

Why does arterial blood pressure rise actively during REM sleep?

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Abstract : A large fluctuation in autonomic function is one of the most important characteristics of REM sleep. Arterial blood pressure (AP) increases during the transition from non-REM to REM sleep, showing phasic surges during REM sleep. REM-associated AP changes involve 1) a long-term recovery process after surgery, 2) circadian rhythm, 3) relationships with ambient temperature. REM-associated AP changes are mediated by sympathetic nerves, buffered by baroreflex, abolished in decerebrated cats, and related to hippocampal theta activity in rats. Furthermore, the midbrain dopaminergic system has been recently found to be involved in increases in REM-associated AP. *J. Med. Invest.* **46 : 11-17, 1999**

Key words : REM sleep, blood pressure, dopamine

INTRODUCTION

Homeostasis is one of the most important concepts in our understanding of the biological mechanisms of somatic, autonomic and endocrine controls. The constant internal environment which consists of the circulatory organic fluid which surrounds and bathes all body tissue is the result of a control mechanism that limits the variability of body state. It is well accepted that arterial blood pressure (AP) is maintained at a constant level via the neural mechanisms of baroreflex, chemoreflex and/or circulating hormonal control, which include free radicals, such as NO. The key neuronal and hormonal mechanisms related to maintaining homeostasis are located in the hypothalamus. Although, during the waking period, the emotional reactions or exercise affect AP, it is reasonable to assume that AP is controlled at a constant level during sleep, since this activity does not involve voluntary movement and/or emotional behavior.

Two stages of sleep exist ; one is rapid-eye-movement (REM) sleep and the other is non-REM

sleep. REM sleep is characterized by arousal electroencephalogram (EEG), rapid eye movements (REMs) and muscle atonia, while non-REM sleep is characterized by a dominant slow wave activity in EEG. REM sleep is also called dreaming sleep, and dreams which contain vivid imagery are often experienced during this state.

During non-REM sleep, autonomic functions such as AP, heart rate (HR) and respiration are controlled and quite stable, showing constant values throughout this stage. However, during REM sleep, significant fluctuations in autonomic functions can be observed (Fig. 1 for example in a rat). AP increases in the transition from non-REM to REM sleep, exhibiting large phasic surges during REM sleep, although the skeletal muscles lose their activity completely. Great autonomic fluctuations during REM sleep can be seen in various mammals, including humans. During REM sleep, our bodies no longer appear to be under the homeostatic control (1).

Why does AP rise actively during REM sleep? Although, at present, this issue remains to be resolved, we report here, in the form of a mini review, A) the neural mechanisms for REM sleep generation, B) the characteristics of REM sleep-associated AP changes, and C) possible mechanisms for AP control during REM sleep.

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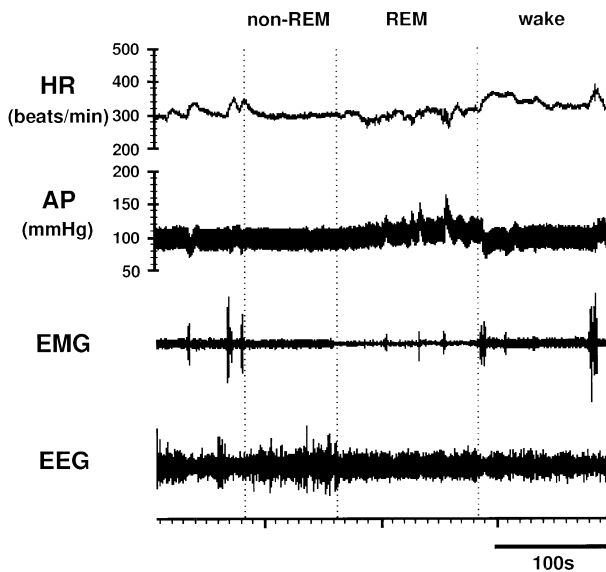


Fig. 1. Representative example of polygraphic recordings, showing changes in heart rate (HR), arterial blood pressure (AP), electromyogram (EMG) and electroencephalogram (EEG) during sleep in a rat.

A. Neural mechanisms for REM sleep generation

In the decerebrated cat whose brain stem is transected at a pre-pontine level, the REM sleep-like stage is characterized by the occurrence of muscle atonia, pontine ponto-geniculo-occipital (PGO) waves and REMs (2, 3). This strongly indicates that the center for generation of REM sleep exists not in the forebrain but in the brain stem.

Sleep-neurophysiologists have considered that interaction between REM-on and REM-off neurons in the brain stem play a critical role in the generation of REM sleep (4-6, Fig. 2). The REM-on neuron is completely silent or functions at a considerably lower level of discharge during waking and non-REM sleep, but their discharge rate is augmented prior to the onset of REM sleep, and then stops firing completely at the end of REM sleep. The REM-off neuron shows a reverse discharge pattern to REM-on neurons. To date, there is abundant evidence that REM-on neurons are largely cholinergic neurons in the pontine tegmentum area, while REM-off neurons include serotonergic neurons in the raphe nucleus, noradrenergic neurons in the locus coeruleus and histaminergic neurons in the posterior hypothalamus. The cholinergic REM-on neurons and aminergic REM-off neurons show the opposite firing pattern with a vigilance change. The increase of firing rate in REM-on and the decrease (cessation) in REM-off neurons are, at least, necessary for the generation of REM-sleep (4-6).

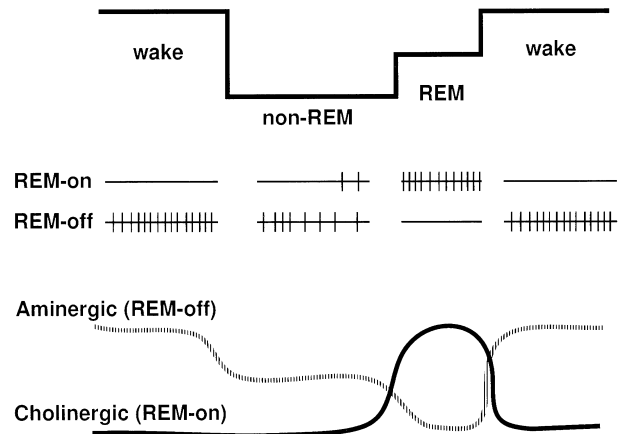


Fig. 2. The model of physiological mechanisms determining alterations in vigilance level. Upper : vigilance level. Middle : the firing pattern of REM-on and off neurons. Bottom : dynamic model of interaction between REM-on (cholinergic) and REM-off (aminergic) neurons with the vigilance change. (modified from ref. 5).

The injection of carbachol, a potent cholinergic agonist, into the restricted area in the pontine tegmental area strongly induces REM sleep (7, 8). On the other hand, atropine, a cholinergic receptor antagonist, completely suppresses REM sleep (6). As a result, it is generally thought that both the activation of cholinergic REM-on cells and the stimulation of cholinergic receptors are important for REM-sleep generation. In contrast, the injection of serotonin into the pontine tegmental area (9) or the electrical stimulation of locus coeruleus where noradrenergic neurons are clustered (10) reduce REM sleep. Furthermore, the noradrenergic agonist suppresses REM sleep. Like cholinergic enhancement, aminergic suppression of REM sleep is now an established principle.

The neurons which execute muscle atonia exist not only in the pontine tegmental area but also in the medulla. These descending neurons are, of course, REM-on type neurons, and are thought to be non-aminergic and non-cholinergic. Although the injection of carbachol into the pontine tegmental area induces muscle atonia, a similar injection in the medulla does not. This indicates that the atonia-inducing neurons in the pons are choline-receptive and those in the medulla are not (7, 11).

It has recently been found that the glutamatergic receptor in the pontine tegmental area may play a role in the control of REM sleep induction (12). The duration of REM sleep is greatly pronounced during the perfusion of kainate via the membrane of a dialysis probe in the pontine tegmental area. This effect is inhibited by the simultaneous injec-

tion of GAMS or CNQX, a specific non-NMDA receptor antagonist, but is not inhibited by AP-5 or MK801, a selective NMDA receptor antagonist, or atropine. It is suggested that the glutamatergic REM sleep-inducing effect is mediated by non-NMDA receptors and independent of the cholinergic system. Using microdialysis techniques, the spontaneously increased rate of release of glutamate in the medulla, which is related to muscle atonia, is observed during REM sleep, and cholinergic stimulation of the pons increases the release of glutamate in the medulla of the cat (13). A glutamatergic pathway from the pontine tegmental area to the medulla is responsible for muscle atonia.

Based on human PET studies (14-16), it has also been confirmed in humans that the pontine brain stem is important to the REM sleep activation of the brain. Furthermore, the limbic and paralimbic regions of the forebrain are preferentially activated in REM sleep compared to waking periods, or to non-REM sleep, indicating that these regions may be related to the emotional aspect of human dreams.

B. Characteristics of REM sleep-associated AP change

B-1. Long-term changes in recovery process from surgery

After surgically implanting equipment in an experimental animal for the purpose of recording biological signals (EEG, AP, etc.), a long-term recovery process in the REM sleep-associated AP change is observed (17, 18). In the acute period after surgery (5-10 days afterward), AP decreases and remains low throughout REM sleep in the cat. In contrast, in the chronic period (in excess of 10 days after surgery), AP increases and shows several phasic surges during REM sleep. The pathophysiological mechanisms of this post-surgical phenomenon are completely unknown.

B-2. Circadian rhythm

A circadian rhythm exists in the AP and HR in rat (19,

20), monkey (21) and human (22, 23). The rat has a polyphasic sleep-wake cycle, and even during the active (dark) phase, it sleeps several times. In the rat, the magnitude of REM sleep-associated AP fluctuation shows a circadian rhythm. The AP fluctuation, expressed by a coefficient of variation (CV%), is larger in the light phase than in the dark phase (24). The AP CV% during REM sleep is inversely correlated to the brain temperature. As injection of interleukin-1 β causes both a high fever and a decrease in the CV% of AP during REM sleep (25), thermoregulation is hypothesized to be related to REM sleep-associated AP changes.

B-3. Effect of ambient temperature (Fig.3)

Changes in ambient temperature (T_a) affect the cardiovascular system during both wake and sleep periods in rats (26, 27). AP and HR increase with decreasing T_a . The increment of AP from non-REM to REM sleep decreases with decreasing T_a . At 28 degrees, HR increases during REM sleep in comparison to non-REM sleep, while at 16 degrees a decrease is observed. The AP CV% during REM sleep decreases as the T_a is lowered.

C. A possible mechanisms for control of AP during REM sleep

C-1. The role of the sympathetic nerve and baroreflex

Subcutaneously injected guanethidine causes peripheral damage to the sympathetic nervous system.

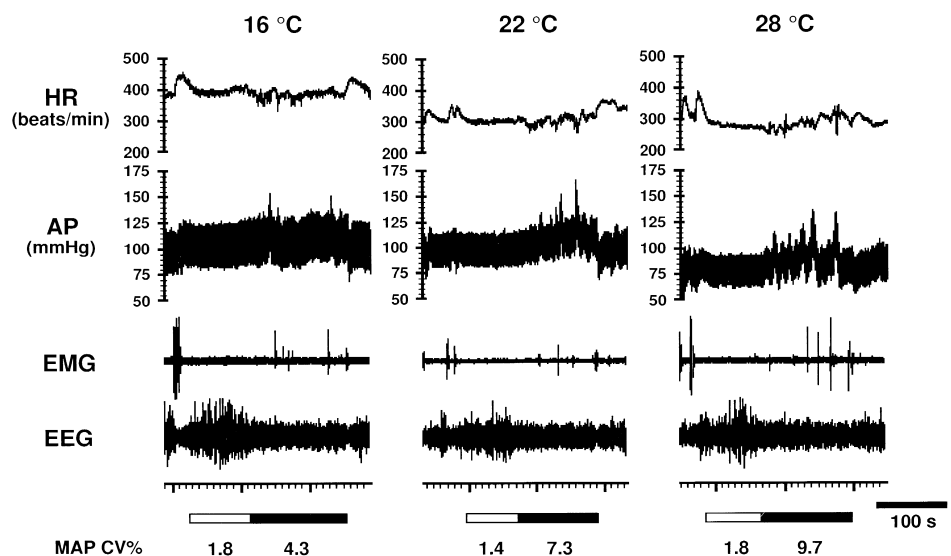


Fig. 3. Representative recordings showing changes in heart rate (HR), arterial pressure (AP), electromyogram (EMG) and electroencephalogram (EEG) during successive non-REM (indicated by horizontal open columns at bottom) and REM (indicated by horizontal closed columns at bottom) sleep at three ambient temperatures. MAP CV% : coefficient of variation of mean arterial pressure.

In rats which have been sympathectomized by treatment with guanethidine, increases in REM sleep-associated AP are abolished (28). In humans, changes in muscle sympathetic nerve activity during sleep have been recorded by means of microneurography (29-31). During REM sleep, the muscle sympathetic nerves show an increase in activity compared to waking and non-REM sleep. These observations suggest that the sympathetic nervous system is involved in increases in AP during REM sleep.

It has been suggested by some researchers that the baroreflex may play a crucial role in the increase of AP observed during REM sleep. In fact, there are several reports which show that sino-aortic denervation (SAD) causes a decrease in AP during REM sleep in the rat and cat (31, 32). Recently, however, we have retested the SAD in the rat using a telemetry system for recording AP, and found that in the case of the SAD rats the increases in AP and HR during REM sleep are much larger than those in sham-operated rats (33). We noted a decrease in AP during REM sleep in the SAD rats in the earlier acute period after surgery. It is possible that the recovery period in the previous experiments was too short and, as a result, the SAD rats showed a decrease in AP during REM sleep. The baroreflex buffers the increase in AP and HR during REM sleep in the rat.

C-2. The role of forebrain structure

In order to investigate the role of the forebrain structure, observations relative to the AP change during sleep were carried out in decerebrated cats (34, 35). Although decerebrated cats lose neural input from the forebrain structure, they show a REM-sleep like phase. During this REM-sleep like phase, AP decreases tonically with no phasic surge, indicating that the neural connection between the forebrain structure and brain stem is necessary for the increase in AP which is observed during REM sleep.

The hippocampus is one of the important limbic structures, and shows a rhythmical sinusoidal EEG (theta wave) during REM sleep, especially in rodents. This appearance of a theta wave is indicative of the pronounced activity of the limbic system during REM sleep. During the waking period, the frequency of the theta wave increases when the animal is physically active. The acceleration of theta wave activity precedes the AP surge during REM sleep in the rat (36). Benzodiazepine, which binds to the GABA receptor and hyperpolarizes the membrane potential, is known to reduce both hippocampal activity and the

theta frequency. The injection of benzodiazepine reduces the increases in both theta frequency and AP during REM sleep. This also indicates the important role of the forebrain including the limbic system on AP changes during REM sleep.

C-3. Midbrain dopaminergic neurons and AP change during REM sleep

Aminergic neurons are considered to be largely REM-off neurons. It has been reported, however, that dopaminergic neurons do not decrease their firing rate during REM sleep (37). As stimulation of the midbrain dopaminergic system increases AP (38, 39), the possibility exists that the dopaminergic system may play a role in the increase in REM sleep-associated AP. Two dopaminergic systems which have been particularly implicated in cardiovascular control are the mesolimbic/mesocortical (A10) and the nigrostriatal (A9) systems. The mesolimbic/mesocortical dopaminergic system originates in the midbrain ventral tegmental area (VTA) and innervates forebrain regions such as the nucleus accumbens, olfactory tubercle, amygdala and hypothalamus. We have injected 6-hydroxydopamine (6-OHDA), a drug which is a catecholaminergic neurotoxin, into the VTA (40, Fig. 4). The increase of AP and HR during REM sleep seen in vehicle-treated rats was suppressed in 6-OHDA-treated rats (Fig.5).

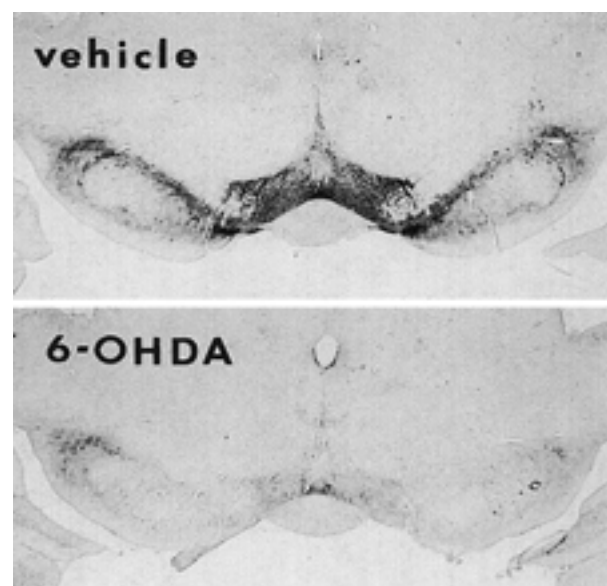


Fig. 4. Examples of brain sections near the injection site, processed for tyrosine hydroxylase (TH) immunohistochemistry, in a 6-hydroxydopamine (6-OHDA)- and vehicle-treated rat. TH immunoreactive neurons in ventral tegmental area are almost absent in 6-OHDA-treated rat. Neuron loss in the 6-OHDA-treated rat appears to extend to the antero-medial part of the substantia nigra.

It is reasonably imagined that REM-off neurons including noradrenergic and serotonergic neurons, which are also damaged by 6-OHDA, are not directly involved in the AP increase during REM sleep, even if their disinhibitory effects play an important role on the AP change. This result, therefore, supports the above mentioned hypothesis that the dopaminergic system may be involved in increased REM sleep-associated AP.

Oneiric behavior (41, 42) during REM sleep, observed in the cat with a pontine tegmental lesion, suggests that the central motor system actively functions during REM sleep, although the actual behavioral action is inhibited by muscle atonia. It has been reported that the AP and HR increase during exercise or voluntary movement, and that the cardiovascular sympathetic outflow increases immediately before, or concomitantly with, the onset of exercise and voluntary movement (43-45). These findings indicate that, during such behavior, descending autonomic activation originates from the higher nervous system (central command), in order to adjust the blood supply for exercise or movement. Thus, it can be hypothesized that, during REM sleep, AP is increased via a central command in parallel with the activated motor system without any actual observed action, and that the midbrain dopaminergic system is involved in this central command to the AP.

CONCLUSIONS AND PERSPECTIVES

Very little is currently known concerning the mechanism and role of the large autonomic fluctuation during REM sleep. Only hints exist as to the involvement of the midbrain dopaminergic neurons on this mechanism. The midbrain dopaminergic neurons have, however, been reported to show a clockwise and regular firing pattern. This regular firing pattern cannot explain the phasic fluctuation of the autonomic nervous system during REM sleep. Clearly, strong inputs from the other sites of the brain into the midbrain dopaminergic system must induce the phasic excitement of the dopamine-associated autonomic control and subsequent phasic events in AP, HR and/or respiration during REM sleep. Inves-

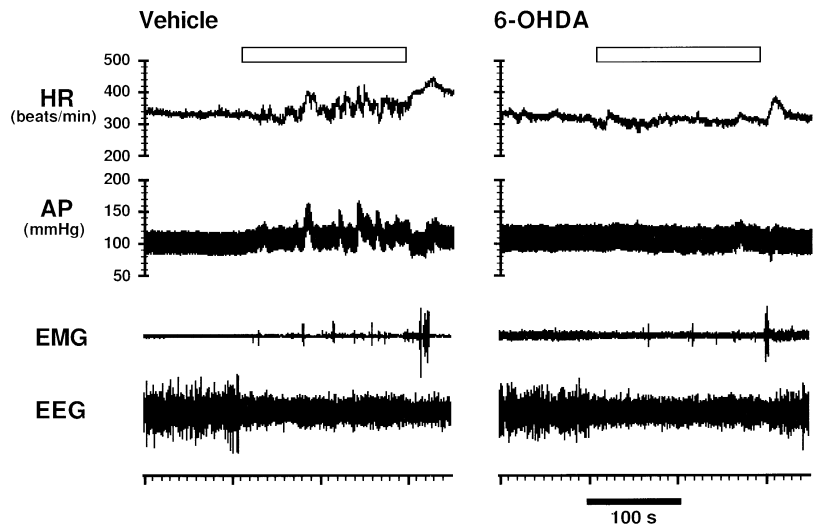


Fig. 5. Representative examples of polygraphic recordings, showing changes in heart rate (HR), arterial blood pressure (AP), electromyogram (EMG) and electroencephalogram (EEG) during sleep in a 6-hydroxydopamine (6-OHDA, right)- and vehicle (left)- treated rat. The upper bars indicate the period of REM sleep.

tigations into the interaction among dopaminergic, cholinergic and/or glutamatergic neurons is now ongoing in our laboratory.

If a relationship exists between imagery or emotion in dreams and autonomic changes during REM sleep, the question " why does arterial blood pressure rise actively during REM sleep? " might be analogous to the question " what mechanism leads to imagery or emotion in dream? "

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