—Reviews—

Psychological Stress-induced Changes in Sleep Patterns and Its Generation Mechanism

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Recent findings have increasingly shown that sleep patterns are significantly influenced by psychological stress, such as social defeat, novelty stress, contextual fear stress, and psychological stress induced by the communication box. However, the exact association between psychological stress and sleep is still poorly understood. Therefore, in the present paper we will review related work based on our recent investigations. We have previously reported that total rapid eye movement (REM) sleep, but not non-rapid eye movement (NREM) sleep that is enhanced by psychological stress induced by the communication box in rats (Cui et al., 2007). In past decades strong evidence showed that neurotransmitters play a key role in the variations of the sleep patterns, such as acetylcholine, GABA and others. In addition to neurotransmitters, the hypothalamic-pituitary-adrenal (HPA) axis is another important factor which influences sleep patterns. Therefore, this review will focus on the involvement of the neurotransmitters and the HPA axis in the changes of sleep patterns in response to psychological stress.

Key words——psychological stress; rapid eye movement sleep; electroencephalogram

INTRODUCTION

Stress is a complex issue, but generally it is defined as a physical or psychological reaction resulting from an individual response to environmental tensions, conflicts, pressures, and similar stimuli.[1)] Psychological stress was recently found to have a prominent effect on sleep patterns, for example, the amount of slow-wave sleep was increased in the subsequent 6 h of sleep after social conflict stress,[2)] whereas the total REM sleep was immediately decreased in rats[3,4)] and mice[5)] after contextual fear stress (Table 1). Furthermore, both our groups and others have previously reported that physical and psychological stress to be induced by the communication box simultaneously in different rats.[6–9)] Physical stress was generated by foot shock, whereas psychological stress was generated by exposure to emotional responses without direct physical stress, namely, they were exposed to visual, smell and auditory stimuli arising from foot shock stressed animals.[10,11)] Therefore, this equipment ideally isolated psychological stress from physical stress.

Concerning sleep patterns, REM and NREM are the most important components of sleep, and are characterized by polysomnographic recordings, namely the electroencephalogram (EEG), electrooculogram (EOG) and electromyelogram (EMG). Figure 1 shows a representative polygraph recording of wakefulness, REM sleep and NREM sleep by EEG, EOG and EMG in a rat. The wakefulness state was characterized by a low voltage fast wave EEG in the cortex and hippocampus, and high amplitude EMG and EOG. The REM sleep state showed a low voltage fast wave EEG, which is similar with that of the wakefulness state and includes the appearance of eye movements. However, the EMG was also low amplitude. Whereas the NREM sleep state was a high voltage slow wave EEG and a low amplitude EMG and EOG.

Based on sleep recordings and the psychological stress induced by the communication box, the associ-

Table 1. The Sleep Patterns in Response to the Different Types of Psychological Stress in Mammals.

Types of psychological stress	Sleep parameters
Social conflict[2)]	NREM sleep ↑
Conditioned fear[3)]	REM sleep ↓
Auditory stimulation[12)]	REM sleep ↑
Novelty[6)]	REM sleep ↓
	NREM sleep ↓

↓: decrease, ↑: increase.

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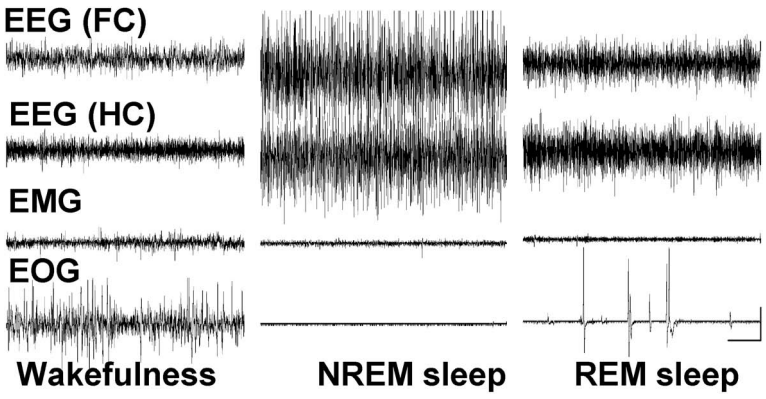

Fig. 1. Typical Recordings of Each Stage of Wakefulness and Sleep in Rats
EEG: electroencephalogram, EMG: electromyogram, EOG: electrooculogram, FC: frontal cortex, HC: dorsal hippocampus, Vertical bar: 200 μV, horizontal bar: 10 s in the panel of right corner.

Table 2. The Changes in Sleep Patterns in Response to Psychological Stress Induced by the Communication Box in Rats.[6,7]

Sleep parameters	Total sleep	Total REM sleep	Total NREM sleep	Total number of REM sleep episodes	Average duration of REM sleep episodes
Effects	⇔	↑	⇔	⇔	↑

↓: decrease, ↑: increase, ⇔: no change.

ation of sleep pattern and psychological stress is discussed in the present paper.

Sleep and Psychological Stress In the communication box, an electric foot shock was used to produce a scrambled electric foot shock (2 mA) through the floor grid lasting for 10 s at intervals of 60 s for 1 h in the physical stress group; whereas the psychological stress group did not directly received foot shock from this apparatus. They could see the rats receiving foot shock *via* three sides of transparent acrylic panels and perceive the sounds and smells. These rats were exposed to various emotional stimuli and felt anxiety from the rats in the compartments with the electric grid floors. Sleep recording was performed after 1 h of psychological stress.[6,7]

Consequently total REM sleep was significantly enhanced due to the prolonged average duration of REM sleep episodes without affecting the total number of REM sleep episodes. However, there was no alteration of total NREM sleep and wakefulness in rats after 1 h of psychological stress (Table 2). These findings seem to contradict the generally accepted idea that stress causes sleep disturbance. Therefore, to clarify the possible mechanism of the present findings, further study was performed on the pharmacologically based neurotransmitters and the HPA axis.

The Cholinergic Mechanism of the Change in Sleep Patterns in Psychological Stress Rats It has been shown that cholinergic neurons in rats are activated by psychological stress, such as auditory stimulation,[12] sensory stimulation[13] and conditioned fear stress.[14] Moreover, it is well known that cholinergic neurons play a key role in REM sleep regulation; for example, REM sleep is enhanced and inhibited by cholinergic agonists and antagonists, respectively.[15–17] Therefore, we undertook to investigate whether cholinergic neuronal activity is related to change of the sleep pattern in response to psychological stress. In the further experiment, which involved intracerebroventricular (i.c.v.) microinjection of atropine, the increased total REM sleep induced by psychological stress during the first 3-h period was dose-dependently inhibited by atropine but not total NREM sleep (Fig. 2), and a significant decrease was observed with a dose of 30 nmol (Fig. 3). However, the injection of atropine significantly inhibited the duration of REM sleep episodes but did not influence the total number of REM sleep episodes in the psychological stress group.[7] Consistent with our results, several studies have shown that cholinergic neurons enhance REM sleep,[15–17] and that the cholinergic antagonist atropine inhibits total REM sleep due to a reduced average duration of REM sleep episodes in cats[15] and rats.[17] Another study reported that the cholinergic reduction of REM sleep was inhibited by auditory stimulation.[12] It is therefore possible that

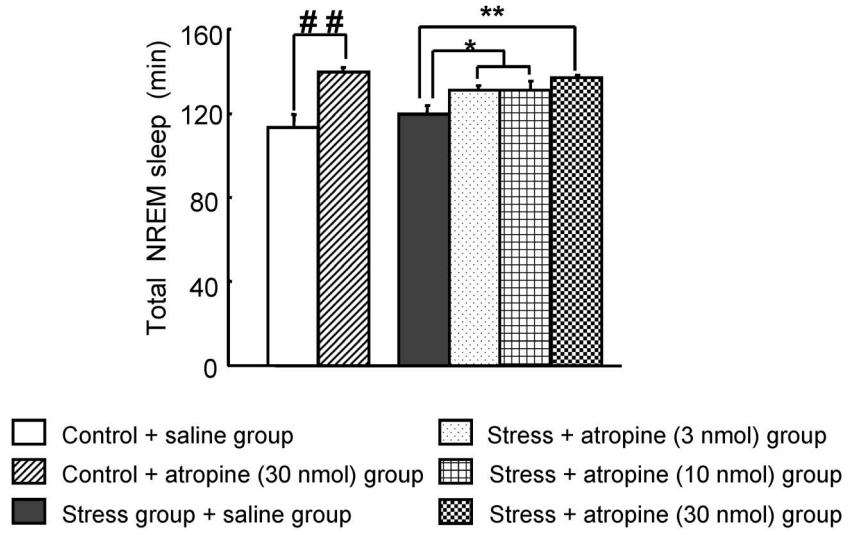

Fig. 2. Effects of Atropine on Total NREM Sleep in the Control and Psychological Stress Group
##$P<0.01$, *vs* control+saline group; *$P<0.05$; **$P<0.01$, *vs* stress+saline group. One-way ANOVA followed by Tukey's test. Data represent the mean±SEM ($n=5$).

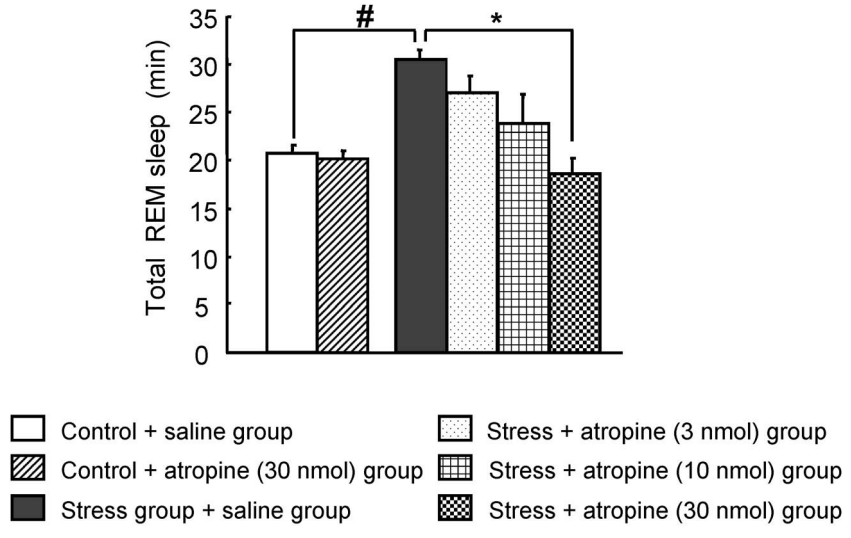

Fig. 3. Effects of Atropine on Total REM Sleep in the Control and Psychological Stress Group
#$P<0.05$, *vs* control+saline group; *$P<0.05$, *vs* stress+saline group. One-way ANOVA followed by Tukey's test. Data represent the mean±SEM ($n=5$).

the cholinergic neurons play an important role in changes in sleep patterns in the present psychological stress group.

The GABAnergic Mechanism of the Change in Sleep Patterns in Psychological Stress Rats

GABA is a main inhibitory neurotransmitter in the mammalian brain, and consists of three subtypes receptor of $GABA_A$, $GABA_B$ and $GABA_C$.[18] With regard to the $GABA_B$ receptor, it is distributed throughout the brain[19] and its function is to inhibit the release of other neurotransmitters and stress hormone secreted by the HPA axis. In rats, for example these include the cholinergic,[20,21] glutamatergic,[22] serotoninergic[23,24] and dopaminergic neuons,[25,26] prolactin,[27] corticosterone[28] and corticotropin releasing hormone.[29] In addition, some evidence also showed that reduced GABA levels were found in the nucleus accumbens, cortex and brainstem of rats exposed to acute forced swimming stress.[30] Similar findings were also found regarding the fact that the hippocampal level of GABA was significantly inhibited by chronic mild stress,[31] and the GABA concentrations in the basolateral region of the amygdala in mice were attenuated by a conditioned fear stimulus.[32] Moreover another group further reported that a $GABA_B$ receptor agonist, baclofen, but not a

$GABA_A$ receptor agonist, muscimol, suppressed the increases in extracellar dopamine release by acute handling-stress.[33] Therefore, to investigate the association between the $GABA_B$ receptor and the change in sleep pattern induced by psychological stress, baclofen (20 pmol) was microinjected into the i.c.v. space. Consequently the enhanced total REM sleep induced by psychological stress was significantly inhibited by the administration of baclofen (Fig. 4). However the total NREM sleep was not altered (Fig. 5). The release by cholinergic neurons predominated in response to the present psychological stress as mentioned above. Furthermore, a local microinjection of baclofen into pedunculopontine tegmentum, which contains a prominent group of cholinergic neurons significantly reduced total REM sleep through the inhibition of cholinergic activity related to an increase in REM sleep.[34] Thus, the reduction of REM sleep was perhaps attributable to the baclofen-induced inhibition of cholinergic activity in the presence of psychological stress.

The Effect of the HPA Axis on the Change in Sleep Patterns in Psychological Stress Rats As for the HPA axis, numerous studies show that the HPA axis plays an important role in the change in sleep patterns by the secretion of stress hormones, such as corticotropin releasing hormone, adrenocorticotropic hormone and corticosterone.[35] In particular the level

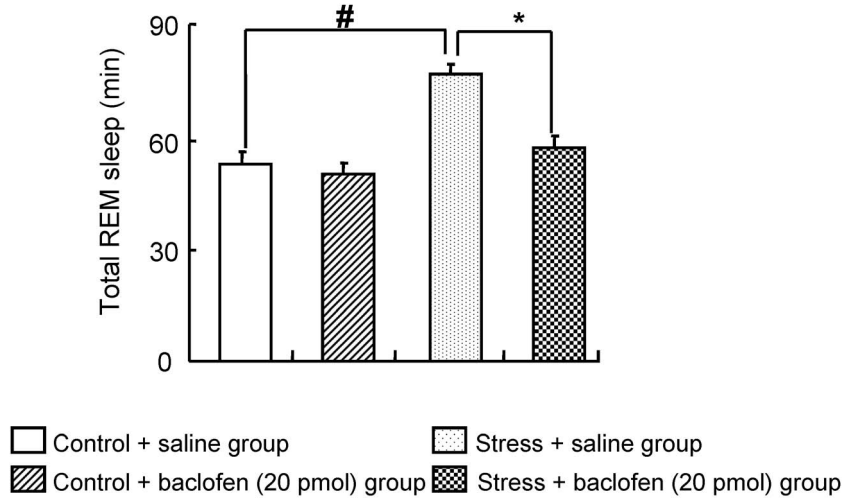

Fig. 4. Effects of Baclofen on Total REM Sleep in the Control and Psychological Stress Group

$^{\#}P<0.05$, $^{\#\#}P<0.01$, *vs* saline group; $^{*}P<0.05$, *vs* psychological stress+saline group. One-way ANOVA followed by Tukey's test or Student's *t*-test. Data represent the mean±SEM ($n=7$).

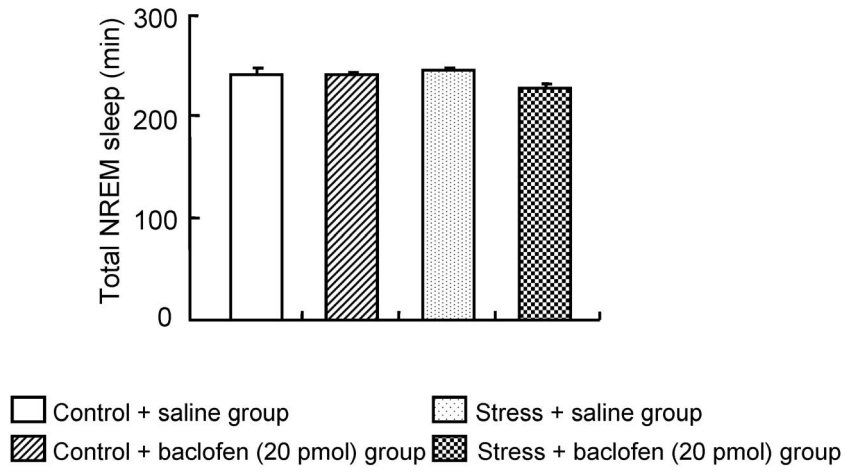

Fig. 5. Effects of Baclofen on Total NREM Sleep in the Control and Psychological Stress Group

One-way ANOVA followed by Tukey's test or Student's *t*-test. Data represent the mean±SEM ($n=7$).

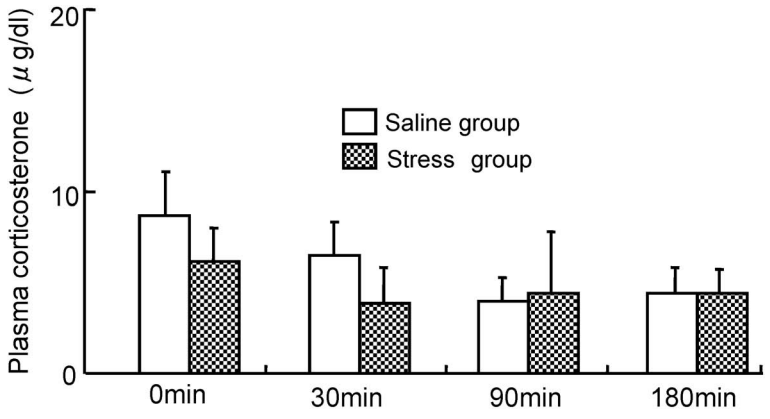

Fig. 6. Effects of Psychological Stress on Corticosterone
Two-way ANOVA followed by Student's *t*-test. Data represent the mean±SEM (n=6).

of serum corticosterone which reflects activity in the HPA axis is frequently used in stress experiments.[35–41] Therefore, the concentration of corticosterone was tested after psychological stress. Surprisingly, the plasma corticosterone level did not increase in response to psychological stress induced by the communication box (Fig. 6). Similar studies have demonstrated that corticosterone levels in rats increase during[10] but not after[9,10,37] psychological stress induced by a communication box. These results indicated that the HPA axis is transiently activated in the present study. Therefore, the present changes in the sleep patterns were probably not attributable to the activated HPA axis.

CONCLUSION AND IMPLICATION

Previously, the psychological stress induced changes in sleep patterns were reviewed in our studies.[6,7] The major finding being that REM sleep was enhanced significantly by the psychological stress of communication box, and these results differ from other psychological stress as listed in Table 1. Therefore, these discrepancies interested us, and we therefore conducted further research to clarify the possible mechanism. In our study the enhancement of REM sleep by psychological stress was inhibited by the microinjection of baclofen, a $GABA_B$ agonist, and atropine, a cholinergic antagonist, separately. Furthermore, baclofen was also found to participate in the changes in sleep patterns *via* an inhibition of cholinergic neurons,[34] suggesting that cholinergic neurons may play a key role in the changes in sleep patterns in response to psychological stress. Another important factor is the HPA axis, the activity of which was monitored by the concentration of corticosterone. However, a significant difference was not observed, based on these results, and it is therefore possible that the enhancement of REM sleep was closely related to cholinergic neuronal activity but not to the HPA axis.

In humans, the influence of stress on sleep is strongly associated with depression.[42] Furthermore, psychological stress is often applied in stress-induced depression models, including social defeat and maternal separation.[43,44] Consistent with our results, increased REM sleep and shorted REM sleep latencies have frequently been observed in depressed patients.[45,46] In general, these two sleep parameters are considered to be predictive of the development of depression.[47,48] Unlike the social stress-induced depression models, the present stress model was not an effective depression model; the changes in the sleep patterns of psychological stress rats, however, may reflect early symptoms of depression. Furthermore, previously our studies focused on the changes in sleep patterns in response to acute stress. However, it is also well known that chronic exposure to stressful life events has been reported to be associated with the development of depressive symptoms.[49] Therefore, the changes in sleep patterns in response to chronic psychological stress need further study in the future.

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