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A mouse model mimicking human first night effect for the evaluation of hypnotics

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ABSTRACT

In humans, a first night effect (FNE) is characterized by increased sleep latency and decreased total sleep time in an unfamiliar environment, but the mechanism and treatment options for this universally experienced acute insomnia are unclear. We continuously recorded electroencephalography (EEG) and electromyogram (EMG) and measured plasma corticosterone levels to develop a mouse FNE model by inducing acute insomnia in mice that have been placed in unfamiliar cage environments. The sleep latency of mice 'moved to clean cages' (MCC) was longer than that for mice 'moved to dirty ones' (MDC). As compared to MDC mice, MCC mice showed stronger decreases in the amount of non-rapid eye movement (non-REM, NREM) and REM sleep, with a lower power density of NREM sleep, increased fragmentation and decreased stage transitions from NREM sleep to wake, and higher variation in plasma corticosterone levels. Treatment of MCC mice with zolpidem, diazepam, raclopride, pyrilamine, except SCH23390 shortened NREM sleep latency. In addition, zolpidem significantly increased NREM and REM sleep with the increase in slow wave activity (1.00–2.75 Hz), while raclopride significantly increased NREM and REM sleep without changing the EEG power density in MCC mice, whereas diazepam increased sleep with a drastic decrease in power density of the frequency band between 1.00 and 4.00 Hz, diazepam also increased the frequency band between 9.75 and 24.75 Hz during NREM sleep. These results indicate that a MCC mouse can mimic a FNE phenotype of humans and that zolpidem and raclopride may be useful drugs to prevent acute insomnia, including FNE.

1. Introduction

Insomnia is a highly prevalent condition ranging from inability to fall asleep promptly to a total lack of sleep. Acute insomnia occurs very frequently when people are in a new and unfamiliar environment where they experience significant difficulties with sleep initiation. First-night effect (FNE) is often observed in unfamiliar environments and considered to result from a person's lack of adaptation to the new sleeping environment (Rechtschaffen and Verdone, 1964). In basic human sleep research, FNE has often been used to study acute insomnia (Kitaoka et al., 2009; Suetsugi et al., 2007). Although acute insomnia is usually transient, it can progress to long-term, chronic insomnia in one third of those affected (Riemann et al., 2009), and 10–15% of patients are eventually diagnosed with moderate to severe stages of the disorder (Morphy et al., 2007). Effective treatments for acute insomnia, including FNE, are still unclear, one reason being the lack of a suitable animal model for drug development and evaluation.

Laboratory animals routinely undergo cage cleaning as part of normal husbandry, an intervention that produces significant alterations in their behaviors, including sleep disturbances (Cano et al., 2008; Tang et al., 2005). In the present study, we sought to determine whether sleep loss in rodents after cage change, as a response induced by an unfamiliar environment and/or the result of transient stress, may provide an animal model for mimicking human FNE. We found that mice moved to a clean cage (MCC) increased sleep latency more than mice moved to a dirty cage (MDC). We then investigated the ability of hypnotics including zolpidem, diazepam, as well as other sleep-inducing substances, pyrilamine, SCH23390, and raclopride, to improve sleep disturbances in MCC mice. Our results indicated that zolpidem and raclopride are highly effective in preventing FNE in MCC mice.

Abbreviations: BZ, benzodiazepine; D_1R, dopamine D_1 receptor; D_2R, dopamine D_2 receptor; EEG, electroencephalography; EMG, electromyogram; FNE, first night effect; H_1R, histamine H1 receptor; KO, knock out; MCC, mice moved to clean cages; MDC, mice moved to dirty cages; NREM, non-rapid eye movement; REM, rapid eye movement.

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2. Materials and methods

2.1. Animals

Male inbred C57BL/6J mice (Experimental Animal Center, Fudan University), 10 weeks old and weighing 24 ± 2 g, were used at the beginning of the experiments. Ambient room temperature was maintained at a constant temperature (23 ± 1 °C) and relative humidity (60 ± 5%) on an automatically controlled 12 h/12 h light/dark cycle (lights on at 08:00). Water and food were available ad libitum. All experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Fudan University Committee on Animal Care and Use. Additionally, all efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data.

2.2. Drugs

Zolpidem, pyrilamine maleate, SCH-23390, and raclopride were purchased from Sigma-Aldrich (Saint Louis, MO, USA), and diazepam from Wako Pure Chemical Industries (Osaka, Japan). All drugs were freshly prepared prior to use, and an injection volume (20 ml/kg) was kept constant through the experiments. The dosage selections, route of drug administration, and injection time of different compounds were based on preliminary experiments and pharmacokinetic considerations. Zolpidem and diazepam were dissolved in saline containing 0.3% Tween 80 and all other drugs were dissolved in saline.

2.3. Polygraphic recording and behavioral state analysis

The implant surgery was performed 10 days after the mice arrived from the supplier and they were allowed a post-surgery recovery period of 10 days. Following the recovery period after the surgery, the mice were housed individually in transparent barrels and habituated to the recording cable for 4 days before polygraphic recordings. Then the polygraphic recordings were recorded continuously for 48 h in freely moving mice.

Cortical EEG and EMG signals were first amplified and filtered (EEG, 0.5–30 Hz; EMG, 20–200 Hz) and then digitized at a sampling rate of 128 Hz and recorded by using SleepSign® (Kissei Comtec, Japan) as described earlier (Huang et al., 2005, 2006). When completed, polygraphic recordings were automatically scored off-line by 4 s epochs as wakefulness, NREM, and REM sleep according to standard criteria (Huang et al., 2001; Yan et al., 2011). As a final step, defined sleep–wake stages were examined visually, and corrected, if necessary.

2.4. Cage change procedure and drug treatment

After 24 h uninterrupted baseline sleep recording, cage change was performed at 10:00 AM (2 h after lights on, when the sleep pressure is high) (Vyazovskiy et al., 2008) on the experimental day. Each mouse was moved either into a clean cage with fresh paper-chip bedding, or a dirty cage previously occupied by another mouse for 5 days to find out the best condition for establishing the FNE mouse model. In addition, mice that only received tail handling and put back to the recording cage served as control. For evaluating effects of drugs on FNE mice, zolpidem (1.25, 2.5, or 5 mg/kg), raclopride (0.5, 1, or 2 mg/kg), diazepam (3 mg/kg), SCH-23390 (30 μg/kg), pyrilamine (5 mg/kg) or vehicle control was injected intraperitoneally, and the mouse then placed immediately into a clean cage with fresh paper-chip bedding at 10:00 AM on the experimental day, following the baseline sleep recording. Afterwards, sleep recordings were obtained for another 24 h after the drug treatment and cage change. All mice were used only once.

2.5. Blood sampling and corticosterone assay

To test the degree to which the hypothalamus–pituitary–adrenal axis was involved in the insomnia observed after placing the mice in a new cage environment, we measured the levels of circulating corticosterone. Blood sampling was performed by cardiac puncture under deep anesthesia immediately after moving mice to another cage and at 30, and 120 min after the mice were placed in a clean or dirty cage. Every blood sampling was conducted within 2 min, which is rapid enough to ensure that the stress imposed in the blood-sampling procedure did not affect corticosterone levels in plasma (Riley, 1960). To obtain the basal corticosterone levels, mouse blood were collected from their home cages at the corresponding time point, where they were undisturbed. All the mice here were used only once and all of the blood samples were collected in the EDTA-coated tubes on ice and immediately centrifuged at 15,000 rpm for 5 min, 4 °C. Plasma samples were collected into the sterilized tubes and frozen at −80 °C until assay. Plasma corticosterone was measured with specific enzyme immunoassay kits (Enzo life science, USA), following manufacturers' protocol.

2.6. Statistical analysis

All results were expressed as means ± SEM (n = 5–8). Time course changes in the amounts of sleep–wake, sleep latency, number and duration of sleep/wake bouts in light/dark phases were compared among groups by using a one-way ANOVA followed by the post hoc Tukey test or non-paired, two-tailed student's *t* tests. In all cases, $p < 0.05$ was taken as the level of significance.

3. Results

3.1. Increased sleep latency in MCC and MDC mice

As shown in Fig. 1A–C, typical examples of EEG/EMG and hypnogram showed a long continued period of wakefulness when a mouse was moved to a clean or dirty cage, or after tail handling in its host cage. The latency to sleep onset, defined as the time from the mouse being moved into another cage to the appearance of the first NREM or REM sleep episode of 20 s or more (Liu et al., 2012; Qiu et al., 2009), was significantly increased in MCC and MDC mice. As compared with the tail-handled control mice, the latency to NREM ($F_{2, 15} = 130.63$, $p < 0.01$) and REM ($F_{2, 15} = 31.08$, $p < 0.01$) sleep was increased in both MCC and MDC mice (Fig. 1D). In addition, MCC mice exhibited a longer latency to both NREM (91.8 ± 1.6 min vs. 69.4 ± 2.8 min, $p < 0.01$) and REM (113.5 ± 6.6 min vs. 91.6 ± 4.1 min, $p < 0.01$) sleep than MDC mice.

3.2. Severe sleep disturbance in MCC mice

Under basal conditions, all mice exhibited a clear circadian sleep–wake rhythm with more sleep during the light period than during the dark period (Fig. 2A). Tail handling at 10:00 (2 h after lights on) induced wakefulness that lasted for little more than 30 min. By contrast, MCC and MDC mice showed the absence of both NREM and REM sleep for more than 1 h after the cage change (Fig. 2B). Interestingly, when compared to MCC mice, MDC mice showed an increment in NREM ($t_{1, 12} = 3.81$, $p = 0.02$) and REM ($t_{1, 12} = 2.83$, $p = 0.02$) sleep during the fourth hour after cage change (Fig. 2B). The total amount of NREM ($F_{3, 20} = 13.08$, $p < 0.01$), and REM ($F_{3, 20} = 31.15$, $p < 0.01$, Fig. 2C) sleep decreased between the second hour after cage change, and the following 3 h, as compared to the baseline. When compared to tail handled mice, only the total amount of NREM sleep of the MCC mice significantly decreased ($F_{3, 20} = 13.08$, $p = 0.02$, Fig. 2C). The mean duration of NREM and REM sleep during 4 h increased 1.16-fold and 1.27-fold, respectively, in the MDC mice, while the mean duration of REM sleep decreased to 79.21% in MCC mice, as compared to tail-handled mice (Fig. 2D). The number of episodes of