveness studies concerned the recovery cycle of excitability (by studying the amplitude of the evoked responses to two consecutive pulses occurring at different delay) which was mainly examined at cortical level. The first study was only devoted to the comparison of waking and NREM sleep and already showed a shortened recovery cycle during sleep (EVARTS et al. 1960), which was an index of disinhibition. Indeed, while during waking, the conditional first thalamo-cortical evoked potential was of large amplitude, the second test response was of very low amplitude, underlining both an activated cortex as evidenced by the first response amplitude and cortical inhibitory processes as shown by the reduced test response. In contrast during REM sleep the test response was of much higher amplitude, the response during NREM sleep being intermediary (ROSSI et al. 1965, DEMETRESCU et al. 1966) **(Figure 6)**. Thus, the highly important results showed by this method, were that there are simultaneously strong activating and inhibitory (control) influences during waking, and in contrast during REM sleep, the cortex is activated, but largely disinhibited, which means a loss of control, allowing all hypotheses related to mind functioning during this sleep stage when compared to waking and NREM sleep (GOTTESMANN 2006, 2010). In humans similar results were described (KISLEY et al. 2003), the new denomination of the protocol being prepulse inhibition.

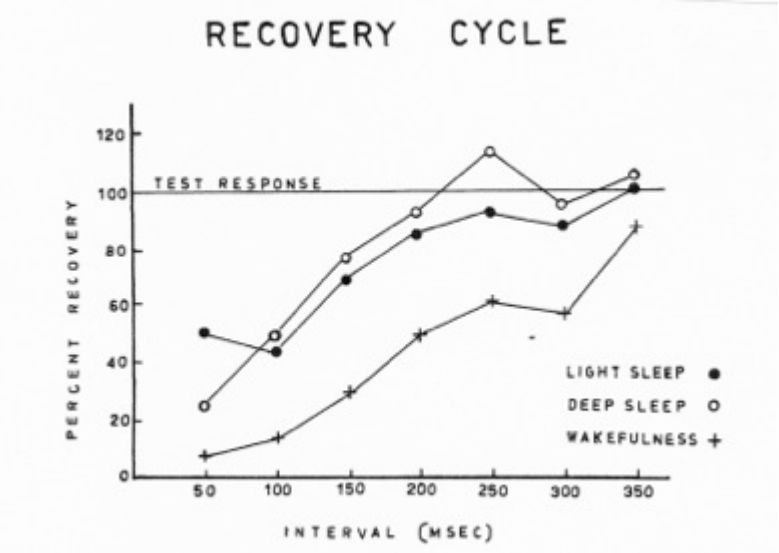

Fig. 6. Recovery cycle of cortical responsiveness. The response to a second pulse stimulation applied to afferent radiations is much more decreased during waking than during NREM and above all during REM sleep. Thus, the first pulse induced a cortical inhibition which lasted much less during sleep. Whereas the REM sleep neuron activation is high as evidenced by the first evoked potential amplitude (see figure 5), this stage also is characterized by the strongest disinhibition (ROSSI et al. 1965).

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Methods of sleep electrophysiological studies

Summary. The chronic preparation with implanted electrodes respects animal's behavior and the automatic scoring of sleep-waking stages of the free moving animal recorded by telemetry allow its precise quantitative approach. All electrophysiological studies devoted to sleep necessitate methods which respect the occurrence of normal behavior. It essentially concerned chronic preparations with central and peripheral inserted electrodes.

Although neurophysiological studies performed in animals began with anesthetized preparations, the majority of them were performed in immobilized animals by compounds like d-tubocurarine which blocking the neuromuscular junction, necessitated respiratory assistance. These are called *acute* preparations. They are of little interest for sleep studies. Only freely behaving animals with implanted electrodes, *chronic* preparations, are used for such studies. The animals are surged under general anesthetics, first a dog under intravenous opium diluted in alcohol in 1656! (DORRINGTON and POOLE); then in humans was used ether in 1846! , chloroform in dogs (GOLTZ 1892), then during decades animal surgery was performed under gamma-aminobutyric acid favoring compounds, like barbiturates, then chloralose, now generally under ketamine, a glutamate antagonist which acts rapidly and mainly inhibits voltage-gated calcium channels. Different cortical, subcortical and peripheral electrodes are placed and, after being linked to a plug, are fasted on the skull by dental or synthetic resins. Thus, the animal are relatively free of movements being linked to the recorder machine by cables. Then appeared miniaturized telemetric recording systems for animals **(Figure 7).** It can be reported that the telemetry system in humans became so performing, that it was possible to record alpha rhythm at closing the lids during parachutist free fall at 150 km/hour, which showed a remarkable dissociation between the brain relaxed state (there were professional jumpers), and the body vegetative stress, since the heart rate was at 150 at each jump, whatever the training (GAUTHIER et al. 1980). **(Figure 8)**. Today, recording of free animals in ethological studies has become common, while the neurophysiological, pharmacological and neurochemical studies prefer head restrained preparations, the body being placed in a hammock.

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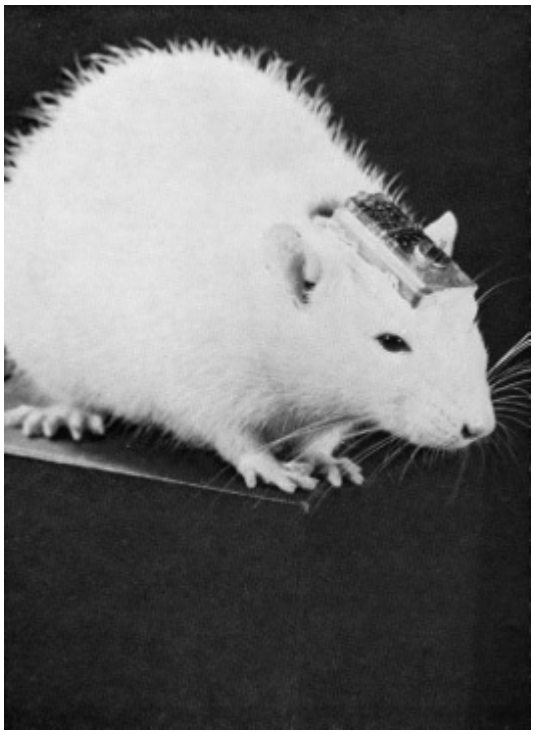

Fig. 7. Telemetric recording of rats. The 1977, 4-channel radiotelemetric transmitter was weighing 4 g including battery and had a 10 day autonomy with a pass-band of 0.22-400 Hz (GOTTESMANN et al. 1977).

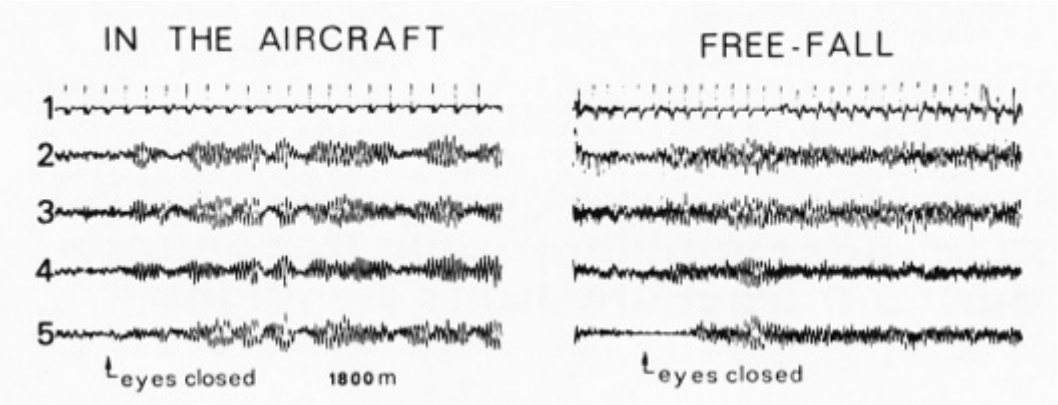

Fig. 8. Telemetric recording of parachutists. During the free-fall, EEG alpha rhythm could be recorded, while the cardiac rhythm was very high (see text). The transmitter was different from that used for rats. (GAUTHIER et al. 1980).

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Methods of sleep quantification

Summary. The automatic scoring of sleep-waking activities in free moving animals are very useful for neurobiological studies.

To analyze and quantify day long sleep-waking recordings takes plenty of time and is open to often fickle results because human variations in attention. Thus, in the last seventies, several teams elaborated scoring systems. The first multichannel off-line program for rats (GOTTESMANN et al. 1971) quantified second by second seven sleep-waking stages: 1/ active waking with cortical rapid low voltage activity and hippocampal theta activity, 1/ quiet waking, without theta, 3/ slow wave stage in the cortex and hippocampus, 4/ frontal cortex spindles increasing in amplitude while sleep deepened, 5/ Intermediate stage which precedes and follows REM sleep, characterized by high amplitude spindles and low frequency theta rhythm, 6/ REM sleep without eye movements, with low voltage rapid cortical activity, hippocampal theta, and dorsal neck muscle atonia, 7/ eye movements periods of REM sleep **(Figure 9)**. The stages were scored second by second and put together up to minutes and hours **(Figure 10)**.

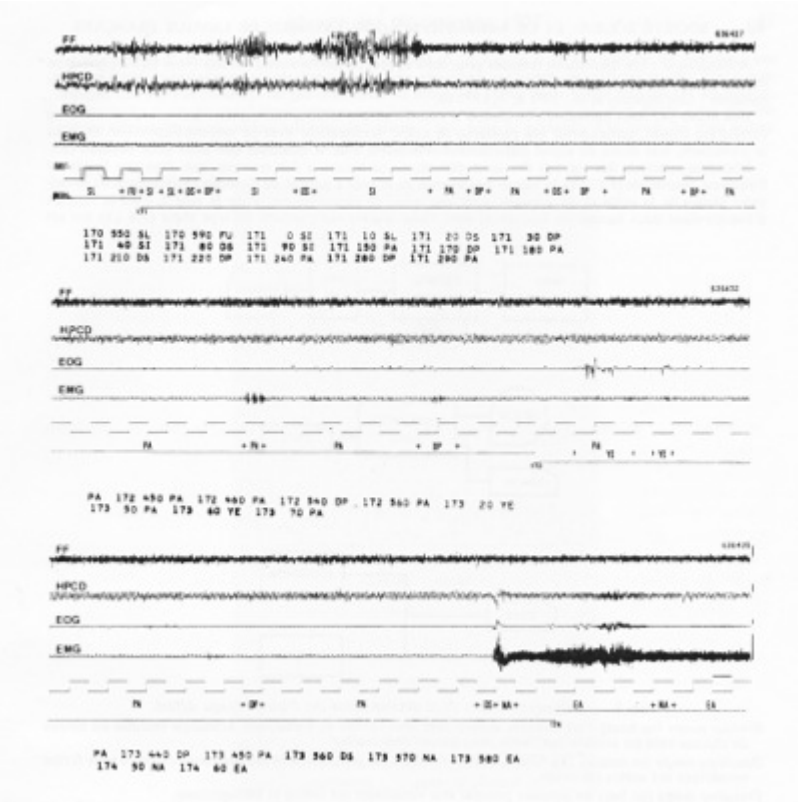

Fig. 9. Automatic scoring of sleep-waking stages in rats. Continuous recording showing the second by second stage identification. EA: active waking. NA: non active waking (without theta activity). SL: slow waves. FU: spindles. SI: intermediate stage. PA: REM sleep. YE: REM sleep eye movements. Each

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stage preceded by D, which did not reach the stage ideal value, was quantified as doubtful corresponding stage and scored separately but also with the most probable stage (GOTTESMANN et al. 1976).

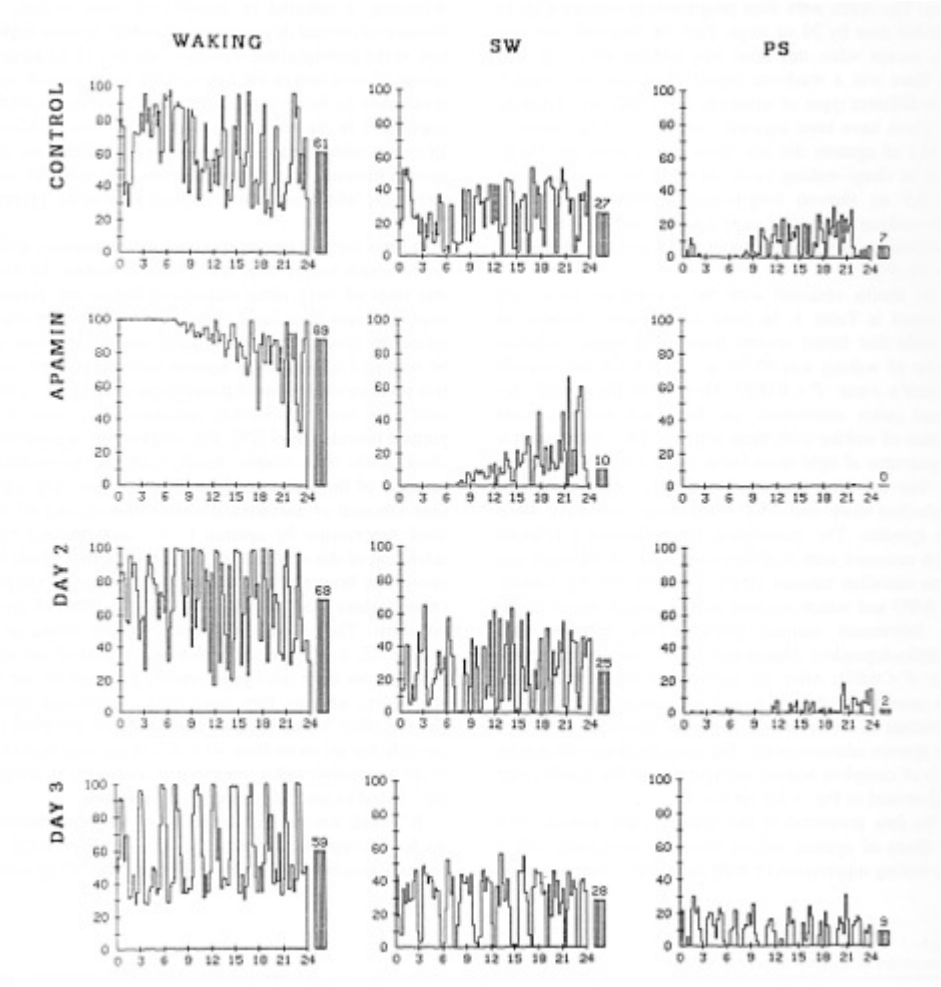

Fig. 10. Sleep-waking automatic obtained histograms for apamin study in the rat. The intracisternal injection of this CA^{2+} -activated K^+ channel blocker induced a transient complete insomnia and a very long total abolition of REM sleep. Even after its reappearance the sleep-waking stages was majorly disturbed (GANDOLFO et al. 1996).

It is of interest that the same year was elaborated a first similar program for humans (GAILLARD et al. 1971). The year after an analysis of evoked potentials was coupled to the determination of sleep-waking stages (GOTTESMANN et al. 1972), and since the muscular activity was quantified, the software could distinguish drugs, like atropine, inducing a dissociation between behavior (arousal) and EEG (NREM sleep). Later on, the automatic scoring system became on-line and was coupled to telemetric recording of rat activity (GOTTESMANN et al. 1977). By this method it was not only possible to obtain

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rapid and accurate results concerning the quantification of sleep-waking stages and related brain responsiveness, with and without pharmacological compounds, but it even allowed to demonstrate unexpected basic neurophysiological results, like the presynaptic origin of the component 2 of the cortical response to afferent stimuli, which was up to then open to discussion (GANDOLFO et al. 1986) **(Figure 11)**.

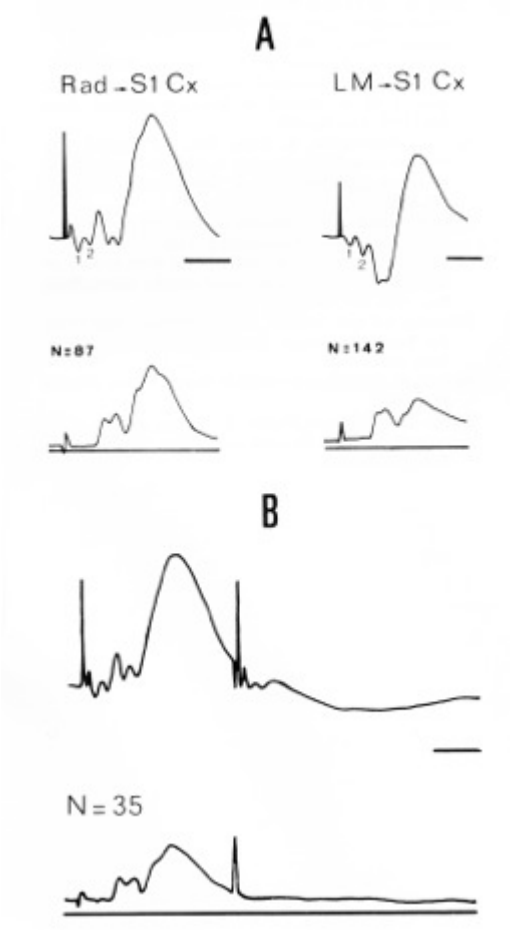

Fig. 11. Importance of automatic study of responsiveness. Top: Mean amplitude and standard variation (below) of cortical (Rad-S1 Cx) and Thalamocortical (LM-S1 Cx) evoked potentials. There is absence of any variability for waves 1 and 2, thus indicating presynaptic origin of both. Bottom. Recovery cycle. Similar absence of variability for waves 1 and 2. There is a strong inhibition of the evoked potential for the second pulse occurring at 17 msec interval. The three figures show the variability for the other cortical components of the evoked response (GANDOLFO et al. 1986).

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Surgery and sleep

Summary. The operations mainly consisted in ablations and transections.

We already have seen that such experiments were performed very early since neodecortication performed did not prevent dog from behavioral sleep (GOLTZ 1892). In the much more recent history, the main transections were made at brainstem level. Performed at the anterior level of the midbrain it was called cerveau isolé preparation and the acute cat showed deep NREM sleep with high amplitude cortical spindles (BREMER 1935), the chronic preparation lately recovering EEG desynchronized patterns (BATSEL 1960, 1964). In contrast, transections at the submedulla oblongata level (encéphale isolé preparation) maintained sleep-waking EEG alternating processes (BREMER 1936). BREMER postulated that arousal in the latter animal was supported by cranial nerve activating influences. These two experiment undoubtly were at the origin of later midbrain reticular stimulation (MORUZZI and MAGOUN 1949). Then was performed the next well know preparation, the midpontine pretrigeminal cat which showed nearly continuous waking (BATINI et al. 1958, 1959 a, b, c). This well documented experiment showed that below situated structures were responsible for cortical synchronizing influences. They were shown to be situated at medulla oblongata level, in the nucleus of solitary tract (BONVALLET and ALLEN 1963).

Another example of transection level was its utilisation in the study of spinal reflexes. In early contemporary history of sleep, it was shown that monosynaptic extensor and flexor reflexes are suppressed during REM sleep by descending influences issued from the inhibitory reticular formation (MAGOUN and RHINES 1946) whereas the polysynaptic flexion reflex only totally disappeared during REM sleep eye movement bursts because of presynaptic inhibition of afferents added to motoneuron hyperpolarization (GIAQUINTO et al. 1963 a, b). Cordotomies showed that the descending influences run the ventral half of lateral funiculi (POMPEIANO 1965).

Following the description of penile tumescence during sleep (OHLMEYER et al. 1944, OHLMEYER and BRILMAYER 1947) (see SCHULZ and SALZARULO (2012)), several authors studied its central mechanims in rats (SCHMIDT et al. 1994). It was shown that spinal transections suppressed erections, mesencephalic transections strongly decreasing them during REM sleep (SCHMIDT et al. 1999), and that ibotenic lesion of the hypothalamus lateral preoptic area suppressed their occurrence during REM sleep, while they were able to occur during waking (SCHMIDT et al. 2000). Recent results show a final dopamine-oxytocin step for penile erection occurrence (MELIS and ARGIOLAS 2011). The established

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strong level of subcortical dopaminergic neuron activity during REM sleep (LENA et al. 2005, DAHAN et al. 2007) supports such process.

Lesions

Summary. Electrical and chemical destructions allowed the identification of brain structures responsible for each of sleep-waking stages.

The nearly first observation of brain lesions influencing sleep-waking was the finding of Economo (1917, 1928) who determined that posterior hypothalamus lesions in humans (encephalitis lethargica epidemia) led to death after hypersomnia, whereas anterior hypothalamus lesions induced fatal hyper arousal. The latter observation was highly probably at the origin of Hess's stimulation of this area (HESS 1931). Economo's finding was reproduced in several animal experiments undertaken by electrolytic lesions produced by direct current first in the posterior hypothalamus (RANSON 1939) the induced coma being followed by recovery of waking in the chronic preparation (MCGINTY 1969). In the same way, after lesion in its anterior part (MAIRE and PATTON 1954) insomnia was confirmed. This experiment gave rise to cell recordings showing increased firing in the preoptic area during NREM sleep and stimulation of this area induced NREM sleep patterns related to local GABA release (STERMAN and CLEMENTE 1962, SZYMUSIAK and MCGINTY, 2008). Also, from the middle of last century, the function of the activating reticular formation (MORUZZI and MAGOUN, 1949) was confirmed by lesions inducing coma (LINDSLEY et al. 1949, 1950). Finally in relation to REM sleep, pontine reticular lesions suppressed REM sleep, moreover inducing, remarkable observation premonitory of later results (JOUVET and DELORME 1965), a hallucinatory behavior (JOUVET and MOUNIER 1960) **(Figure 12).**

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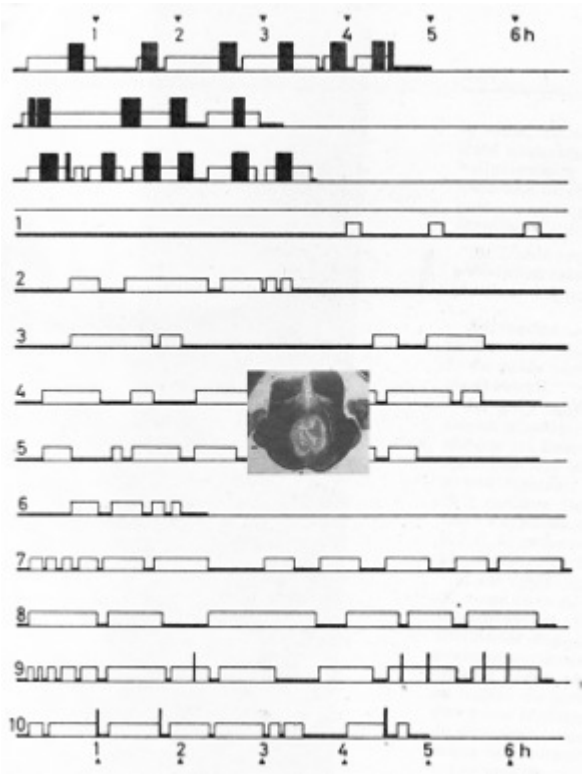

Fig. 12. Effect of pontine electrolytic lesion on sleep-waking stages in the cat. REM sleep (duration in black squares before lesion) disappeared after lesion for at least 9 days (see text) (JOUVET and MOUNIER 1960).

However, electrolytic lesions had a major inconvenient: they destroyed local cells as well as passing fibers. Therefore, nowadays, ibotenic and kainic acid have excito-toxic effects, strongly activating the structure up to destroy the local neurons without affecting passing fibers (DATTA and HOBSON 1995).

Finally, it can be recalled that more frequently in the past, chemical compounds were able to destroy specific kinds of neurons. For example, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxy-dopamine (6-OHDA) injected in a structure only destroyed dopaminergic neurons (LIMA et al. 2009). In the same way, 5,7 dihydroxy-tryptamine (5,7 DHT) destroyed serotonergic neurons, but had to be associated with desipramine to protect noradrenergic neurons by blocking this transmitter transporters, thus preventing the uptake of the toxin (ADRIEN et al. 1981).

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Pharmacology

Summary. The intraperitoneal, intracisternal and intracerebral injections have led to major informations about sleep mechanisms.

The next historical step in sleep story was the intraperitoneal (ip), intracisternal (icv) and even intracerebral injection of compounds interfering with neurotransmitters. Among them was ip administration of atropine and eserine, muscarinic receptor blocker, and anticholinesterase, respectively. They were shown the first to inhibit, the second to enhance REM sleep, showing a cholinergic step in the support of this stage (JOUVET 1962). This involvement of acetylcholine was confirmed by intracerebral infusion of cholinergic agonists (exotremorine and carbachol) in the pontine reticular formation (GEORGE et al. 1964) which massively increased REM sleep. In the same way, ip injection of reserpine which decreased central level of serotonin and catecholamines by inhibition of the monoamine oxydase, suppressed NREM as well as REM sleep (MATSUMOTO and JOUVET 1964) the former being re-established by 5-HTP, the precursor of serotonin, the latter by L-dopa, the precursor of dopamine and noradrenaline. Moreover, reserpine disinhibited the appearance of PGO spikes which became continuous. They progressively disappeared after ip injection of 5-HTP (DELORME et al. 1965), thus showing a serotonergic support. Para-chlorophenylalanine (PCPA) the inhibitor of serotonin synthesis also induced insomnia (DENOYER et al. 1989)… The involvement of noradrenaline for waking and REM sleep was confirmed by inhibition of dopamine □-hydroxylase, the enzyme responsible for noradrenaline synthesis which decreased REM sleep (SATOH and TANAKA 1973) as well as did the presynaptic □2 receptor agonist clonidine (GAILLARD 1983) which reduces noradrenaline release. This last result is only one example of the numerous experiments performed with pre- and postsynaptic receptor agonists and antagonists of each transmitter modulating neuron functioning and consequently sleep-waking cycle. It can be added that a more recent finding showed that the knock-out mice missing the gene of □-hydroxylase had decreased waking amount and also confirmed above described decrease of REM sleep (OUYANG et al. 2004). Thus, systemic and brain administered compounds were mostly important from the moment when their neurotransmitter target was identified.

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Histochemistry and Immunochemistry

Summary. The mapping of central transmitters allowed to correlate brain functioning and transmitters.

The determination of a brain neurochemical atlas induced major progresses in sleep research. Dahlström and Fuxe presented the first central map for serotonin and catecholamines (DAHLSTRÖM and FUXE 1964, FUXE 1965). Independently that it was a crucial discovery for treatment of Parkinson disease, it rapidly gave rise to researches showing that the neurons of the noradrenergic locus coeruleus nucleus in the dorsal pons, fire at highest level during waking, decrease their activity during NREM sleep and become silent during REM sleep (HOBSON et al. 1975, ASTON-JONES and BLOOM 1981). In the same way, serotonergic dorsal (MCGINTY and HARPER 1976) and medial (RASMUSSEN et al. 1984) midbrain raphe nuclei showed the same variation of functioning. Consequently, both transmitters have a major for forebrain functioning during waking, but also have a permissive role for the appearance of REM sleep. Moreover, the visualisation of these neuron terminals permitted to learn that monoamines (as well as acetylcholine (DESCARRIES et al. 1997), particularly in the forebrain, are mainly not released at synaptic junction, but rather diffusely at varicose level (FUXE et al. 1968, DESCARRIES et al. 1977), thus with a rather tonic influence without immediate degradation, because of absence or low level of local catecholamine methyl-transferase (COMT) or of uptake by transporters into the presynaptic terminals. Finally, it permitted to study REM sleep pharmacological modulations, for example by GABA and glutamate (LUPPI et al. 2006). This kind of approach considerably enriched the anterograde and retrograde tracing which began with horseradish peroxydase to find the origin of a tract or the different targets of a nucleus. Nowadays, new aproaches like c-Fos visualization, use of biotin dextran amine and cholera toxin B are often used for anterograde and retrograde tracing.

Neurochemistry

Summary. The dosage of transmitters allowed to precisely identify the involvement of neurotransmitters in each of sleep-waking stages.

Today, several methods are used for the dosage of central transmitters involved in sleep-waking processes. As example of such approach, we would like to describe the results obtained on rats by our laboratory (LENA et al. 2005). The study was devoted to the dosage of dopamine, noradrenaline and glutamate in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) in the free moving animal, the sleep stages of which were scored automatically, second by second, see above. Because of the necessary length of stages to obtain enough liquid to proceed to the dosage, only three stages were

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retained : waking, NREM and REM sleep. The brain samples were collected by microdialysis. It consisted to perfuse both structures by a probe made of a very thin membrane to collect only fluids (3mm and 2mm long in the mPFC and NAc, respectively), with a flow rate of 1 µl/minute. The perfusion liquid was Ringer's solution. After a 4-hour stabilization period, dialysates were collected at 2-minute intervals with a fraction collector maintained at 4°C and stored at -80°C before analysis by capillary electrophoresis. Dialysates collection coupled to electrophysiology lasted approximatively 6 hours, and it was necessary to synchronize the scored sleep-waking stages with the dialysate. It is useless to finely describe the capillary electrophoresis method used for the dosage which, however, is more recent than the often used high-performance liquid chromatography (HPLC) method. It can only be retained that the dosage was preformed on 2 minute samples, thus on 2 µl of perfusate.

Noradrenaline (NA) level was highest during waking and minimal during REM sleep in mPFC and NAc **(Figure 13)**. All differences berween the stages were statistically significant. This result is in accordance with the established results showing a decrease of noradrenergic firing of locus coeruleus neurons from waking to their silence during REM sleep (see above), although in the limbic system NA fibers are also issued from other brainstem NA nuclei. The interesting point was that the maintenance of a given level of noradrenaline during REM sleep also confirmed the diffuse release of the transmitter at varicose level with immediate destruction by enzymes. A similar NA deficit of inhibitory control processes is observed in schizophrenia (FRIEDMAN et al. 1999, LINNER et al. 2002).

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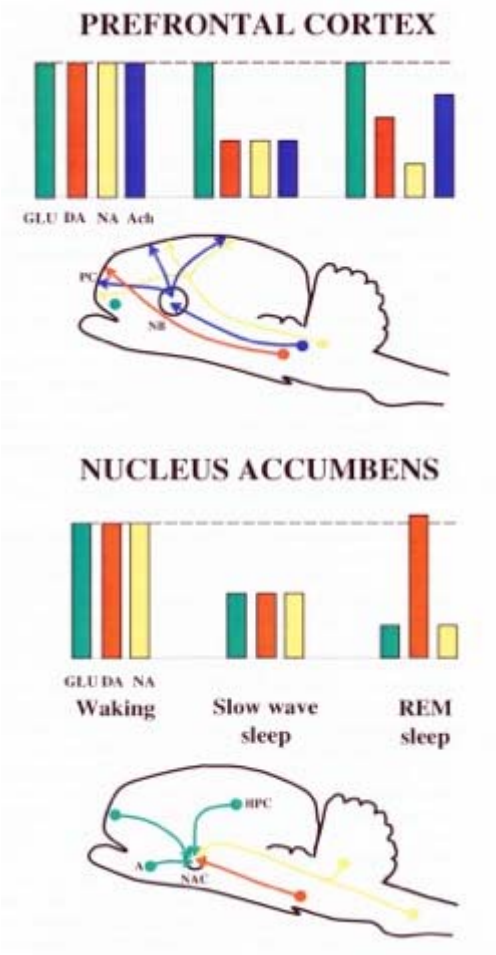

Fig. 13. Neurochemical study during sleep-waking stages in the rat. Glutamate (GLU) release in the prefrontal cortex is mainly issued from local neurons. In nucleus accumbens it is issued from the prefrontal cortex, hippocampus and amygdala. Dopamine (DA) is issued from the midbrain ventral tegmental area. Cortical noradrenaline (NA) is issued from locus coeruleus, but, in nucleus accumbens, it also comes from medulla oblongata nuclei. Cortical acetylcholine (Ach) is issued from forebrain nucleus basalis which is controlled by mesopontine cholinergic neurons. For result explanation, see text (GOTTESMANN 2006).

In mPFC dopamine (DA) was highest during waking, minimal during NREM sleep and at intermediate level during REM sleep. The decrease of DA during REM sleep is of interest, since it could explain the characteristic loss of reflectiveness during dreaming, as well as in schizophrenia (ABI-DARGHAM and MOORE 2003) .

In contrast, NAc dopamine level was slightly highest during REM sleep when compared to waking and was minimal during NREM sleep. This result is in accordance with the above description of REM sleep high frequency bursts of neuron firing releasing more transmitter. It is of highest importance,

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since it is long well known that this structure is involved in schizophrenia during which DA receptors and DA level are increased (MACKAY et al. 1982). Our result also reinforced the theory of schizophrenic-like mentation during REM sleep (see GOTTESMANN 2006, 2010).

Glutamate level was unchanged at mPFC level during sleep-waking stages. This is also encountered in schizophrenia since in this area, glutamate transporter mRNA expression is unchanged in this disease (LAURIAT et al. 2005). In contrast, in NAc, glutamate level was highest during waking and minimal during REM sleep, and it is established that glutamate deficit promotes vivid dreaming (REEVES et al. 2001) and psychotic symptoms (GRACE 2000, HERESCO-LEVY 2000).

Another study by voltametry, an *electrochemistry technique,* showed similar variations of serotonin to that of NA at cortical level (CESPUGLIO et al. 1990) while microdialysis obtained results also evidenced a lower level of acetylcholine during REM sleep when compared to active waking (MARROSU et al. 1995), which is also encountered in schizophrenia (COLLERTON et al. 2005).

Finally, in the way opened by Parkinson's studies, particularly by the scandinavian school (BRUDIN et al. 1986, SHIN et al. 2012), some transplants involving the graft of fetal neurons in animals showing sleep disturbances have been undertaken to restore a normal state (MCRAE-DEGUERCE et al. 1988, JOHN et al. 1998)

Thus, all neuron firing studies, as well as responsiveness results and all neurochemical findings underline during the REM dreaming sleep stage a strong similarity with schizophrenia. This sleep stage characteristics are candidate endophenotypes of schizophrenia (GOTTESMANN and GOTTESMAN (2007).

Last method, the genetic approach of sleep is in strong development (even in flies (KUME et al. 2005)), with knock-out studies eliminating the gene of either one enzyme synthetizing a given neurotransmitter as mentioned above (OUYANG et al. 2004), or suppression of a receptor modulating the functioning of neurons (BOUTREL et al. 1999). Moreover, researches on gene transfert to explore sleep consequences have become common (BLANCO-CENTURION et al. 2013) and are in way of promising progresses for treatment of human sleep disorders like narcolepsy (FRANKEN and TAFTI 2012).

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Conclusion

The progressive increase of knowledge in the neurobiological support of sleep-waking behavior was undoubtly related to the successive appearance of new methods from the past century, up to now. It is of interest that the main electrophysiological and pharmacological methods have given rise to similar results generally first in animals then in Man. This also becomes the case for the nowadays neurochemical and genetic results.

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