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Original Article

Differential Effects of Psychological and Physical Stress on the Sleep Pattern in Rats

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In the present study, we investigated the acute effects of 2 different kinds of stress, namely physical stress (foot shock) and psychological stress (non-foot shock) induced by the communication box method, on the sleep patterns of rats. The sleep patterns were recorded for 6 h immediately after 1 h of stress. Physical and psychological stress had almost opposite effects on the sleep patterns: In the physical stress group, hourly total rapid eye movement (REM) sleep and total non-REM sleep were significantly inhibited, whereas psychological stress enhanced hourly total REM sleep but not total non-REM sleep. Further results showed that total REM sleep, total non-REM sleep, total sleep and the total number of REM sleep episodes in 5 h were reduced, and that sleep latency was prolonged compared to the control group. On the other hand, in the psychological stress group, the total REM sleep in 5 h was increased significantly due to the prolongation of the average duration of REM sleep episodes and reduced REM sleep latency. In addition, the plasma of corticosterone increased significantly after physical stress but not after psychological stress. These results suggested that the sleep patterns, particularly the patterns of REM sleep following physical and psychological stress, are probably regulated by 2 different pathways.

Key words: psychological stress, physical stress, REM sleep, EEG

The communication box method, developed by Ogawa and Kuwabara [1], has been widely used to study physical (foot shock) and psychological stress (non-foot shock) in mammal species [1–8]. Two different kinds of stress, physical and psychological, are induced simultaneously in different animals using this apparatus, and many behavioral and physiological changes occur [1, 7]. Psychological stress is generated by exposure to emotional responses without direct physical stress, for example, the visual, olfactory and auditory stimuli that arise from foot-shock-stressed animals [3, 4]. Thus, psychological stress is separated from the physical stress in this method.

In previous sleep studies, different types of stresses such as foot shock stress, swimming stress and immobilization stress were compared [9, 10]. These stresses were induced using different apparatus and time courses. Thus, a direct comparison of the effects of these stresses on sleep patterns has various limitations. In contrast, the communication box method is superior to these methods, because physical stress and psychological stress are induced simultaneously without these limitations [2–5, 7].

Stress has been strongly implicated in the regula-

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tion of sleep, and it induces many sleep disorders in humans and animals [9–14]. Foot shock stress is widely used in stress studies [2–5], and previous research has shown that foot shock stress inhibited total REM sleep in rats after acute [5] and chronic stress [10]. The psychological stress induced by the communication box is completely different from foot shock stress. A growing body of scientific evidence has demonstrated that psychological stress is linked to many diseases, including upper respiratory infection [15, 16] and autoimmune disorders [17, 18]. The sleep patterns of rats in response to psychological stress have been studied; for example, slow-wave sleep was increased in the 6 h of sleep following social conflict stress [19], and contextual fear resulted in an immediate decrease of total REM sleep in rats [20, 21] and mice [22].

However, no reports have studied the changes in the sleep patterns of rats exposed to physical and psychological stress induced using the communication box method. Therefore, the purpose of the present study was to investigate the acute effect of 2 different kinds of stress induced by the communication box method on the sleep patterns of rats.

Materials and Methods

Animals. Male Wistar strain rats (at 8–10 weeks of age) were obtained from Charles River (Yokohama, Japan). All animals were housed 2 rats/cage (42 cm long × 26 cm wide × 15 cm high). The animal room was maintained at 22 ± 1 °C under a 12 h/12 h light/dark cycle with lights on from 7:00 AM. Food and water were available *ad libitum*. Animal experiments were performed in compliance with the Guidelines for Animal Experimentation and with the approval of the Committee of Animal Experimentation, Ehime University School of Medicine. Every effort was made to minimize the number of animals used and their suffering.

Surgery. The animals were anesthetized by injection of sodium pentobarbital (50 mg/kg, i.p.), and electrodes for the recording of electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) were implanted. The electrodes for EEG recording, consisting of a twisted pair of stainless steel wires (tip diameter, 0.2 mm) insulated except for the last 0.5 mm of the tips, were stereotaxically implanted (SR-5, Narishige, Tokyo, Japan) in the frontal cortex and dorsal hippocampus (A: 4.3 mm, L: 2.5 mm, V: 2.5 mm) according to the stereotaxic apparatus [23]. The EEG from the cortex and hippocampus was recorded against a ground electrode placed over the frontal bone. The EMG was recorded from the neck with the same stainless steel electrodes. The EOG was recorded with a silver ball electrode (0.2 mm in diameter), which was placed in the orbit. Each electrode was connected to the pins of a small socket, which was fixed to the skull with dental cement together with 2 screws driven into the skull. Seven days were allowed for recovery from the surgery.

Stress procedures and sleep recording. The rats were then divided into 4 groups after surgery recovery, with 7 rats in each group. The 4 groups were as follows: the untreated group, the control group (exposure to communication box without any stress), the physical stress group and the psychological stress group. All animals were used only once.

Physical and psychological stress was induced using a communication box according to the method previously described [8]. This box (90 × 90 × 90 cm) was equipped with a floor grid composed of 0.5-cm-diameter stainless steel rods placed 1.3 cm apart. The box consisted of 9 small compartments (30 × 30 cm) divided by transparent plastic walls. In the current study, we used 2 compartments. Plastic plates were placed on the grid floors of 5 compartments to prevent the rats from receiving electric shocks. An electric foot shock generator (MSG-001, Toyo Sangyou, Toyama, Japan) was used to produce a scrambled electric foot shock (2 mA) through the floor grid lasting for 10 sec at intervals of 60 sec for 1 h.

Rats placed directly on the electric grid floors were used as the physical stress group, while rats placed in compartments with plastic plates on the grid floor were used as the psychological stress group. The rats in the psychological stress group could see the rats receiving the foot shock via 3 transparent acrylic panels and could perceive the sounds and smells. These rats were exposed to various emotional stimuli from the rats in the compartments with electric grid floors. These rats were only exposed to psychological stress without any physical stress.

EEG, EMG and EOG were recorded with an electroencephalograph (Model EEG 5113, Nihon Kohden,

Tokyo, Japan) while the animals were allowed to move freely from 10:00 to 16:00. Each rat was moved into the recording plastic cage ($30 \times 18 \times 24$ cm), which was placed in a soundproof and electrically shielded box ($100 \times 100 \times 100$ cm). All electrophysiological recordings were started simultaneously when the rat was put into the cage, and continued for 6 h (from 10:00 to 16:00) after two 6 h sleep recording adaptations. The signals were amplified and filtered (EEG, 0.5–30 Hz; EMG, 16–128 Hz, EOG, 0.1–30 Hz) simultaneously and stored on a computer hard disk for offline analyses. The sleep states were automatically classified by 10-s epochs as wakefulness, non-REM sleep and REM sleep by OPS023 software (Nihon Kohden, Tokyo, Japan), according to the criteria previously described [24]. The following parameters were used: sleep latency (from sleep recording to the onset of consecutive 120s sleep), REM sleep latency (from the onset of consecutive 120s sleep to the first onset of REM sleep), average duration of REM sleep episodes, total number of REM sleep episodes, total REM sleep, and total non-REM sleep over a 5 h time period. In addition, hourly total REM sleep and total non-REM sleep time were calculated during the 6 h sleep recording.

Plasma corticosterone assay. The plasma corticosterone level was measured at 0, 30, 90 and 180 min after the stress ended in all groups (n = 6), and 50 μl blood samples were drawn from the jugular vein using the Auto Blood Sampling System (DR-II, EICOM Co., Ltd., Kyoto, Japan) after 4 days of recovery from jugular vein surgery, according to the method described in our previous study [25] and another report [26]. Rats were adapted to the Auto Blood Sampling System for at least 4 h every day. Blood samples were centrifuged for 15 min at 3,000 rpm, and the separated plasma was stored at -20 °C until analysis. Plasma corticosterone was assayed by a specific commercial kit for rats (Assay Designs, Ann Arbor, MI, USA). The sensitivity of the assay was 26.99 pg/ml.

Statistical analysis. All values are presented as means ± S.E.M. Plasma corticosterone, hourly total REM sleep and non-REM sleep time during the 6 h sleep recording were analyzed by two-way analysis of variance with Tukey's test. Other parameters were analyzed by a paired Student's *t*-test or one-way analysis of variance with Tukey's test. Differences were considered to be statistically significant when $p < 0.05$.

Results

Typical EEG, EMG and EOG recordings of each stage in brain activity, wakefulness, non-REM sleep and REM sleep, are shown in Fig. 1. The wakefulness stage consisted of low-voltage fast waves in the frontal cortex, rhythmical desynchronization of hippocampal theta waves, high activity of EMG and the appearance of eye movements. The non-REM sleep stage consisted of high voltage slow waves in the frontal cortex, synchronization of hippocampal theta waves, low activity of EMG and the disappearance of eye movements. The REM sleep stage consisted of low-voltage fast waves in the frontal cortex, rhythmical desynchronization of hippocampal theta waves similar to that in the wakefulness stage, but extremely low activity of EMG and the appearance of rapid eye movements.

Fig. 2 shows the effects of physical and psychological stress on hourly total REM sleep in rats after stress. Columns represent the mean ± S.E.M (n = 7). The physical and psychological stress caused hourly total REM sleep to deviate in nearly opposite ways from the total REM sleep observed in the control and untreated groups. In the physical stress group, hourly total REM sleep was significantly inhibited until 5 h after the stress compared to the control group; however, the psychological stress group showed a significant increase in the hourly total REM sleep, which persisted for 4 h. In addition, hourly total REM sleep in the control group was not significantly different from that of the untreated group.

The effects of physical and psychological stress on hourly total non-REM sleep in rats are shown in Fig. 3. Hourly total non-REM sleep decreased from 0–1, 1–2 and 3–4 h but not in other time periods in the physical stress group. In contrast, in the psychological stress group, hourly total non-REM sleep decreased significantly only during the 2–3 h time period compared to the untreated group, but not compared to the control group. There was no significant difference between the untreated and control groups.

Physical stress increased sleep latency significantly ($p < 0.05$) compared to both the untreated and control groups; however, it did not affect REM sleep

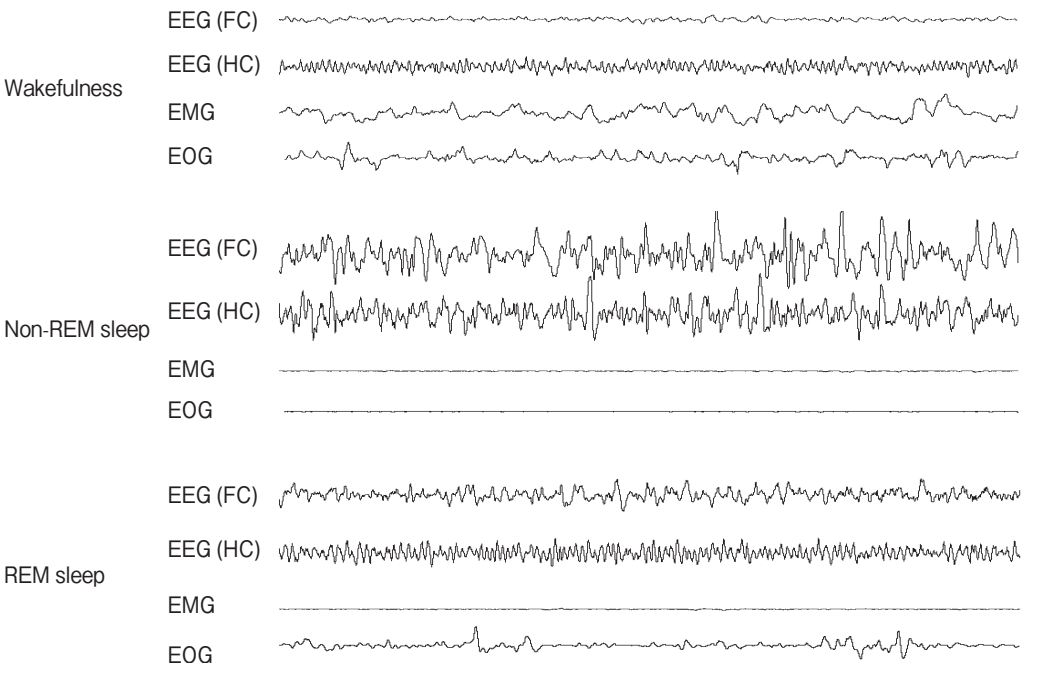

Fig. 1 Typical recordings of each stage of wakefulness and sleep in rats. EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; FC, frontal cortex; HC, dorsal hippocampus. Vertical bar: 200 μV, horizontal bar: 1 sec in the panel in right corner.

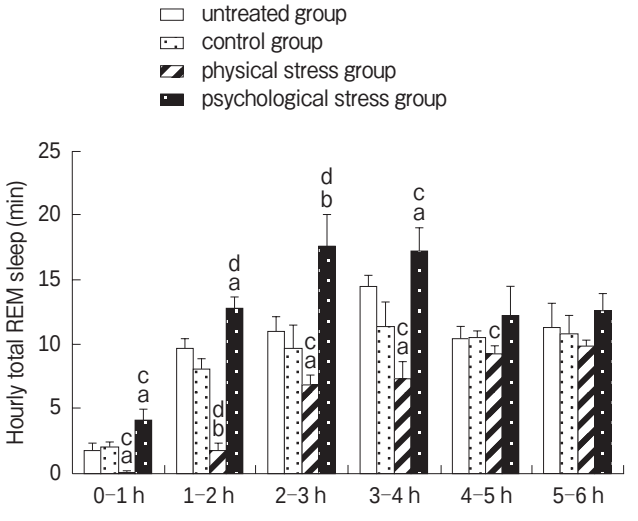

Fig. 2 Effects of physical and psychological stress on hourly total REM sleep in rats. $^{a}p < 0.05$; $^{b}p < 0.01$ compared to the untreated group. $^{c}p < 0.05$; $^{d}p < 0.01$ compared to the control group.

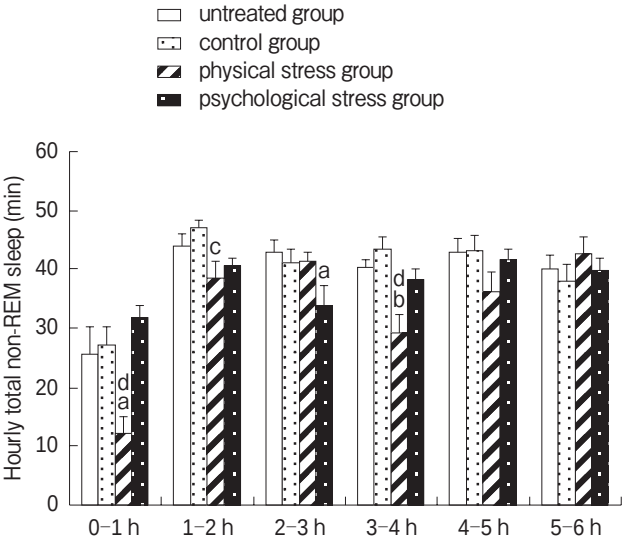

Fig. 3 Effects of physical and psychological stress on hourly total non-REM sleep in rats. $^{a}p < 0.05$; $^{b}p < 0.01$ compared to the untreated group. $^{c}p < 0.05$; $^{d}p < 0.01$ compared to the control group.

latency. On the other hand, psychological stress shortened the REM sleep latency significantly ($p < 0.05$) compared to the untreated and control groups. However, it did not affect sleep latency (Fig. 4).

Fig. 5 shows total REM and total non-REM sleep calculated over a 5 h time period. Physical stress inhibited both total REM sleep and total non-REM sleep significantly compared to the untreated and control groups. In contrast, psychological stress enhanced total REM sleep significantly compared to the untreated ($p < 0.05$) and control groups ($p < 0.01$), but did not enhance total non-REM sleep.

The total number and average duration of REM sleep episodes over a 5 h time period under physical and psychological stress are shown in Figs. 6 and 7, respectively. In the physical stress group, the total number of REM sleep episodes was reduced significantly ($p < 0.05$) compared to the untreated and control groups; however, psychological stress had no effect on the total number of REM sleep episodes as shown in Fig. 6. On the other hand, in the physical stress group, the average duration of REM sleep episodes was inhibited significantly compared to the untreated group but not the control group; however, in the psychological stress group, the average duration of REM sleep episodes was significantly prolonged compared to the untreated and control groups as shown in Fig. 7 ($p < 0.05$).

In Fig. 8, the total sleep over a 5 h time period was also calculated. In the physical stress group, the total sleep was inhibited significantly compared to the untreated and control groups ($p < 0.05$). Total sleep was not influenced by psychological stress.

In Fig. 9, plasma corticosterone was tested at 0, 30, 90 and 180 min after stress. In the physical stress group, plasma corticosterone increased significantly at 0 and 30 min after the physical stress compared to the untreated and control groups ($p < 0.01$),

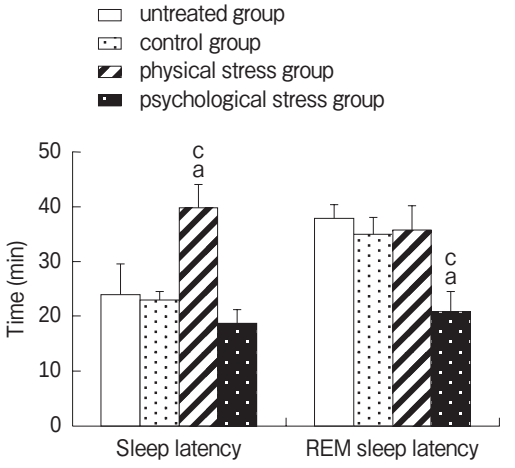

Fig. 4 Effects of physical and psychological stress on sleep latency and REM sleep latencies in rats. [a]$p < 0.05$ compared to the untreated group. [c]$p < 0.05$ compared to the control group.

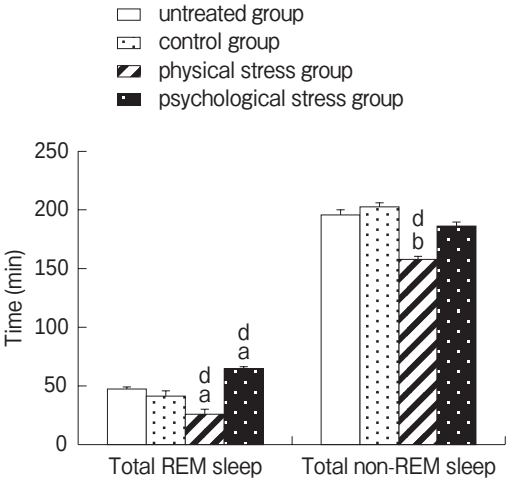

Fig. 5 Effects of physical and psychological stress on total REM sleep and non-REM sleep over 5 h of sleep recording in rats. [a]$p < 0.05$; [b]$p < 0.01$ compared to the untreated group. [d]$p < 0.01$ compared to the control group.

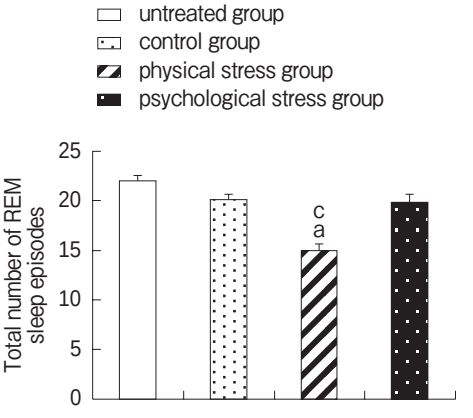

Fig. 6 Effects of physical and psychological stress on total number of REM sleep episodes over 5 h of sleep recording in rats. [a]$p < 0.05$ compared to the untreated group. [c]$p < 0.05$ compared to the control group.

and then returned to the control level after 90 min. However, the plasma corticosterone did not increase significantly after the psychological stress.

Discussion

In the present experiment, the acute effect of physical and psychological stress induced by the communication box method on sleep patterns in rats was investigated. Interestingly, physical and psychological stress had almost opposite effects on sleep in rats. Psychological stress enhanced hourly total REM sleep over 6 h of sleep recording, particularly in the first 4 h. However, hourly total non-REM sleep was almost unaffected. On the other hand, hourly total REM sleep and non-REM sleep were inhibited in the first 5 or 4 h. These results indicated that the effects of physical and psychological stress on sleep lasted up to 4 or 5 h. Thus the opposite effects of physical and psychological stress on sleep could not be simply attributed to the variation of sleep latency in the first hour (Fig. 4). Further results also showed that total REM sleep over 5 h declined due to the reduction of the total number of REM sleep episodes in the physical stress group. These results confirmed the findings of previous reports [9] which showed that the inhibition of total REM sleep by foot shock was related to the total number of REM sleep episodes in the 6 h of sleep recording after the stress. Another research group also found that REM sleep was reduced for some hours after inescapable electrical foot shock, and this reduction was not followed by a rebound [27]. Although measurements over longer periods of time are necessary, this result could explain why there is no REM sleep rebound several hours after the reduction of REM sleep in the physical stress group.

In contrast, hourly total REM sleep was increased in the psychological stress group using the communication box method. The significant enhancement of total

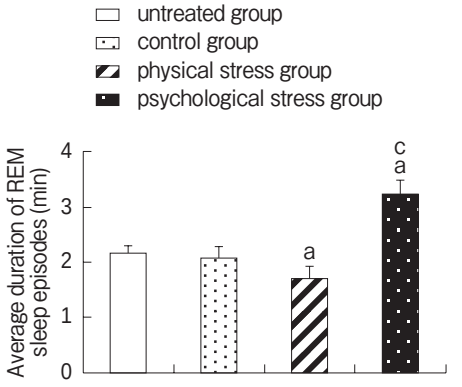

Fig. 7 Effects of physical and psychological stress on average duration of REM sleep episodes over 5 h of sleep recording in rats. $^{a}p < 0.05$; compared to the untreated group. $^{c}p < 0.05$; compared to the control group.

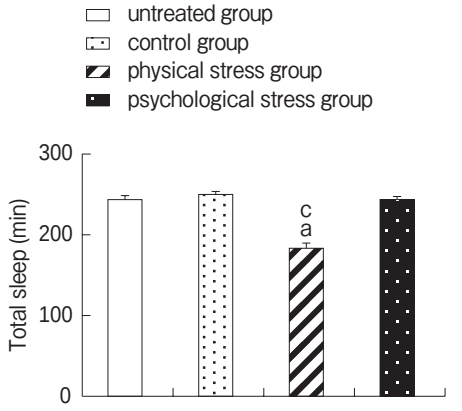

Fig. 8 Effects of physical and psychological stress on total sleep over 5 h of sleep recording in rats. $^{a}p < 0.05$ compared to the untreated group. $^{c}p < 0.05$compared to the control group.

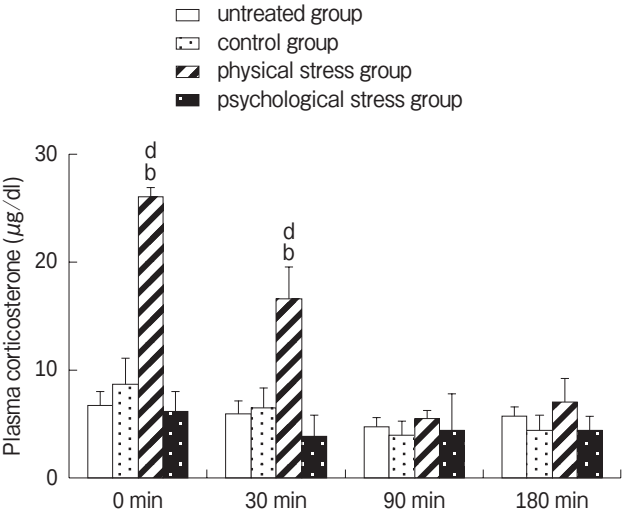

Fig. 9 Plasma corticosterone after physical and psychological stress in rats. $^{b}p < 0.01$ compared to the untreated group. $^{d}p < 0.01$ compared to the control group.

REM sleep over a 5 h period that was induced by psychological stress was due not only to reducing the REM sleep latency, but also to the prolongation of the average duration of REM sleep episodes. On the other hand, one group found that 1 h of social conflict increased EEG slow wave sleep in the subsequent 6 h of sleep [19]. Contextual fear, another classical psychological stress, caused an immediate reduction of total REM sleep in rats [20, 21]. One group further reported that the reduction of total REM sleep by contextual fear was related to the decrease in the total number of REM sleep episodes in the 4 h of sleep recording performed after this type of stress [20], whereas in our research, the increase of total REM sleep over a 5 h period after the psychological stress was due to the average duration of the REM sleep episodes. Although these studies are difficult to compare directly with the present study due to differences in species, age and environment, different mammal species have shown a variety of REM sleep amounts ranging from 40 min to 6 h per day [28]. Thus, the different effects of psychological stresses other than our psychological stress on sleep patterns suggested that the change in REM sleep due to psychological stress may be related to the attribution of the psychological stresses.

In addition, rats in the control group, physical stress group and psychological stress group that were exposed to the communication box for 1 h always stayed awake in the apparatus; however, there was no significant difference in sleep pattern between the untreated and control group during the 5 h following this treatment. These results are consistent with previous reports, which have shown that mild stress or sleep deprivation for 1 or 2 h did not modify sleep parameters in rats [29, 30]. On the other hand, although physical stress inhibited total sleep due to a reduction of total REM sleep and non-REM sleep, psychological stress hardly affected total sleep (Fig. 8). These results also indicated that the increase of total REM sleep induced by psychological stress during the 5 h following the stress administration could not be simply attributed to sleep rebound.

Previous research has shown that changes of sleep patterns in response to stress could be mainly attributed to disorder of the HPA axis and neurotransmitters [9, 12, 13]. With regard to the HPA axis, the plasma corticosterone level, which reflects HPA axis activity, is most frequently used as an index of experimental sleep and anxiety [31, 32]. Thus, the plasma corticosterone was tested after stress, and in the physical stress group it had increased at 0 and 30 min after foot shock stress, a result that was consistent with many other reports [7, 9, 33]. In addition, plasma corticosterone returned to the control level at 90 min. However hourly total REM sleep was inhibited until 5 h after physical stress. This discrepancy may be attributed to other neurons activated by physical stress. In addition to the HPA axis, neurotransmitters such as orexin, galanin, serotonin and dopamine are also considered to participate in sleep regulation [34, 35], Serotonin and dopamine were particularly increased by physical stress [36, 37], and were related to the inhibition of REM sleep [38, 39]. Thus, it is conceivable that the activated HPA axis and some neurotransmitters may have participated in sleep regulation in the present physical stress group.

In the psychological stress group, we also found that the plasma corticosterone was not increased significantly in comparison to the untreated and control groups after psychological stress, and some reports have shown that the corticosterone level of rats was not changed by acute psychological stress in comparison with the level in rats receiving foot shock stress at a different intensity [3, 7, 31]. The above results suggested that the psychological stress induced by the communication box was not directly related to the electrical intensity of the foot shock in the physical stress group, and corticosterone levels in the psychological stress group also did not increase directly due to the changed intensity of the foot shock in the physical stress group after the stress. Thus, in the present study, the HPA axis was not activated in the psychological stress group during sleep recording after stress. The effect of psychological stress on sleep patterns in rats could not be attributed to the HPA axis alone. Another group also reported that REM sleep deprivation stress for 3 or 6 h which increased REM sleep could not activate the HPA axis. This result was similar to our results involving psychological stress. This research group further found that REM sleep deprivation stress was related to galanin but not arginine vasopressin, oxytocin or orexins [34]. However, whether galanin participates in sleep regulation must be studied further in the present psychological stress group.

In the present study, physical and psychological stress had almost opposite effects on the sleep patterns of rats. Total REM sleep and total non-REM sleep over a 5 h period were inhibited by physical stress, whereas total REM sleep was increased in the psychological stress group. On the other hand, in the physical stress group the changes in sleep patterns were related to the activation of the HPA axis and several neurotransmitters. In contrast, the changes in sleep patterns in the psychological stress group may be related more to non-HPA axis factors; therefore, sleep patterns, particularly REM sleep in response to physical stress and psychological stress, are probably regulated by 2 different pathways.

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