REVIEW

Eur J Anat, 3 (3): 163-175 (1999)

The anatomy of dreaming, and REM sleep

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SUMMARY

Most neuroscientists today agree that the richest and best structured dreams occur during REM sleep. In fact, the structures responsible for REM sleep, the anatomy of which is controversial, are necessary for normal dreams. The pontine tegmentum structures with a definite role in the control of different events characterizing REM sleep (EEG activation, atonia, PGO activity and rapid eye movements) are precisely located. However, the exact site of the structure that can simultaneously trigger all the manifestations of REM sleep, with all its bioelectrical and behavioral manifestations, is still controversial. We have demonstrated that the ventral part of the oral pontine reticular nucleus is the nodal link, acting like an orchestra conductor, of the extense neuronal network that harmoniously generates and maintains REM sleep. Here, a systematic multidisciplinary study of the ventral part of the oral pontine reticular nucleus borders, connectivity, neuronal and synaptic morphology, and chemical structure, at light and electronmicroscopic levels, as well as functional studies of unitary recordings, and electrical and chemical stimulation of *in vitro* and *in vivo* preparations are reported. All our data illustrate the complex morpho-functional organization of the neuronal network responsible for the generation and maintenance of REM sleep. The final part of this article summarizes the current literature on PET imaging studies of REM sleep, which coordinate well with our functional anatomic results and with the notion that during REM sleep, the structures in the cerebral cortex responsible for the different aspects of declarative memory consolidation (medial orbitofrontal cortex, hippocampus, parahippocampal cortex, etc.) and the association cortex areas most directly related with these structures are activated.

Key Words: Paradoxical sleep - brainstem reticular formation - ventral part of the oral pontine reticular nucleus - PET - memory.

INTRODUCTION

It is most people's belief that the best dreams are those that we dream when we are awake. However, today most neuroscientists agree that the richest and best structured dreams occur during REM sleep.

We wish to start this contribution with a short reflection on a fragment of conversation between Don Quijote and Sancho, from the book by Miguel de Cervantes: *"I don't understand", replied Sancho, "I only know that when I sleep, neither have I dread, hope, work, nor glory; and blessed be the one who invented sleep, the cape that covers all human thoughts, the food that satiates hunger, the water that banishes thirst, the fire that heats cold, the cold that tempers ardor and, finally, the general currency with which all things are bought, the scale and weight that equals the shepherd to the king and a foolish man to a wise one. Only one thing is wrong with sleep, according to what I have heard, and that is that it resembles death, since there is only a little difference between a sleeping man and a dead one".* According to San-

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Submitted: September 10, 1999
Accepted: December 9, 1999

cho sleep is a passive state, *"it resembles death"*, because it suppresses wakefulness, but sleep is also an active state, with a special and rich mental activity, of which dreams –so well described by Sancho– are the best expression. And in dreaming there are, for Sancho, several paradoxes, an example of which is: *"the scale and weight that equals the shepherd to the king and a foolish man to a wise one"*. One should not forget that the best structured dreams take place during REM sleep.

Sleep therefore is not only an active and periodically necessary phenomenon, but is also a very diverse process. Five different phases have been described for sleep in man; they have been experimentally reduced to three sleeping phases in cats (Fig. 1): light sleep; slow wave sleep; and REM sleep. Together with the wakefulness phase, these comprise the four phases of the sleep-wakefulness cycle in cats.

Today we know that this cycle is circadian. The pacemaker for this circadian cycle is the suprachiasmatic nucleus, which is modulated by light through the retino-hypothalamic pathway (Fig. 1)

Although work on the intimate mechanisms involved in the sleep-wakefulness cycle continues, the structures responsible for the phases of wakefulness, light sleep and slow wave sleep are fairly well-known today. The most significant structures, their connections, and some of the neurotransmitters they use are represented in figure 1. However, the structures responsible for REM sleep, the neurotransmitters they use and their connections are still under study. REM sleep-generating structures must establish connections with the structures controlling the other sleep-wakefulness cycle states.

Experiments with lesions and brainstem transections have established that the rhomboencephalon is the central nervous system region necessary for the generation of REM sleep (for a review, see Reinoso-Suárez, 1998). In addition, studies using electrical or chemical stimulation and unit recordings have made it possible to determine the precise location of the structures responsible for the different events characterizing REM sleep: atonia; PGO activity: EEG activation and rapid eye movements. Figure 2 shows the most important of these structures for atonia, PGO activity, EEG activation and rapid eye movements. However, the exact location of the structure that can simultaneously trigger all the manifestations of REM sleep -that is to say the conductor of this complex neural network; the inducer of REM sleep, with all its bioelectrical and behavioral manifestations- is still controversial.

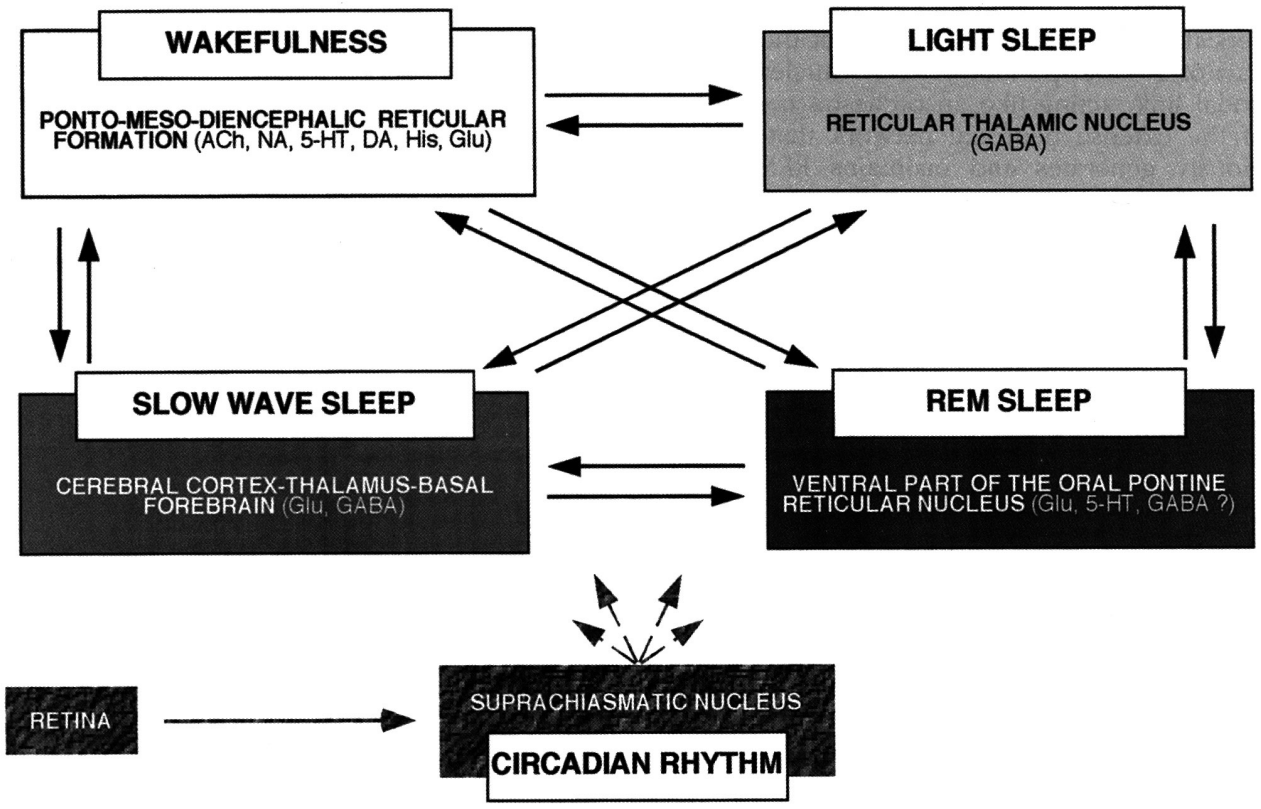

Fig. 1.– Scheme of the wide neuronal network responsible for the organization of the different sleep-wakefulness cycle phases. ACh: acetyl-choline, NA: noradrenaline, 5-HT: serotonin, DA: dopamine, His: histamine, Glu: glutamate, GABA: gamma amino butiric acid. Modified from Reinoso-Suárez, 1998.

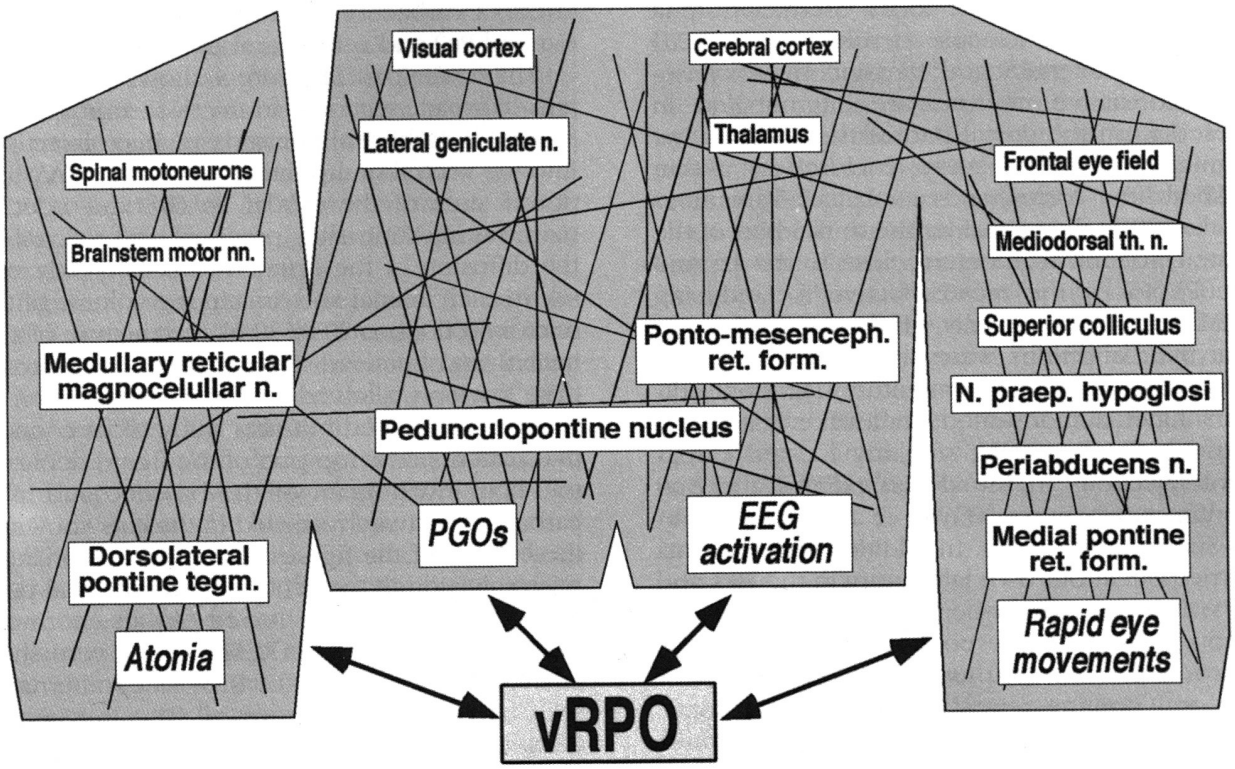

Fig. 2.– Schematic representation of the neuronal network reponsible for the signs characterizing REM sleep, conducted by the vRPO. Modified from Reinoso-Suárez, 1998. n: nucleus, nn: nuclei, th: thalamic, ret. form: reticular formation, mesenceph: mesencephalic, prae: praepositus, tegm: tegmentum.

REM sleep induction and maintenance site

One important approach was made by Baghdoyan et al. in 1984. Using injections of the long-acting cholinergic agonist carbachol into the pontine tegmentum, these authors increased REM sleep. In contrast, injections of a carbachol solution in the midbrain or in the medullary reticular formation decreased REM sleep and increased wakefulness.

The pontine tegmentum is, however, very large, and therefore systematic quantitative studies mapping the ability of pontine-delivered carbachol to evoke REM sleep could only be performed at the end of the 80's. The results of three of these studies are represented in figure 3, a scheme of a parasagittal section of the cat brainstem. In that figure we have reconstructed the injection sites of the three studies from the coordinates given in the three publications. The first study corresponds to Baghdoyan et al. (1987). They showed that the pontine injection sites that produce REM sleep with latencies of 0-20 minutes are those located in the area outlined by a thick dashed line, in the most ventral and rostral part of the caudal pontine reticular nucleus. The second study, depicted by an intermediate dashed line, corresponds to Vanni-Mercier et al. (1989). Those authors concluded that the only brainstem area from which carbachol would induce REM sleep with a 10 minute latency or less was the mediodorsal pontine

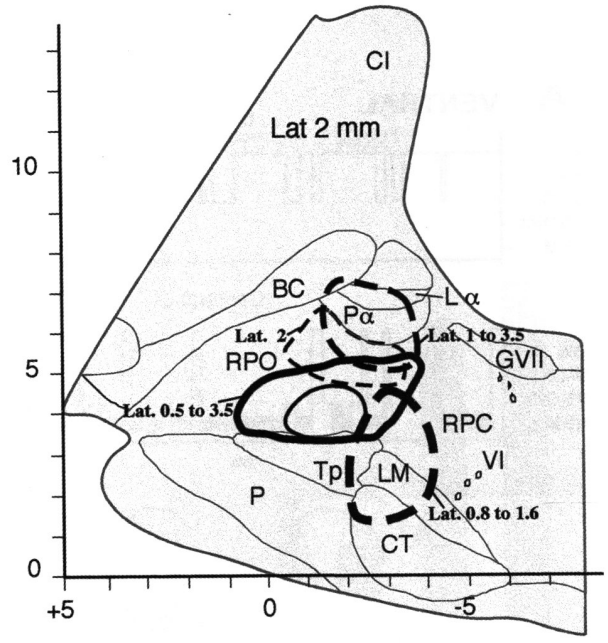

Fig. 3.– Schematic drawing of a parasagittal section of the cat brainstem. The locations of carbachol injections from where different authors have induced REM sleep, are represented by different line types (see text). The anteroposterior, lateral and vertical stereotaxic coordinates are depicted in the figure. The whole extension of the lateral stereotaxic coordinates is written besides each group of injections. Lat.: lateral.

tegmentum, namely the locus coeruleus alpha (Lα) and the peri locus coeruleus alpha (Pα) nuclei. Cholinergic- and tyrosine hydroxylase-immunoreactive neurons are intermingled in these loci in the dorsal part of the oral pontine tegmentum. A third study, enclosed by a thin dashed line, corresponds to that of Yamamoto et al. (1990); they consider the dorsal part of the rostral pontine tegmentum close to the Lα and the Pα to be the most effective for inducing REM sleep. Paradoxically, all three groups insist that their injections were situated dorsally and orally in the pontine tegmentum. Different authors have demonstrated an awake state with muscular atonia using similarly located carbachol injections in the dorsal part of the oral pontine tegmentum (Hayes et al., 1984; Reinoso-Suárez et al., 1994). In addition, experiments carried out at our own laboratory in the 70's and 80's, using small diathermocoagulation lesions throughout the entire pontine tegmentum area, showed that the lesions in the ventral part of the oral pontine reticular nucleus (thin continuous line in figure 3) were the only ones whose only sleep effect was to produce a significant decrease in REM sleep (De Andrés et al., 1985). At the end of the 80's we found increased REM sleep after small microinjections of a carbachol solution in this same region (Reinoso-Suárez et al., 1994).

All this led us to re-examine the participation of the pontine tegmentum in sleep-wakefulness states in adult cats. We started by studying the effect of carbachol microinjections in the dorsal (Lα and Pα) and ventral oral pontine tegmentum.

The lower part of figure 4 shows two brainstem coronal sections from two animals that received carbachol-peroxidase microinjections into the ventral oral pontine tegmentum (**A'**) and dorsal, area of the caudal Pα (**B'**). In order to map the injection sites precisely and to confine the diffusion of the drug, we injected only one site in each animal and limited the volume of the microinjections to 20 to 30 nl of a mixture of carbachol and horseradish peroxidase. This procedure not only allowed accurate identification of the area stimulated but also study of its connective patterns. The top part of the figure depicts a two-hour hypnogram of the baseline and after carbachol delivery recorded in the cats shown at the bottom of the figure. The animal receiving a microinjection in the ventral part of the oral pontine reticular nucleus showed (**A**) an enormous increase in REM sleep (REM) with a very short latency. Long episodes of REM sleep alternated with short periods of arousal. The increase in REM sleep was 65-fold in relation with the control over the first hour in all of the animals used in this experiment. A dramatic decrease in slow-wave sleep was observed after the ventral microinjections. No statistically significant differences were observed in the amount of wakefulness after ventral microinjections of carbachol. The animal that received the microinjection dorsally, in the Pα, showed a profound increase in wakefulness (**B**). No REM sleep was observed

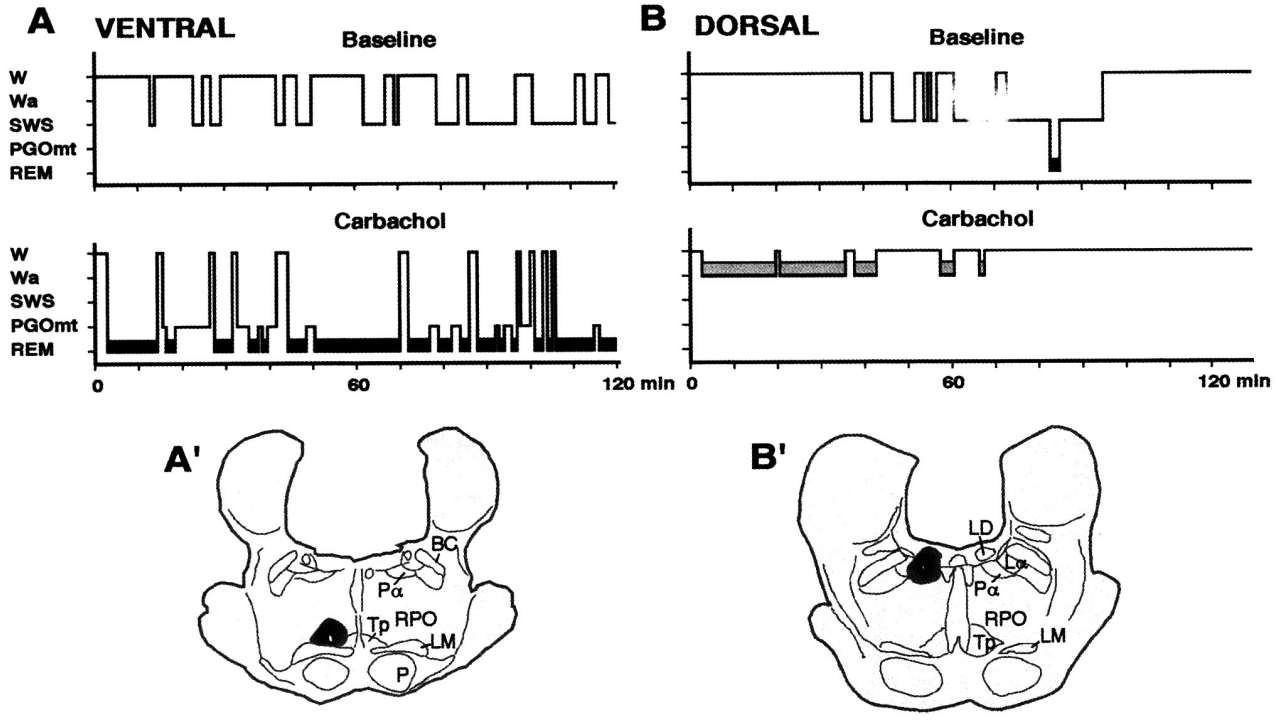

Fig. 4– Hypnograms of the two first hours recordings (a and B) of baseline and after carbachol solution microinjections ventral (A') and dorsally (B') situated. W: wakefulness, Wa: wakefulness with atonia, SWS: slow wave sleep, PGOmt: PGO with muscular tone. Modified from Reinoso-Suárez et al., 1994.

during the first two hours after the carbachol microinjection in the caudal part of the Pα. A long period of atonia (Wa, wakefulness with atonia) appeared shortly after carbachol delivery. *The results of this first study indicate that the ventral part of the oral pontine reticular nucleus (vRPO), represented by thick continuous line in figure 3, is the location of the REM sleep induction site in the brainstem.*

Figure 5 summarizes the results of 32 microinjection sites in the vRPO. We found a dose-related increase of REM sleep that was due to the increase in both the duration and the number of REM sleep episodes. No statistical dose-related effect was observed in the decrease of the latencies to REM sleep onset. Very low doses (0.04 mg) –ten times lower than the lowest dose normally used by other authors (0.4 mg)– produced REM sleep with a latency similar to that of the higher doses. However, a dose-related effect was observed in the latencies to onset of slow wave sleep (SWS): from 13 minutes in the control, to one hour and 20 minutes at the lowest doses (0.04 mg), rising to 17 hours and 40 minutes at the highest doses (Garzón et al., 1998; Reinoso-Suárez et al., 1994). The increase in REM sleep was associated with a dose-related decrease in the amount of time spent in both SWS and light sleep, but did not modify the time spent awake. *All these results show that the vRPO is a very sensitive site for the induction and maintenance of REM sleep.*

Furthermore, this cholinergically-induced REM sleep mimics the signs of spontaneous REM sleep. The polygraphic recordings of all the studies made until now were scored conventionally by visual inspection. We have performed EEG power spectral analyses to compare the EEG features of ventral pontine carbachol-induced REM sleep with those of spontaneous REM sleep. Twenty-one different sites within the vRPO were examined. After carbachol microinjection (20 nl) to any of the sites, the neocortical (occipital and frontal) and hippocampal electrical activities observed during carbachol induced REM sleep were similar to those present in spontaneous REM sleep (Garzón et al., 1997). *We thus propose that the REM sleep induced by microinjection of carbachol in the vRPO is a valid model for natural REM sleep.*

Connections of the vRPO, the REM sleep induction site

In addition, the vRPO provides the morphological substratum for these functions. Our anatomical results, after peroxidase-carbachol microinjections in the ventral part of the oral pontine reticular nucleus, are summarized in figures 1 and 2. Figure 2 represents the rich reciprocal connection that the vRPO has with the subsystems responsible for the different signs of paradoxical sleep: atonia, PGO activity, EEG activation and rapid eye movements. Through

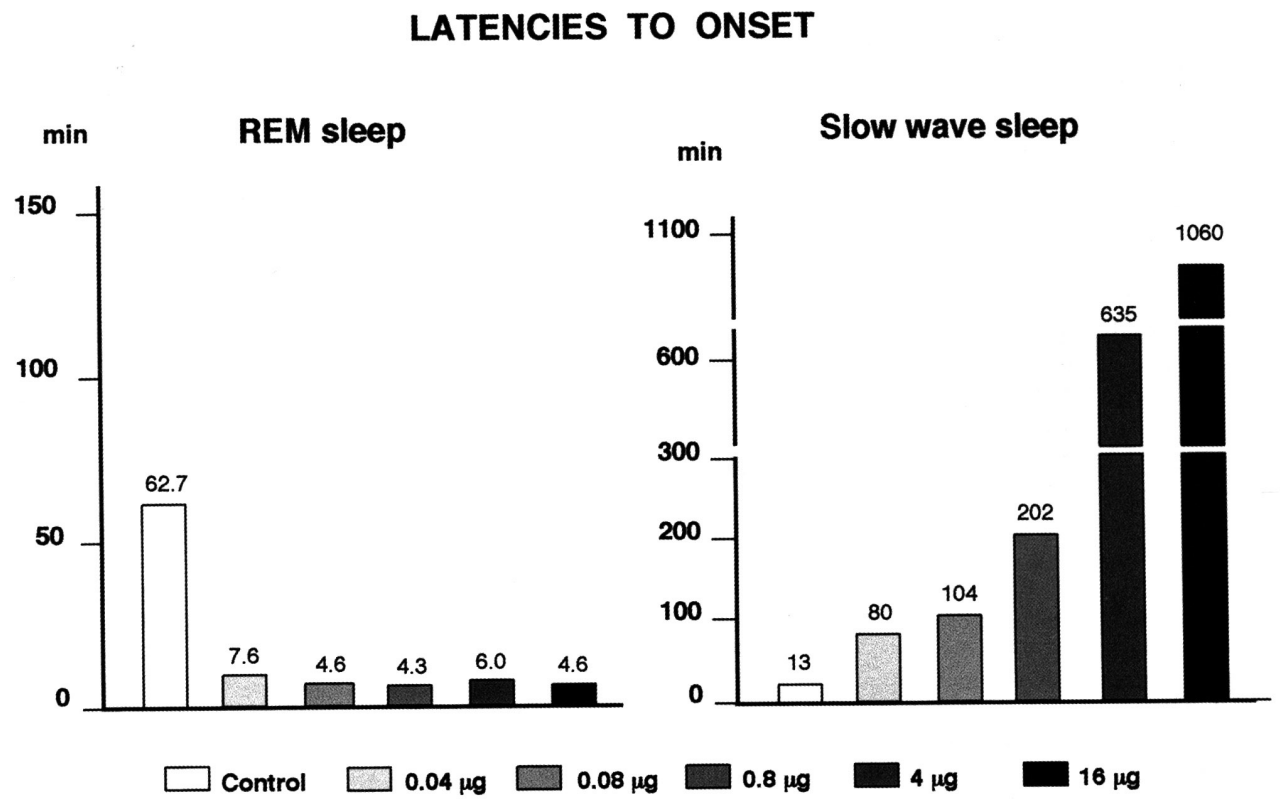

Fig. 5– Histogramms showing the latencies of the first REM and slow wave sleep onsets after different doses of carbachol microinjections in the vRPO. Taken from Reinoso-Suárez et al., 1994 and Garzón et al., 1998.

these connections the vRPO can simultaneously trigger all the manifestations of REM sleep; that is, it is the conductor of this complex neural network and allows a harmonic execution of all its bioelectrical and behavioral manifestations. Figure 1 summarizes the connections of the vRPO, the REM sleep induction site, with the structures that control other states of the sleep-wakefulness cycle. These connections may accurately provide the anatomical basis for the organization of reciprocal interactions between all of these structures, resulting in alternation of the different states of the cycle.

According to the connections represented in these two figures, the vRPO must contain catecholaminergic, serotonergic, histaminergic, acetylcholinergic, glutamatergic, GABAergic, etc. fibres that originate in the structures connected with the vRPO (in both figures); there are also fibres that originate in structures connected with the vRPO that are not represented in the figures. Our group and many others have demonstrated the existence of these fibers as well as their different chemical natures. The existence of serotonergic, GABAergic and glutamatergic neurons has also been demonstrated (Rodrigo-Angulo et al., 2000; unpublished results). However, we do not know the chemical nature of the cells that project from the vRPO to any of these structures, nor the precise origin of the fibres with any given chemical identity that end in this REM induction site. We are also unaware of the effect of these neurotransmitters on the different vRPO neurons or the receptors involved in all these connections. All these questions are currently under study in our laboratory.

Borders of the REM sleep induction site

The first step was to define the precise border of the REM sleep induction structure in the brain stem. To this end we made microinjections of 20 nl of a carbachol solution at different doses in all the structures of the pontine tegmentum. We observed that the only structure in which cholinergic stimulation induced REM sleep with a short latency, a type of sleep bioelectrically and behaviourally similar to spontaneous REM sleep, was the vRPO, situated at the following stereotaxic coordinates: AP 0.5 to -3.5, L 0.5 to 3.5 and V 3.5 to 5.0 –thick continuous line in figure 3– (Reinoso-Suárez et al., 1994; Garzón et al., 1995; De Andrés et al., 1998; Manquillo et al., 1998). At large doses, the microinjections located dorsally, in Lα and Pα, produced an increase in wakefulness, while small doses in the caudal part of Pα only produced some of the signs that characterize REM sleep, but not all, and therefore not REM sleep. The same results were seen after rostral, ventral or caudal carbachol solution microinjections. These injections have been extremely useful in determining the caudal border of the REM sleep induction site, because over the last years other researchers have located this site throughout the medial pontine reticular formation. Microinjections in the rostral part of the caudal pontine reticular nucleus produced some of the signs of REM sleep: eye movement, atonia and PGO, but not EEG activation, and the EEG was synchronized. Real REM sleep appeared only after a long delay. A delayed increase in REM sleep also occurred when the microinjections were made close to any of the borders of the vRPO, probably when the carbachol solution diffused to the REM sleep induction area. We believe that injections of 500 or 250 nl of carbachol in the case of Baghdoyan et al. (1987), or of 250 nl in the case of Yamamoto et al. (1989), or 200 nl in the case of Vanni-Mercier et al. (1989) could readily have spread to the vRPO area (Fig. 3), in which we have demonstrated that a very tiny amount of a carbachol solution at low concentration at any level of its surface produces a persistent and dramatic increase in REM sleep with brief latency. Actually, at present most authors chemically induce REM sleep by injections in this ventral area of the oral pontine reticular nucleus.

The finding that the border between the oral and caudal pontine reticular nucleus is a boundary for a rostral EEG activating region and a caudal synchronizing region after chemical microstimulation was very exciting (Garzón, 1995; Garzón et al.,1995). Thirty-five years ago using small diathermocoagulation lesions we demonstrated the existence of a border between activating and synchronizing structures at this level of the brainstem (Camacho-Evangelista and Reinoso-Suárez, 1964). On superimposing the results of the two techniques the coherence between them, the nearly (quasi) perfect overlapping of the areas determined by both experimental approaches, can be appreciated.

Multidisciplinary study of the vRPO

With a view to answering the other questions and reaching a better understanding of this interesting region, a systematic study of its morphology and chemical structure was undertaken at light and ultrastructural levels as well as *in vitro* and *in vivo* functional studies. These studies should help our understanding of the complex mechanisms involved in the organization of the broad network necessary to induce and maintain REM sleep.

We carried out *in vitro* studies of the electrophysiological properties of morphologically identified neurons in the ventral part of the oral pontine reticular nucleus (Núñez et al., 1997, 1998). Intracellular recordings were performed in rat brain slices with standard procedures. The results demonstrated the presence of two types of neurons in the vRPO with different functional and morphological features. All type I and most

type II cells were depolarized by acetylcholine, carbachol and muscarine. The effects of tetrodotoxin and atropine strongly suggested that this depolarization would be mediated by the activation of post-synaptic muscarinic receptors. A small number of type II neurons was also hyperpolarized through the activation of post-synaptic muscarinic receptors. Glutamate also evoked a long-lasting depolarization and spike firing, an effect that was also produced by NMDA and histamine. However, GABA and serotonin evoked hyperpolarization in the two types of vRPO neurons. Subsequent to these results, *in vivo* experiments, performed in freely moving cats, demonstrated that glutamate microinjections in the vRPO increase REM sleep (Garzón et al., 1996).

The results of our *in vitro* studies are consistent with those of the *in vivo* studies on the unitary activity of neurons of the vRPO recorded in cats under urethane anesthesia. Two different types of neurons have also been described on the basis of their morphology, spontaneous activity and patterns of response to chemical and electrical stimulation (Rodrigo-Angulo et al., 1997). Type I cells were orthodromically activated by contralateral vRPO and ipsilateral pedunculopontine tegmental nucleus (TPp) electrical stimulation (probably through glutamate and acetylcholine neurotransmitters, respectively) and were inhibited by ipsilateral reticular thalamic nuleus stimulation (probably through the GABA neurotransmitter) (Fig. 6). Recently, also using the same preparation, Rodrigo-Angulo et al. (1999) have demonstrated that iontophoretic injection of atropine, an antagonist of cholinergic muscarinic receptors, blocks the effect of electrically stimulating the TPp on two types of vRPO neurons (Fig 7). Iontophoretic injections of CNQX, the antagonist of AMPA glutamatergic receptors, blocks the effects of electrical stimulation of the contralateral vRPO on vRPO neurons (Fig. 7). These results demonstrate that the TPp and contralateral vRPO modulate the activity of vRPO neurons and consequently the generation and maintenance of REM sleep through the neurotransmitters acetylcholine and glutamate respectively. Presumably, other brain structures such as the cerebellar nuclei, use glutamate to stimulate vRPO neurons, since the most significant effect of lesions that include the cerebellar projection to the vRPO is a decrease in REM sleep (De Andrés and Reinoso-Suárez, 1976) (Fig. 6); the rostral raphe nuclei must use serotonin, since Portas at al. (1996) have demonstrated that microdialysis with a 5-HT receptor antagonist in the dorsal raphe nucleus reduces or suppresses serotonergic activity in the dorsal raphe nucleus and increases REM sleep (Figs. 6 and 9).

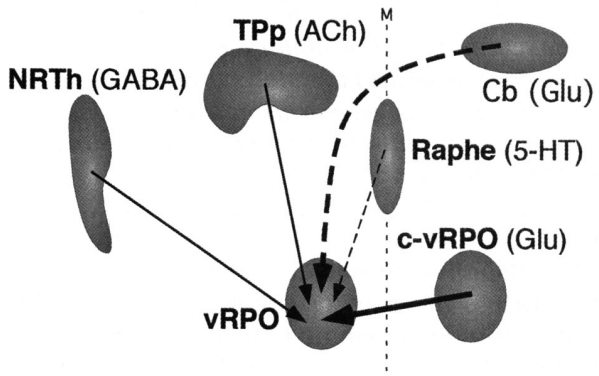

Fig. 6– Schematic representation of the vRPO afferent connections (arrows) from five different brain structures whose influence on REM sleep or on vRPO neuronal activity has been demonstrated. The relative density of the connections is indicated for the thickness of the arrows. The putative neurotransmitters implicated are indicated in brackets. M. midline.

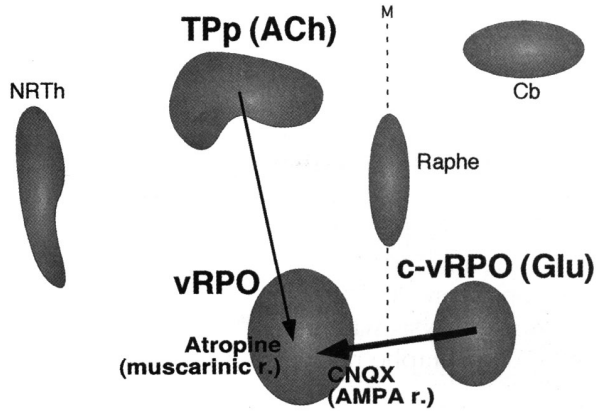

Fig. 7– Schematic represention sumarizing the experiments described in Rodrigo-Angulo et al., 1999, illustrating the effects produced by the TPp and c-vRPO on the vRPO neurons mediated by ACh throughout the muscarinic receptors, and by glutamate throughout the AMPA receptors. r: receptors.

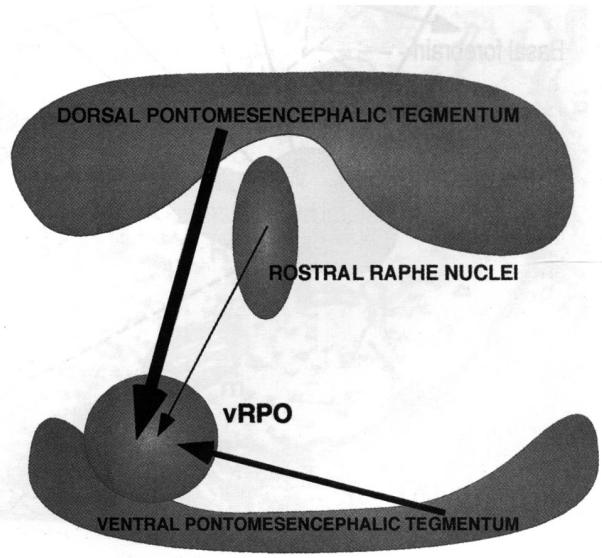

Fig. 8– Scheme summarazing the serotonergic innervation of the vRPO according to Rodrigo-Angulo et al., 2000.

It may be concluded that the balance between the excitatory and inhibitory actions of the structures that project to the vRPO through their neurotransmitters triggers and maintains REM sleep in intact animals by increasing the activity of vRPO neurons

Which cells originate these serotonergic, GABAergic, cholinergic, etc. fibers innervating the vRPO? The results demonstrate an organization that is much more complex than what had previously been assumed. As an example, figure 8 summarizes our recent results on serotonergic innervation of the vRPO (Rodrigo-Angulo et al., 2000). Only 13% of the serotonin reaching this nucleus arose in the raphe nuclei and 87 % came from serotonergic cells distributed in dorsal and ventral pontomesencephalic structures other than the raphe nuclei. Consequently, the serotonergic modulation of REM sleep may mainly be the result of the activation of these non-raphe pontomesencephalic structures.

The complex functional organization of the neuronal network responsible for the generation and maintenance of REM sleep

These results afford an opportunity to think about the functional complexity of the broad neuronal network that increases the neuronal activity of the ventral pontine tegmentum. Recently, as mentioned previously, it has been demonstrated that microdialysis with a 5-HT receptor antagonist in the dorsal raphe nucleus reduces or suppresses serotonergic activity in the dorsal raphe nucleus and increases REM sleep (Portas et al. 1996). The authors assume that the increase in REM sleep is mediated by a disinhibition of cholinergic dorsolateral mesopontine neurons. Without addressing the possibility that the microdialysis could diffuse to other groups of serotonergic neurons close to the raphe nuclei, we observed that the rostral raphe nuclei projection to the dorsolateral mesopontine cholinergic structures is also small, and similar in size and proportion to the one to the vRPO. Consequently, and considering only these three structures (dorsal raphe nucleus, dorsolateral mesopontine cholinergic neurons and vRPO), the increase in REM sleep in this experiment may have a double origin (Fig. 9): 1) the reduction of 5-HT release at the ventral oral pontine tegmentum would disinhibit those neurons and, 2) the disinhibition of dorsolateral cholinergic mesopontine neurons, which we have demonstrated to be the source of the cholinergic innervation of the oral pontine tegmentum, would increase acetylcholine release in the ventral pontine tegmentum and, consequently, excite this nucleus. Both simultaneous actions increase the activity of the vRPO neurons and in consequence increase REM sleep.

As we have mentioned, in a normal sleep-wakefulness cycle all the previously described connections to the vRPO, with their large variety of neurotransmitters, participate in the level of activity of the vRPO neurons. Activation or inhibition of any of the components of the network

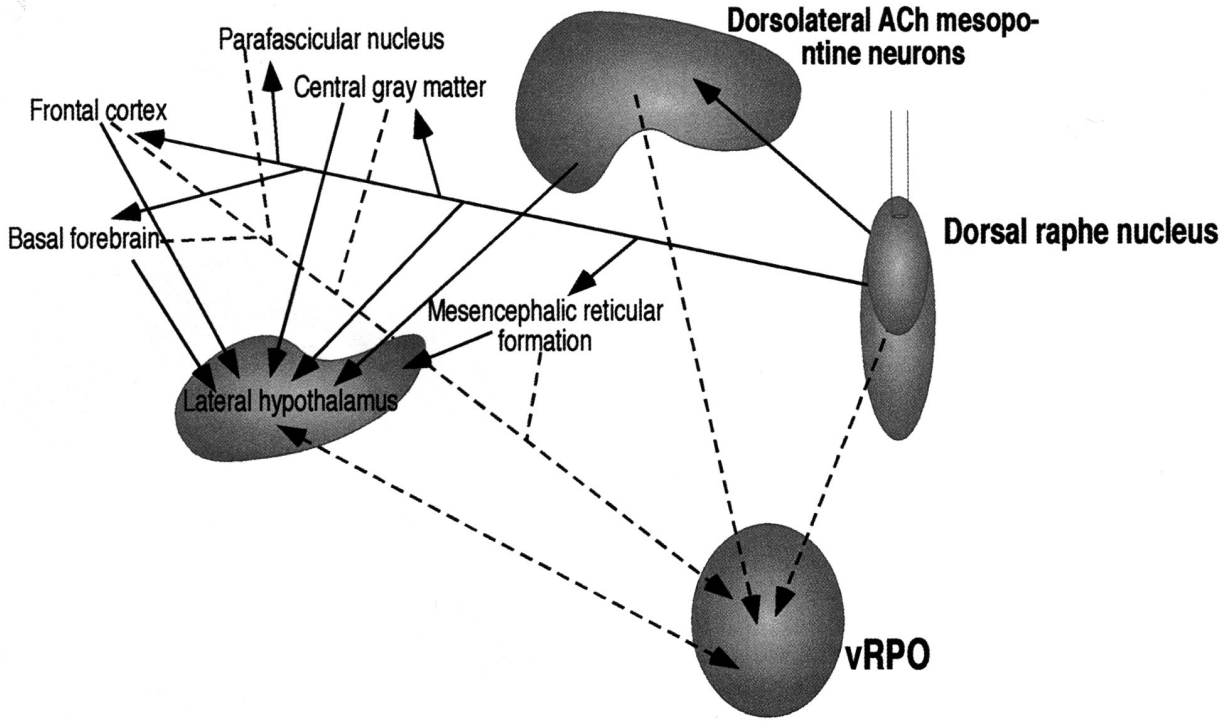

Fig. 9– Partial scheme of the neuronal network linking the dorsal raphe nucleus and the VRPO (arrows). Plain lines represent the dorsal raphe nucleus connections and the interconnections of the other network components. Afferent connections to the vRPO are represented by dashed lines.

would activate or inhibit not just a single element of its components, but several. The previous example showed how suppression of dorsal raphe serotonergic activity disinhibited not only the dorsolateral cholinergic mesopontine neurons, but also directly disinhibited vRPO neurons (Fig. 9). In addition, many other brainstem and prosencephalic structures that project to the vRPO are possibly disinhibited by the suppression of the dorsal raphe serotonergic activity from which they receive connections. Some of theses structures are represented in figure 9: the mesencephalic reticular formation, the central gray matter, the parafascicular thalamic nucleus, the lateral hypothalamus, the basal forebrain and the frontal cortex. Disinhibition of all these structures would increase excitatory neurotransmitter release in the vRPO, and consequently produce REM sleep. As an example, one of these structures, the lateral hypothalamus, also receives connections from most of the other components of the network. We have recently investigated the pattern of its reciprocal connections with the vRPO by injecting the hypothalamus with biotinylated dextran amine to study the pontine terminals and the retrogradely-labeled neurons under electron microscopy. The results demonstrated the complexity of the synaptic terminals of the hypothalamic fibres in the vRPO (Sánchez-Valle et al., 1998). As an example, a labeled hypothalamic terminal with round vesicles contacting a dendrite of a vRPO neuron simultaneously made presynaptic contact with another hypothalamic labeled terminal and with another unlabeled terminal that, in turn, formed an asymmetric synapse with the same dendrite. This is only one example of the complicated synaptic organization at the level of the vRPO that we have been systematically investigating over the past few years. There are six types of axon terminals, which mainly differ in the shape and density of their synaptic vesicles as well as in the ultrastructure of their synaptic contacts. These terminals may form symmetric, asymmetric or intermediate synapses on the different parts of vRPO neurons (Fig 10). Symmetric synapses are more numerous than asymmetric and intermediate

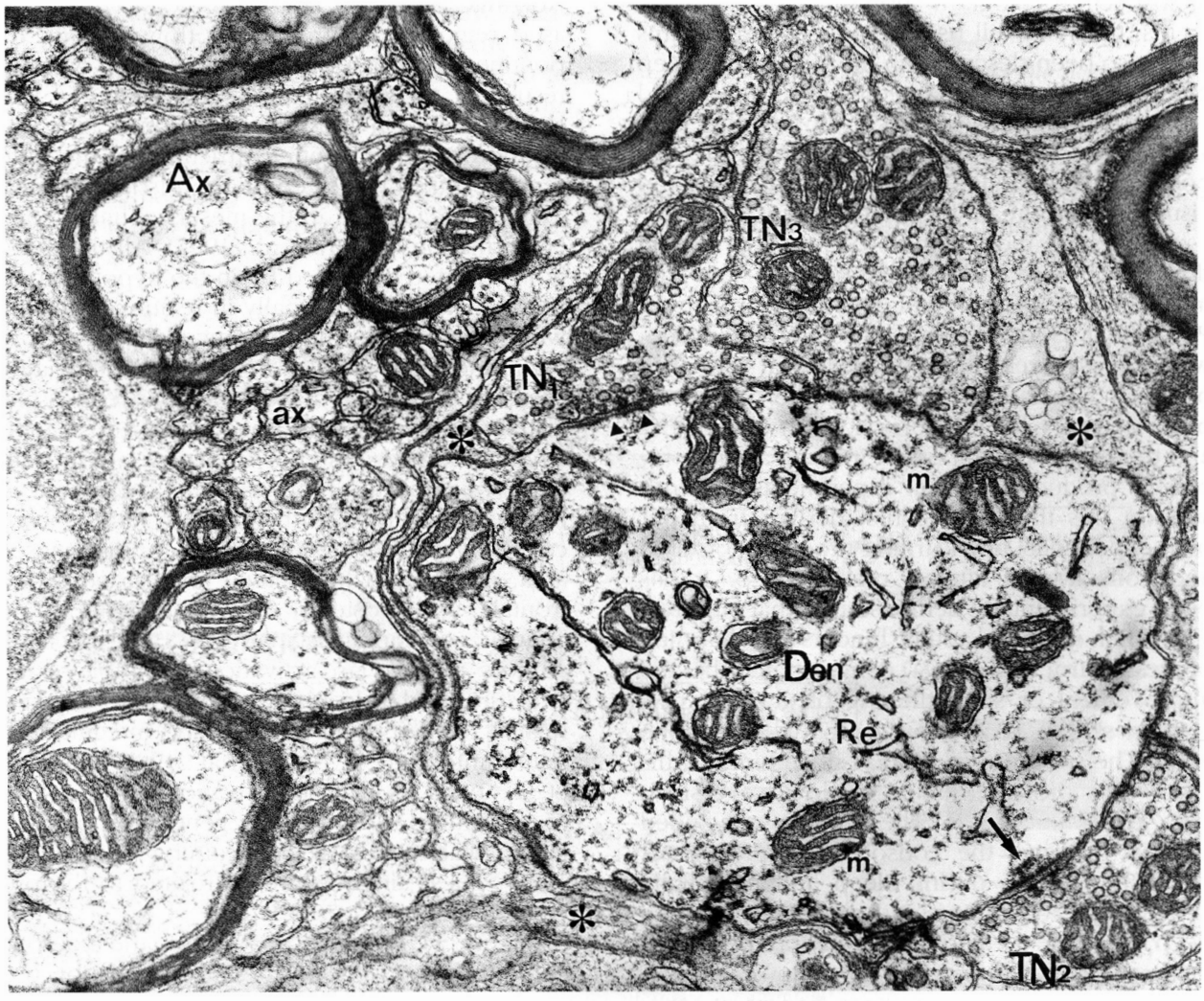

Fig. 10– Electron micrograph showing the neuropil of the ventral oral pontine reticular nucleus. A dendrite (Den) containing numerous mitochondriae (m) and endoplasmic reticulum cisternae (Re) is surrounded by astrocytic processes (*) and three axon terminals. One of these terminals (TN1) forms symmetric synaptic contact (arrow head), while the other (TN2) forms asymmetric synaptic contact (arrow). Unmyelinated (ax) and myelinated axons (Ax) are also present in the neuropil. x 45.000.

synapses on neuronal perikarya; however, the most common type of synapses observed on dendrites are asymmetric. It is also interesting to note that there are significant differences in the percentages of the three types synapses on differently-sized dendrites (de la Roza and Reinoso-Suárez, 1998, 2000).

All these data demonstrate the complex functional organization of the neuronal network that is responsible for the generation and maintenance of REM sleep and that has the vRPO as its axial component (Figs. 1 and 2). In the light of this, it is very difficult to understand the simplistic theories that attempt to explain the functional organization of REM sleep and consequently the treatment of its disorders.

Dreams, REM sleep and memory

The complex neuronal network responsible for the normal REM sleep episodes of an individual is also necessary for normal dreams. Dreams take place during REM sleep. In fact, if we wake someone up when their electroencephalogram is activated, their muscle tone is lax and their electro-oculogram shows rapid eye movements, they will tell us a dream. Today, dreams have also been described in the slow wave sleep phase, but all the data agree that the richest and best structured dreams occur during the REM sleep phase; the density of REM sleep correlates positively with the likeliness of bizarre, vivid and visually active dream images (Braun et al., 1998).

At present, most authors believe that during dreams, or more precisely during REM sleep, the information in the cerebral cortex is reorganized. Possibly it is during this phase of the sleep-wakefulness cycle that the reciprocal influence between association cortices and the hippocampus, necessary for the consolidation of memory and therefore very important in the learning process, is produced. Several experimental findings support this theory. The first derives from our own experience: any learning process is ordered and consolidated after a night's sleep. It has been experimentally demonstrated that suppressing REM sleep in adults hinders the learning process. Karni at al. (1994) demonstrated that the improvement or strengthening of a visual perception skill depends on the REM sleep of one night. The suppression of REM sleep hinders this task, while the suppression of slow wave sleep does not influence it. The authors concluded that, in humans, the consolidation process of memory is active during sleep and essentially depends on REM sleep and not on slow wave sleep. In rodents and in carnivora the 'theta' rhythm is recorded in the hippocampus as a special rhythm with a high voltage and great regularity during REM sleep. Synaptic potentiation has been considered to be the cellular equivalent of memory; it occurs over a long time by the repetitive stimulation of the hippocampus and is called LTP (long term potentiation) (Bliss and Collingridge, 1993). LTP is achieved most easily in the hippocampus when the stimulus is applied simultaneously with the peaks of the 'theta' waves in REM sleep (for a review, see Winson 1993). It seems that the information acquired during wakefulness is re-expressed in the circuits of the hippocampus during sleep, as proposed in some consolidation theories of memory (Reinoso-Suárez, 1995).

Imaging studies during REM sleep in humans are to a large extent coherent with the previously described results. The results in this area were obtained using the technique of PET scanning. We are aware of the limitations of this technique, because oxygen consumption and neuronal activity are co-localized but the delayed blood flow is not; in the future, functional magnetic resonance imaging focused on this initial phase should yield much higher spatial resolution (Vanzetta and Grinvald, 1999). A summary of four recent PET studies is offered in Table 1 (Maquet et al., 1996; Braun et al., 1997, 1998; Nofzinger et al., 1997). The authors found increased regional cerebral blood flow (BF) in the pontine reticular formation, in keeping with our results of the importance of the vRPO in REM sleep generation and the maintenance and participation of other pontine structures in the different aspects of this sleep phase. Also, one author found increased BF in the mesencephalic reticular formation (Braun et al., 1997). All these authors reported increased BF in the hypothalamus; in the thalamus, principally in relation with slow wave sleep phases; in the amygdala, basal forebrain and basal ganglia; in unimodal association cortices, very well demonstrated in extrastriate visual areas; in medial orbitofrontal and anterior cingular cortices; anterior insula, parahippocampal gyrus, and the hippocampus. Decreased BF has been observed in the primary sensory cortices, is well documented in the primary visual area, prefrontal (dorsolateral and lateral orbitofrontal) and posterior cingular cortices, and angular and supramarginal gyri (Table 1). These authors refer to an activation of limbic-related structures and a decrease in activity in structures related to high order analysis and integration of neural information (Braun et al., 1997; Nofzinger et al., 1997) as well as activation of the extrastriate cortices related to the generation of visual images during REM sleep dreaming (Braun et al., 1998). These findings are all related to the process of memory consolidation.

Figure 11 schematically shows the neuronal network responsible for neural information processing and storage, and the structures considered to be responsible for declarative memory consolidation (Reinoso-Suárez, 1995, 1997). Imaging studies during REM sleep have demonstra-

Table 1.– Regional cerebral blood flow measured by PET during REM sleep

Increase:
Pontine and mesencephalic reticular formation
Cerebellar vermis
Hypothalamus and *thalamus*
Basal ganglia, amygdala, basal forebrain
Medial orbitofrontal, anterior cingulate, parahippocampal cortices and anterior insula
Hippocampus
Unimodal association cortices (extrastriate visual areas)
Decrease:
Primary sensory cortices *(primary visual cortex)*
Dorsolateral prefrontal and *lateral orbitofrontal* cortices
Angular and *supramarginal* gyri
Posterior cingulate cortex

Composed with the results of Maquet et al., 1996; Braun et al., 1997, 1998; Nofzinger et al., 1997. Structures described in 2 or more papers are in italics.

ted a decrease in activity in structures related to neural information processing, mainly in their two anatomical extremes: in the primary sensory cortices, which prevent the arrival of new external information for processing, and in the prefrontal cortex and other cortical areas related to high order analysis, integration and processing. Thus, during REM sleep the cerebral cortex is subjected to internal stimuli, originating in the pontine tegmentum, that activate the structures responsible for the different aspects of memory consolidation (medial orbitofrontal cortex, hippocampus, parahippocampal cortex, etc.) and the association cortex areas most directly related to these structures. The information in the cerebral cortex is reorganized through this allo- and iso-cortical activation; a reciprocal influence between association cortices, the hippocampus and the other structures involved in the consolidation of memory is produced. It may consequently be proposed that this transference of information produces dreaming as an epiphenomenon of REM sleep. That is to say, we dream when we register the information transfer within the cortical neuronal nets to consolidate our memory, and doing so correctly requires all the complex brain mechanisms described above.

Epilogue

We would like to end with the stanza Calderón de la Barca puts in " the liberated" Segismundo's mouth at the end of Act III, scene iv, of the drama "Life Is a Dream":

"Do not wake me if I sleep,
and if 'tis true, do not make me sleep.
Yet be it truth or be it dream,
What counts is doing good."

Doing good things and defending the truth is the only way to advance without paradoxes in our understanding of sleep mechanisms.

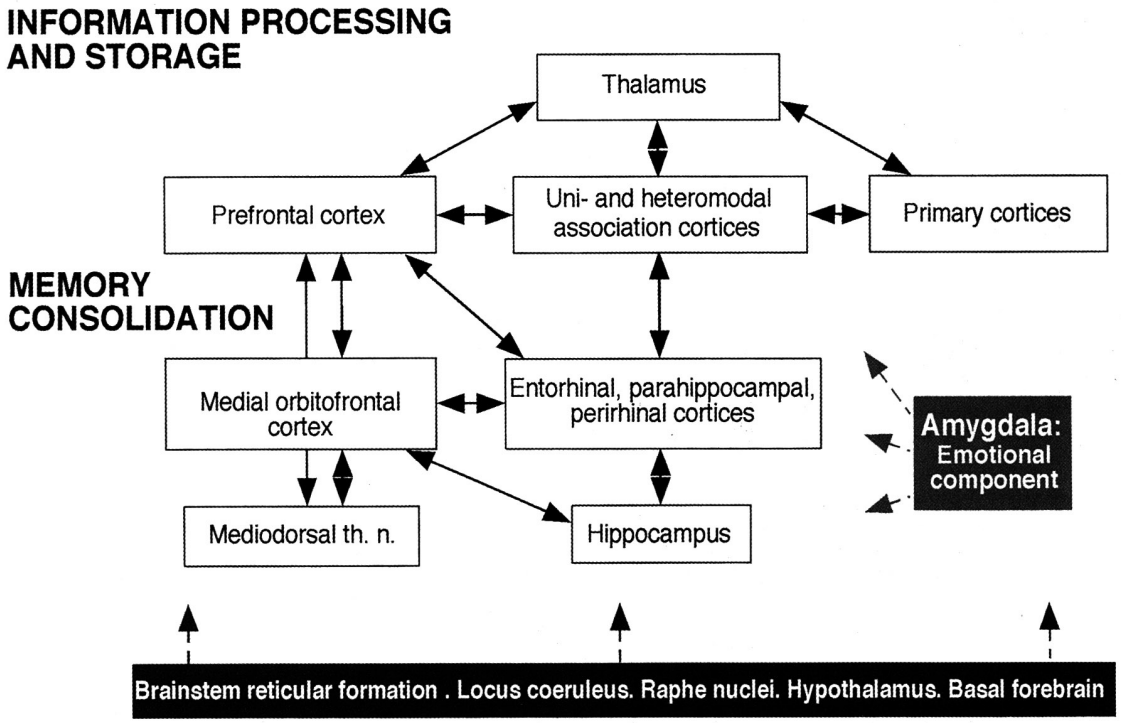

Fig. 11– Schematic representation illustrating the neuronal network responsible for the processing and storage of the information as well as for the consolidation of declarative memory. Modified from Reinoso-Suárez, 1997.

Abbreviations

BC: brachium conjunctivum
c-vRPO: contralateral vRPO
Cb: cerebellum
CI: inferior colliculus
CT: trapezoid body
GVII: genu of the seventh nerve
Lα: locus coeruleus alpha nucleus
LD: laterodorsal tegmental nucleus
LM: medial lemniscus
NRTh: thalamic reticular nucleus
P: pyramidal tract
Pα: perilocus coeruleus alpha nucleus
RPC: caudal pontine reticular nucleus
RPO: oral pontine reticular nucleus
Tp: pontine tegmental nucleus
TPp: tegmento pedunculopontine nucleus
vRPO: ventral oral pontine reticular nucleus

Acknowledgements

We thank Ms. C.F. Warren for linguistic assistance. This work was supported by grants DGICYT PM95-0034 and DGICYT PM98-0005.

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