

**Michel JOUVET**

**MECHANISMS OF THE WAKING-SLEEP-DREAM CYCLE**

*A brief profile of Professor Michel Jouvet*

- Born 16 november 1925, at Lons Le Saunier (Jura), France. Married with Anne Tellinge (1974), 4 childrens : Diane, Philippe, Jean-Christophe, Frédéric.
- 1944-1945 : Volunteer for Maquis in Jura then fighting with Alpine troops on the Alps in Alsace and northern Italy as a sergeant.
- 1946 : Medical school in Lyons
- 1954-1955 : Research in Pr Magoun Laboratory. VA Hospital Long Beach, California (USA)
- 1956 : MD Thesis : Etude EEG Liaisons Temporaires dans le cerveau
- 1958 : Assitant Professor of Experimental Medicine – Medical School Lyons.
- 1965 : Professor and chairman
- 1964 : Director of Group U 52 (Molecular Neurology) of the National Institute of Health and Medical Research (INSERM)
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  - o Demonstration that paradoxical sleep is not a phase of light sleep, but another state (with waking & sleep)
  - o First description of the death of the brain in man
  - o Monoaminergic theory of regulation of waking sleep
  - o Research of the function of dreaming
- Books :
  - o Le Château des Songes – O. Jacob, 1992 (translated in Japanese)
  - o Le Sommeil et le Rêve – O. Jacob, 1992 (translated in Japanese)
  - o Le Grenier des Rêves (with M. Gessain). Essai – O. Jacob, 1997
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  - o Le voleur des songes – O. Jacob, 2004
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The brain structures and neurotransmitters that command and regulate the cycle of waking slow wave sleep and paradoxical sleep (during which most dreams occur) have been delimited during the past three decades.

In this review, I shall successively summarize the organization of the network of cells group which collaborate to induce and maintain waking. Then, I shall describe the hypothalamic preoptic system which induces slow wave sleep according to a circadian “clock”. Finally, the three systems which constitute paradoxical sleep (PS) will be summarized.

Since most of the impetus to discover waking and sleep systems were started by a very gifted. Neurologist it is fair to write his name at the beginning of this review.

### I. Von Economo, the Encephalis lethargica and the waking system :

In 1916, Constantin Von Economo, a Viennese Neurologist, began to receive numerous patients who were suffering from what has been named “Encephalis lethargica” or “sleeping sickness”. Most of these patients sleep for 20-24h, waking only to eat and drink but many died. Von Economo found a lesion at the junction of the brainstem and forebrain in their brain.(Figure 1). Then, Von Economo thought that there should be an arousal system ascending from the brainstem that kept the forebrain awake.

During the following years, it became possible to register the electrical activity of the brain with electroencephalogram (EEG) and it was demonstrated that waking was characterized by a low voltage fast cortical activity (Arousal reaction) and sleep was responsible for cortical spindles and slow wave. Using this technique in cats, in 1950, H.W. Magoun and G. Moruzzi, and their colleagues demonstrated that the cortical fast EEG was suppressed by destroying (by coagulation) the brainstem reticular formation (2). Then the concept of an ascending mesencephalic reticular activating system was adopted by most neurophysiologists at this time.

However, new methods appeared which permitted to destroy only cell bodies (injection of Kainic or Ibotenic acids into the reticular formation) whereas coagulation destroyed also ascending fibers. With this new technique Denoyer and al (3), in Lyons, demonstrated that the total destruction of the cells of the mesencephalic reticular formation did not impair either behavioral waking or EEG arousal. For this reason, the suppression of waking after coagulation of the mesencephalic reticular formation could have been provoked by the interruption of ascending fibers coming from other systems located below.

### II. The waking system (4)

Thanks to the development of new neuro-anatomical methods (histofluorescence, immunohistochemistry) it has been possible to map out new neural systems which release different neurotransmitters.

Since these systems are organized as a network, it is quite difficult to understand the intimate organization of the systems which collaborate for inducing and maintaining waking.

However the following data may show how it has been possible to demonstrate the active participation of some systems in the executive mechanisms of waking.

### **The noradrenergic system :**

The principal part of the system is located in the pons, at the level of the locus coeruleus whose unitary activity increases during waking and decreases during sleep. The specific lesioning of the locus coeruleus with selective poison induces a temporary diminution of waking. Neuropharmacological experiments have also demonstrated that amphetamine increased waking whereas the inhibition of catecholamins synthesis (dopamine-noradrenaline) suppresses the amphetaminic waking. The effect of amphetamine upon dopaminergic systems is probably responsible for tolerance and dependence. A new drug, the Modafinil, which also acts upon catecholamine does not induce tolerance nor dependence and it is believed that it acts post-synaptically on central alpha adrenergic receptors.

### **The extensive network of waking**

The tonic activation of cortical neurons is the result of both the direct activation of the telencephalon and the inhibition of the pacemakers responsible for the spindles and slow wave characteristic of slow wave sleep.

Three groups of neurons which project to the cortex are sufficient (but not necessary) for cortical desynchronization.

#### 1. The posterior hypothalamic system

This system contains the only histaminergic group located in the nucleus tuberomammillaire (4).

#### 2. The diffuse thalamic system

The intralaminar thalamic neurons project to every part of the cortex. Their transmitters are excitatory amino acids (aspartate – glutamate).

#### 3. The basal telencephalic system

It is composed of neurons which synthesize acetylcholine and/or GABA which project both to the cortex and thalamic nuclei. This system may be altered by degenerative process in Alzheimer disease.

These 3 systems are activated by brainstem ascending neurons :

1. The mesopontine cholinergic nuclei project upon the thalamus where acetylcholine (ACH) acts according 2 ways : hyperpolarisation thru muscarinic inhibition of reticular neurons (which belong to the sleep system) and a nicotinic activation of cortical and thalamic neurons.
2. The mesencephalic reticular formation : neurons containing aspartate and glutamine project massively upon thalamic neurons. Together with mesopontine cholinergic neurons, the mesencephalic reticular formation is only a part of the waking system but no more the only waking system as it was believed at the beginning.
3. The magnocellular reticular bulbar nucleus, cholinergic projects to the mesencephalic reticular formation, the cholinergic mesopontine and basal telencephalon. They constitute the so called reticulo-hypothalamo-cortical pathway. The stimulation of the magnocellular bulbar nucleus induces a long lasting arousal.

Besides the noradrenergic locus coeruleus, the nuclei of the raphe contain serotonin and project to the hypothalamus and the cortex. Their neurons are active during waking, but their lesion provoke a long lasting insomnia (this contradiction will be explained in the next chapters).t

Besides these ascending waking systems which are responsible for cortical arousal (then for consciousness and memory) there are 2 other systems which modulate motricity and sympathetic tone. The first one is the dopaminergic nigro-striatal system whose lesion is responsible for Parkinson disease.

The second system is situated in the medulla and commands the sympathetic system which contains adrenalin and a peptide (NPY). This system is responsible for the adaptation of vegetative reactions during waking.

In summary, the regulation of waking is a complex phenomenon which activates several different structures. None of these systems, isolated, is necessary for waking. Thus the necessary and sufficient condition for the induction and the maintain of waking is the reunion of sufficient condition which are responsible for waking.

### III. Von Economo “Schlaf Zentrum” and the structures and mechanisms responsible for slow wave sleep

#### Passive or active sleep ?

During the 1950-60, the discovery of the mesencephalic reticular formation as a “waking system” did open the hypothesis of an active sleep system which would inhibit it. The so called “principe of economy” led some scientists to postulate some “ad hoc” process of “passive deactivation”. However, the discovery of paradoxical sleep whose mechanisms are active, and the demonstration that lesion of the raphe system was followed by insomnia could only be explained by an active sleep system.

### A. The serotonergic theory of sleep

The destruction of the raphe system which contains of serotonin (5 hydroxytryptamin or 5HT) is followed by a total insomnia which may last 2 weeks in the cat. The duration of the insomnia is correlated with the decrease of cerebral 5HT.

On the other hand, the inhibition of the synthesis of 5HT with P. chlorophenylamine (PCPA) which inhibits the tryptophan hydroxylase (the first step of 5HT synthesis) is followed by a total insomnia which is also proportional to the decrease of central 5HT. Moreover, a secondary injection of 5 hydroxytryptophan (5HT) the precursor of 5HT restores SWS and PS after a latency of about 1 hour.

These experiments effectuated in the 1970 were the basis for a serotonergic theory of sleep according to which 5HT would inhibits the waking system (6).

However, it was shown latter that the unitary activity of 5HT neurons were maximal during waking and almost silent during PS (7) and the development of voltammetry demonstrated that the release of 5HT was more important during waking than during sleep (8). Then it was impossible that 5HT liberation would be synchronically responsible for sleep and the 5HT, theory of sleep was abandoned.

It has revived more recently as the theory that 5HT plays a diachronic role in inducing sleep :

Firstly, the hypnogenic target of 5HT has been discovered. In an insomniac PCPA treated cat, only local injection of a very small dose of 5HT in the preoptic area (the “*Schlafzentrum*” of Von Economo) is followed by the return of sleep (9). Then it was shown that the destruction of the cell bodies of the preoptic area induced a long lasting insomnia.

Since the waking systems are organized as a network, there should be some pathway coming out the preoptic area to inhibit the waking systems in some specialized targets. The research of these targets was obtained by local injection of Muscimol (a GABA agonist) for inducing sleep in an otherwise insomniac cat (either after PCPA or by lesion of raphe system). After most part of the encephalon were micro injected, it was found that there were only 2 hypnogenic targets. One in the posterior hypothalamus and the other in the periaqueducal grey matter since injections of small dose of Muscimol only in these areas were followed by long period of SWS (10).

Then, the mechanisms of sleep may be summarized as followed : during waking, 5HT neurons of the raphe system fire like a clock (1 – 2 Heztz). It is likely that the 5HT neurons which project also to the main clock of the suprachiasmatic nuclei (see below) are calculating the duration of waking. The liberation of 5HT in the preoptic area trigger GABA neurons located in a pathway descending to the posterior hypothalamus and the periaqueducal grey. Then, the inhibition of the waking network will liberate a pace maker system located in the thalamus which is responsible for the cortical spindles and slow wave (which contribute to the unconsciousness of sleep).

There is also another sleep inducing system situated in the medulla at the level of the nucleus of the solitary tract. This system, which receives informations from the “internal milieu” though the vago aortic nerves, projects also to the preoptic area.

#### The executive system of slow wave sleep (figure 4)

The GABAergic neurons of the reticular nucleus of the thalamus are responsible for the spindles. Slow wave are produced at the cortical level since neo decortication suppresses this activity. They are the result of the summation of hyperpolarisation of the pyramidal cells of the V layer which are induced by GABA inter neurons. Such a rhythmic activity does not permit the cortex to elaborate cognitive processes which necessitate a fast cortical activity as during waking or dreaming.

#### Structures and mechanisms of paradoxical sleep (4) (11)

I have given the name of “paradoxical” sleep (PS) to this state which behavior looks like sleep, but which is paradoxically characterized by a fast cortical activity similar to the arousal reaction of waking (11). The term rapid eye movements (REM) sleep is not appropriate since the owl (which does not move its eyes) or the mole (which has no eye) present normal PS but of course have no REM sleep !

PS which occurs only in warm blooded animals (birds and mammals) is characterized by both behavioral and central components : i.e. : a total atonia of the neck muscle, rapid eye movements, a specific central activity of large spikes which can be recorded from the pons, the lateral geniculate nuclei and the occipital cortex. The so called PGO activity, and a fast cortical activity (figure 6).

As early as 1960, it was shown that the pontine reticular formation is necessary and sufficient for PS to occur. Indeed, on the one hand, as shown in figure 5, the total removal of the cerebral structures in front of the pons does not suppress PS since the so called “pontine cat” still presents periodical PS episodes with rapid lateral eye movements and total atonia of the muscle (11). On the other hand, destruction of the dorso lateral pons suppresses PS without interfering with waking and slow wave sleep. Again, with the development of new techniques, it has been possible to map out the main systems which enter into plays during PS.

#### The muscular atonia during PS and the “oneiric behavior” (14)

The striking muscular atonia which occurs during PS is the result of an activation of a group of neurons located in the region of the locus coeruleus  $\alpha$ (alpha) and peri  $\alpha$  and the magnocellular bulbar nucleus. These bulbar neurons descend in the spinal cord and release the neurotransmitter glycine which inhibits the spinal motoneurons. The pontine locus coeruleus neurons have cholinergic receptors, this is why the injection of Carbachol (a cholinergic drug) may trigger immediately postural atonia and PS. The suppression of postural atonia (either by lesion in the cat) a by degenerative diseases in man suppresses the inhibition of PS (12). There are no disturbances of waking or slow wave sleep, PS still occurs without atonia. Then the cat stand up and display different behaviors (attack-play-toilet) but it does not react to visual stimuli and still display a myosis and retraction of the nictitating membranes as during sleep. Oneiric behaviors have also been observed in human subjects (mostly males between 50-60 years). There are often aggressive behaviors and the dreamer may attack his wife in



his bed. When awakened, the subject will describe a dream in which he was fighting a bear or a lion !

B. The PGO activity (see Fig. 2 – Fig. 6) originates from the pontine tegmentum and peribrachial region. These “PGO on” neurons discharge in burst before and during PGO activity. This PGO neurons are cholinergic and can be activated by injection of reserpine. PGO activity is relayed in the lateral geniculate nuclei and may act upon many thalamic and cortical area (where it can be recorded with micro electrode). There are some evidences, in monozygotic twins that PGO activity and the REM of PS have some genetic components. For this reason it has been speculated that PS (and PGO) may program a so called “individuation” in human subjects (15).

C. The cortical activation during PS

The fast cortical activity of PS is triggered both by the peribrachial pontine tegmentum and the bulbar magnocellular nucleus. Some of these neurons are cholinergic and project to the thalamus and posterior hypothalamic neurons which relay to the cortex.

Circadian regulation of the waking sleep cycle (16)

Most human beings are awake during the day and sleep during night. (It is the contrary for the rat). If a man is kept in isolation in a cave, under a continuous illumination, without any temporal cues, he will sleep every day at about the same time (usually a little later every day). This is the proof that there is a clock in the brain which is able to measure about a day (circa – dies). The circadian rhythmicity of the sleep waking cycle depends upon the supra chiasmatic nuclei (SCN). These two small nuclei located above the optic chiasma are receiving information from the retina. They are the “master clock”. The output of the SNC is directed toward the supraventricular area and the dorsomedial nucleus of the hypothalamic which is also related to sleep in the VLPO. There are some new data which also show that the NSC may release a neuropeptide : the vasopressin. This peptide, injected in the cerebro-spinal fluid increases the duration of waking whereas the antagonists of vasopressinergic receptors decrease it (4).

TABLE I

	NA	DA	H	ACH	5HT	MRF
1	+	+	+	+	+	+
2	+	+	+	+	+	?
3	+	+	+	+	+	+
4	+	+	+	?	0	?
5	+	+	+	+	0	?
6	0	0	0	0	0	0
7	0	0	0	0	+	0

Participation of systems noradrenergic (NA – locus coeruleus)

Dopaminergic (DA nigro striatal system) – Histaminergic (H)

Cholinergic (ACH mesopontine) – Serotonergic (5HT – N raphe dorsalis) and the mesencephalic reticular formation (MRF) to the process of waking

1 : increase of the unit activity during waking

2 : increase of the liberation of the neurotransmitter during waking

3 : the stimulation of the system with excitatory amino acide may increase waking

4 : the inhibition of the synthesis of the neurotransmitter decreases waking (presynaptic effect)

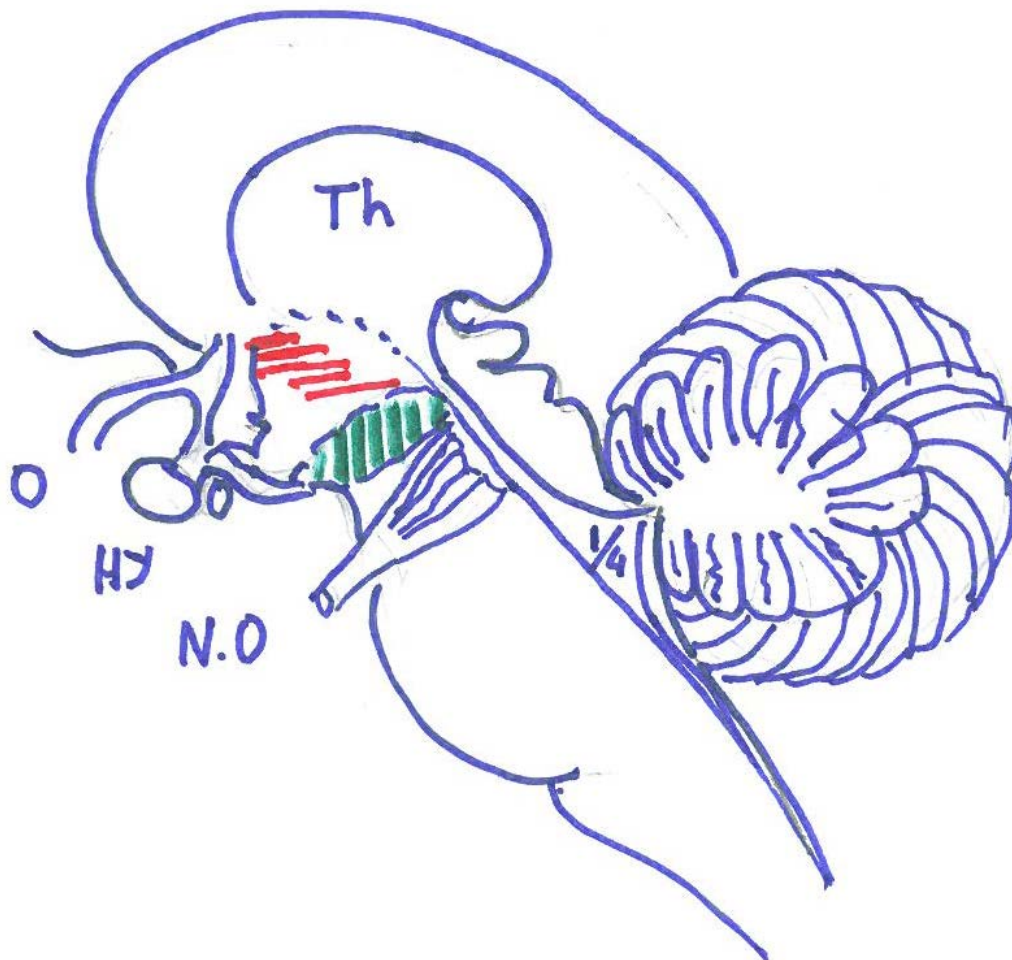
5 : the injection of antagonists of some receptors may decrease cortical arousal and/or waking behavior

6 : the destruction of cell bodies may decrease waking for a long period

7 : the destruction of cell bodies may increase waking.

This table demonstrated, on the one hand, that there is not any special system which obey to conditions 1 to 6, then they should act trough a network, and on the other hand that the 5HT system has some ambiguous state as an “homeostatic” system.

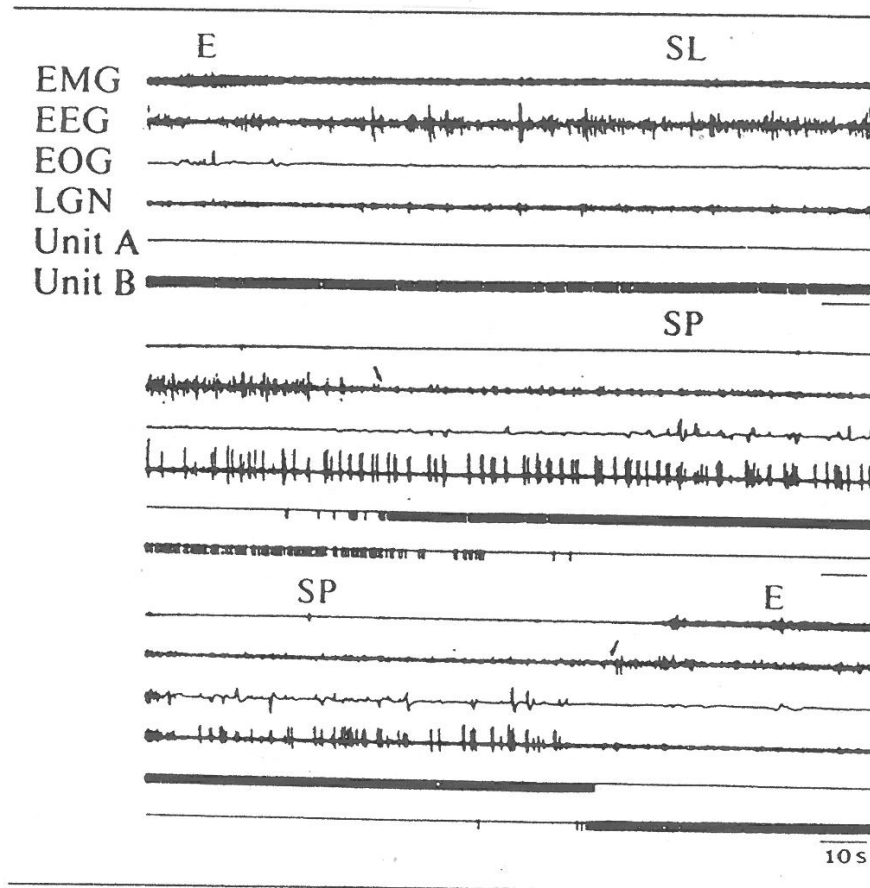
+ : the condition is realized. 0 : the condition is not realized. ? : it has not yet be possible to test the condition (from reference 4)



**Figure 1**

A drawing of the human brainstem, taken from Von Economo's original work. It illustrates the site of the lesion (diagonal hatching in green) at the junction of the brain stem and forebrain that caused prolonged sleepiness and the site of the lesion (horizontal hatching in red) in the anterior hypothalamus that caused prolonged insomnia.

O = optic nerve - HY = hypophysis - NO = oculomotor nerve (III) 1/4 fourth ventricle



**Figure 2**

Polygraphic recording of waking sleep cycle in a cat chronically registered

EMG : electromyogram of the neck muscles

EEG : electrical activity of the parieto occipital cortex

EOG : electrooculogram which record eyes movements

LGN : recording from the lateral geniculate nucleus (to register the PGO activity)

Unit A : recording with microelectrode of the unitary activity of a neuron from the bulbar magnocellular nucleus. This neuron (SP on) fire only during PS

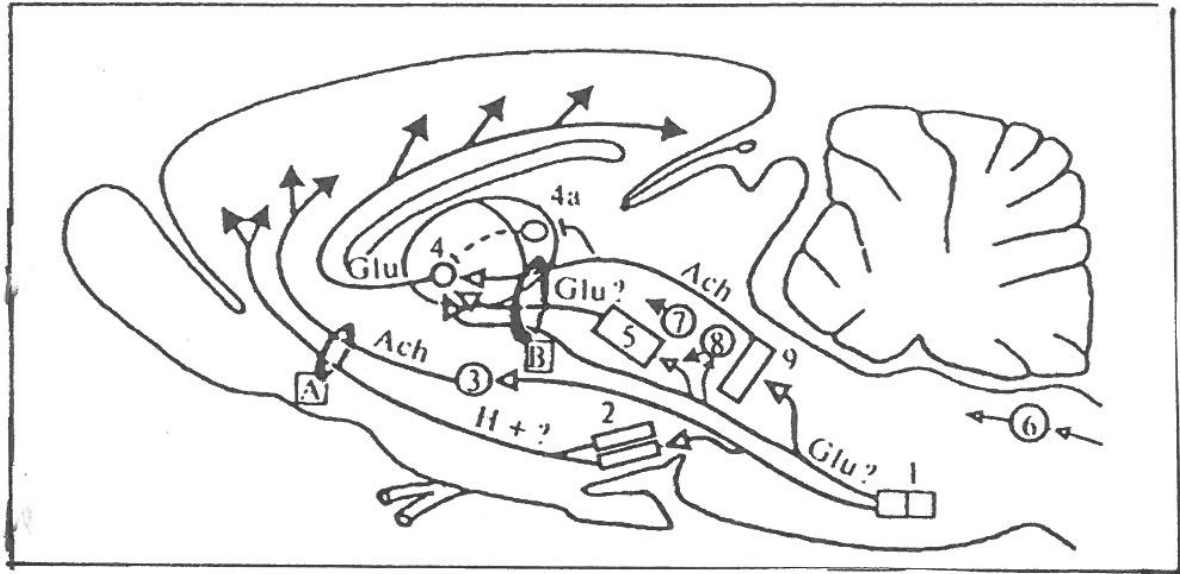
Unit B : recording of a SP off neuron located 500 mm from unit A

E : waking with fast low voltage activity (arousal reaction) : increased EMG activity

SL : slow wave sleep with high voltage slow wave of cortex and decrease of the EMG. The unit B is still active as during waking

SP : paradoxical sleep : total suppression of EMG activity, fast cortical activity, note the PGO activity and the eye movements, Unit A is activated.-Waking (E) comes back with the return of EMG activity, unit A stops and unit B is again activated.

Time scale : 10 sec.



**Figure 3**

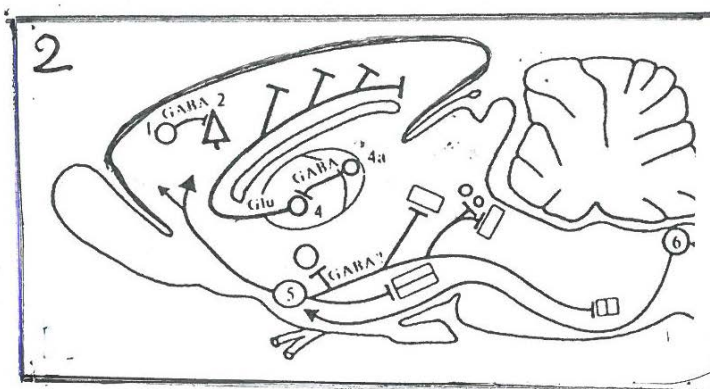
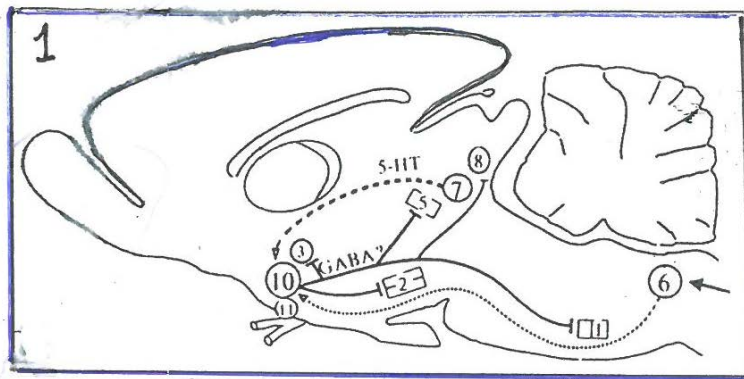
**The waking system**

A : reticulo-hypothalamo-cortical pathway

B : reticulo-thalamo-cortical pathway

1. Bulbar magnocellular nucleus
2. Posterior hypothalamus with the histaminergic tubero mamillary nucleus
3. System of the basal telencephalon, basal nucleus of Meynert (ACh)
4. Intralaminar nuclei of the thalamus (Glutamine) (4a). Reticular nucleus of the thalamus responsible for slow wave sleep. This system could be inhibited during waking
5. Mesencephalic reticular formation it is much greater than on this drawing and most of the ascending fibers coming from the medulla and the pons are also situated at this level (this is why a lesion by coagulation would induce a coma and suppresses cortical fast activity because the interruption of the ascending pathways which cannot activate more rostral system
6. Complex of the solitary tract which receives vegetative afferences coming from the organism thru the vagus and sino aortic nerves
7. Rostral raphe (5Ht)
8. Complex of the locus coeruleus (noradrenalin)
9. Mesopontine nuclei (ACh)

From Valatx (1995)

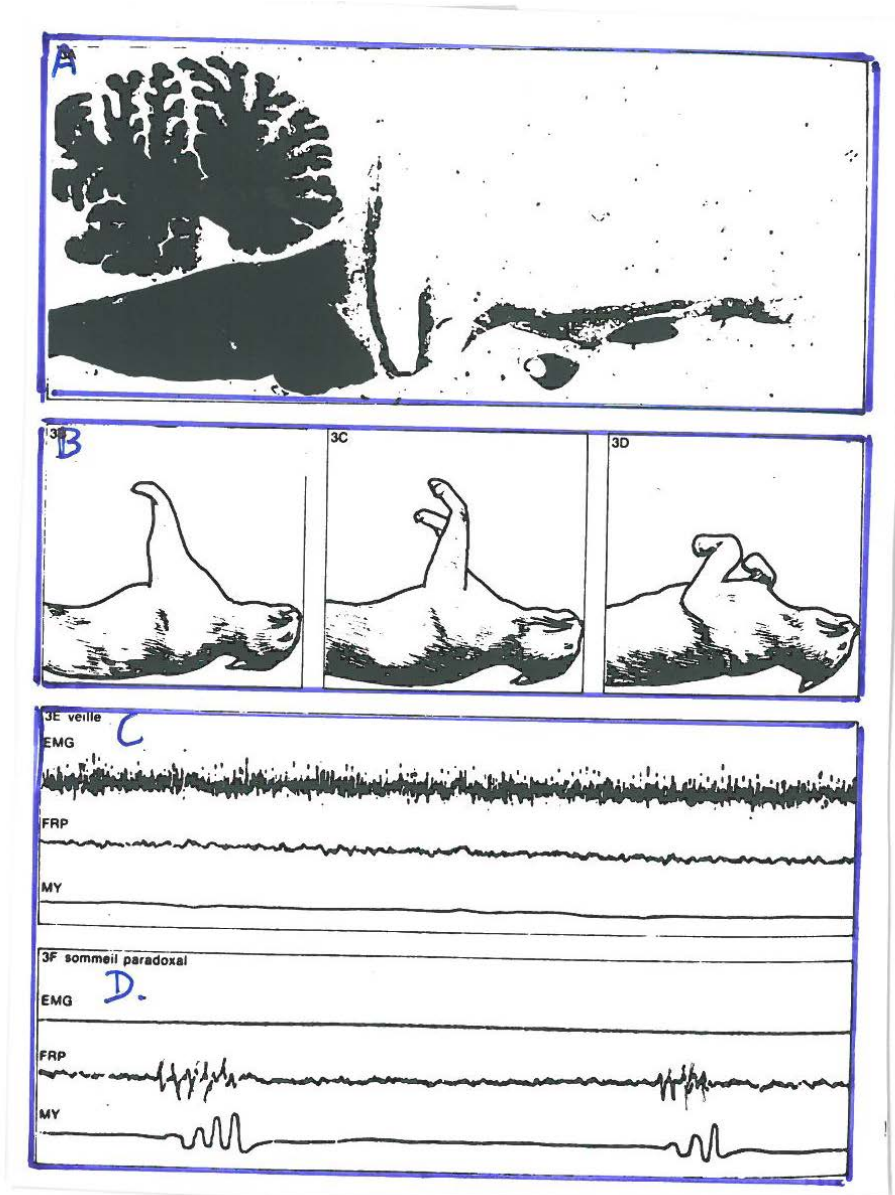


**Figure 4**

**The two stages for going to sleep**

1. Serotonergic stage (inhibition of waking network)
 

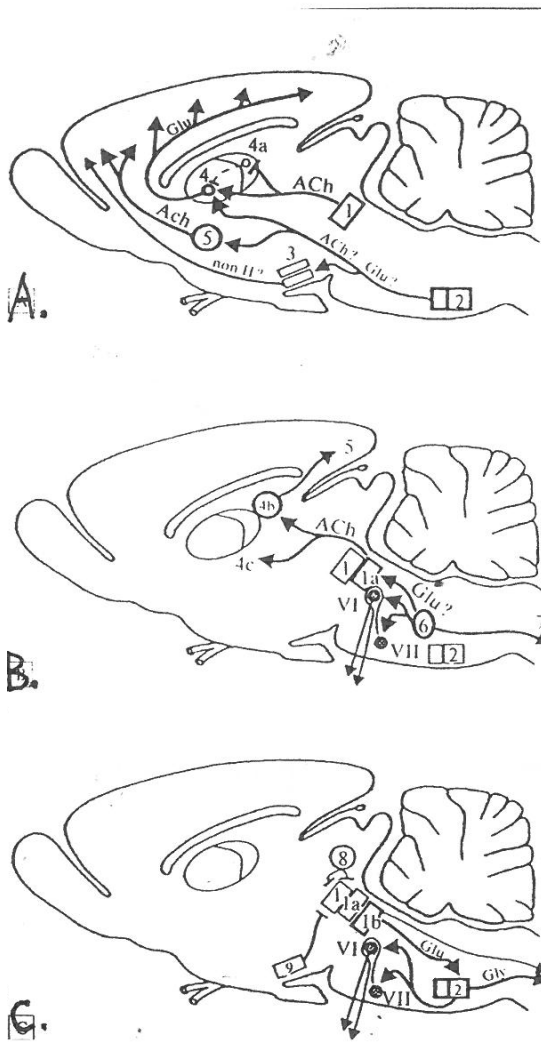
The dorsal raphe nucleus (7) is active during waking. It sent projection to the preoptic region (ventral lateral preoptic nucleus – VLPO) (10) and the main clock (supra chiasmatic nucleus : SCN) (11). The liberation of 5HT at this level will induce (after a period of time which is “calculated” by the circadian clock of SCN) an “homeostatic” GABAergic descending system coming from the VLPO which will inhibit the waking network at the level of the posterior hypothalamus (2) or the periaqueducal grey (8). System descending from the VLPO inhibits the N. of Meynert (3), the mesencephalic reticular formation (5) and the bulbar waking system (1). The solitary tract (6) is also activated.
2. Thalamo-cortical stage (liberation of the thalamic pace maker) cortical pace maker responsible for sleep slow wave (0.5 – 2 Hertz)
  - 1) Interneurons GABAergic
  - 2) Pyramidal cell of the V to cortical layer
  - 3) Nucleus of Meynert
  - 4) Thalamic pacemaker responsible for cortical spindles
  - 4a) Reticular nucleus that surrounds the thalamus. It is GABAergic and will inhibits the intralaminar nuclei.



**Figure 5**

- A. Pontine preparation. All the cerebral structures in front of the pons have been removed by surgery. This preparation may survive for several weeks provided that the hypophysis is left, and that the internal temperature is regulated in an incubator
- B. During paradoxical sleep, the pontine cate which is in a state of decerebrate rigidity loss its muscular tonus
- C. During “wake” there is an increase of the electromyogram of the neck muscle, a fast activity in the pons and no eye movements
- D. Paradoxical sleep. Total absence of EMG activity (atonia) some rhythmical activity in the pons, synchronous to the eye movements (From Jouvet 11).

This is the proof that paradoxical sleep is triggered from the pons and does not depend from other supra pontine structures.



**Figure 6**

A Schematic representation of three of main network of paradoxical sleep

- A. Cortical activation 1) cholinergic neurons of the pons (1) act upon the nicotinic receptors of the intralaminar nuclei of the thalamus (4) and muscarinic receptors of the reticular nucleus (4A) of the thalamus.  
2) magnocellular nucleus of the medulla (7) projects to the posterior hypothalamus (3), the thalamus (4) and the basal nucleus of Meynert (5)
- B. Phasic PGO activity : the “pontine PGO” on (1a) projects to the thalamus and the lateral geniculate nuclei and the pulvinar (4c). Ocular and facial nuclei receive afferences (glutamate ?) from the pontine reticular nucleus which seems to be the main generator of phasic activity
- C. Muscular atonia : the principal input is provided by the bulbar magnocellular nucleus (2) which neurons “PGO on” glycinergic project upon the spinal motoneurons and the oculo motor nuclei (VI-VII). An inhibitory control of PS network is located in the periaqueducal grey matter (8) (from VALATX – 1995)



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