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Research report

Paradoxical sleep deprivation modulates depressive-like behaviors by regulating the MAOA levels in the amygdala and hippocampus

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ABSTRACT

Paradoxical sleep is closely associated with depression, and brain monoamine oxidase A (MAOA) plays an important role in depression. However, the precise relationship between sleep and depression and the role of MAOA in this process remains unknown. Therefore, we established a paradoxical sleep deprivation model using the "multiple small platforms over water" protocol. Mice deprived of paradoxical sleep for 3 days showed no depressive-like behaviors; however, mice deprived of paradoxical sleep deprivation for 5 days (P5d) showed decreased locomotive activity in the first 3 days after P5d. Additionally, the P5d mice showed depressive-like behaviors one week after P5d, with a longer immobility time and a decreased sucrose preference rate. In addition, the levels of the MAOA protein and mRNA in the amygdala and hippocampus significantly increased. Furthermore, the immobility time and sucrose preference rate of P5d mice recovered when the mice were injected with phenelzine. The P5d mice displayed depressive-like behaviors, which were likely modulated by the MAOA levels in the amygdala and hippocampus.

1. Introduction

Sleep accounts for more than one-third of the human lifetime, and it plays an important role in various physiological functions, such as metabolism (Xie et al., 2013), the endocrine system (Gold et al., 2013), the immune system (Irwin et al., 2008), cognition (Euston and Steenland, 2014; Muehlhan et al., 2014) and moods (Baglioni et al., 2010; Kamphuis et al., 2012). Therefore, sleep deprivation is believed to cause serious damage (Rechtschaffen et al., 1983). Forty-eight hours of paradoxical sleep deprivation (PSD) induce a two-fold increase in cortisol levels, and 72 h of PSD promotes the expression of the interleukin gene in mice (Kang et al., 2013).

Major depression, also known as depressive disorder, is a typical mood disorder in which the patients exhibit a persistent depressed state. The morbidity of depression in the United States is 16.2%, and a gradual increasing trend has been observed (Slattery and Cryan, 2012). People with a poor sleep quality are more likely to develop depression than individuals with a good sleep quality (Szklo-Coxe et al., 2010). Insomnia is the first symptom of depression to appear and the last symptom to disappear (DeWeerdt, 2013). A short duration of sleep deprivation has been shown to quickly and substantially improve depression symptoms (with an effectiveness of 60%). However, this improvement does not last long (Allard et al., 2007; DeWeerdt, 2013); as soon as sleep resumes, depressive symptoms rapidly reappear. Researchers have not clearly determined whether sleep deprivation leads to depression.

Monoamine oxidase A (MAOA) is a key enzyme involved in degrading monoamine neurotransmitters in animals and humans (Barnett et al., 2011). Different MAOA upstream variable number of tandem repeats (uVNTR) variants are associated with differences in the transcriptional activity of the MAOA promoter (Deckert et al., 1999), which result in different levels of expression of the MAOA gene. The allele of the MAOA uVNTR polymorphism that results in high levels of expression (the high activity-related allele) has been reported to be associated with depression-induced suicide in males (Du et al., 2002). In this study, we used the "multiple small platform over water" protocol to establish the PSD model and tested the mice using the open field test (Leroy et al., 2009), the forced swimming test (FST) (Gao et al., 2014) and the sucrose preference test (Brenes Saenz et al., 2006) after paradoxical sleep deprivation. Short-term PSD (3 days) caused anxiety-like behaviors, and prolonging PSD to 5 days (P5d) caused depressive-like behaviors in the mice. Additionally, the depressive-like behaviors

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observed in the P5d mice were abolished by the MAOA inhibitor phenelzine.

2. Results

2.1. Changes in behavior induced by 3 days of paradoxical sleep deprivation

Twenty mice were divided into two groups (the CON group and P3d group). The mice were placed in their original cages and allowed to rest for 24 h after P3d; then, the mice were assessed using the open field test on day 2 and the forced swimming test (FST) on day 3. The mice were simultaneously habituated to the sucrose preference test from days 1 to 3, and their sucrose preference rates were assessed on days 4 and 5 after P3d. When the mice were subjected to P3d, their locomotive activity (total distance traveled in the open field test) was not different from the CON group ($t = 0.981$, $P = 0.343$, Fig. 1A). However, the P3d group spent less time in the center of the open field than the CON group ($t = -4.870$, $P = 0.000$, Fig. 1B), but the time spent in the open and closed arms of the elevated plus maze was not different (time spent in the open arm: $t = 0.143$, $P = 0.888$; time spent in the closed arm: $t = 0.833$, $P = 0.415$, Fig. 1C and D). The P3d and CON groups did not exhibit depressive-like behaviors (time spent immobile in the FST: $t = 0.143$, $P = 0.888$; sucrose preference rate in the sucrose preference test: $t = 0.833$, $P = 0.415$, Fig. 1E and F). Thus, the P3d mice showed increased alertness in new situations but did not exhibit anxiety-like or depressive-like behaviors.

2.2. Changes in behavior after 5 days of paradoxical sleep deprivation

One hundred and eighty mice were divided into 3 groups: baseline (BL) group, control (CON) group and P5d group. The mice were placed in their original cages, allowed to rest for 24 h after P5d, and then were assessed in the open field test for 10 days (n = 6 mice/-day/group; each mouse was tested only once, for a total of 3 groups × 6 mice × 10 day). Beginning on the day the animals showed no differences in locomotive activity between groups, the mice were assessed using the FST (n = 6 mice/group/day; each mouse was tested only once, with a total of 3 groups × 6 mice × 7 days). All remaining mice were simultaneously assessed using the sucrose preference test starting on day 4 after P5d (n = 18 mice/-group; the sucrose preference test was performed on days 7 and 8 after P5d). When the mice were subjected to 5 days of paradoxical sleep deprivation, their locomotive activity (total distance traveled in the open field test) significantly decreased for approximately 3 days after P5d and returned to normal levels beginning on day 4 ($P < 0.05$, Fig. 2A). The 3 groups did not display differences in the time spent in the center of the open field ($P > 0.05$, Fig. 2B). Interestingly, the immobility time of the P5d mice in the FST was

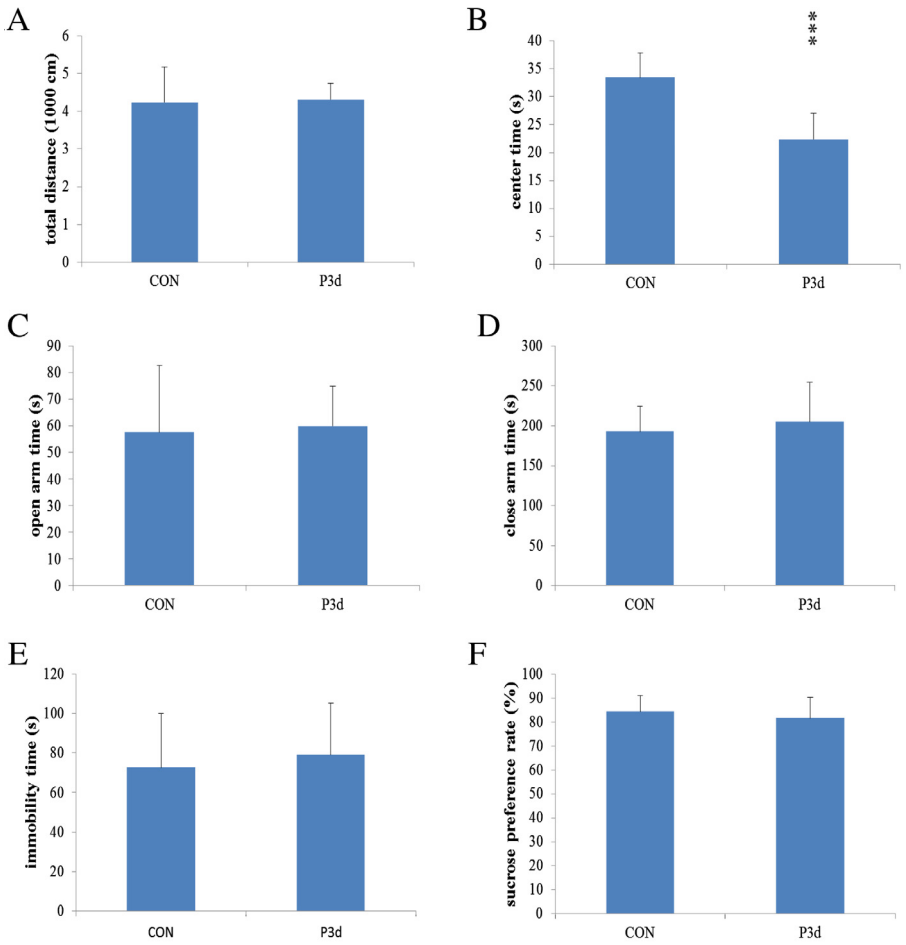

Fig. 1. Open field, forced swimming and sucrose preference tests after exposure to P3d. A: The total distance traveled by the P3d mice was similar to the CON mice (4240.75 ± 928.86 vs 4307.75 ± 443.43). B: The P3d mice spent less time in the center of the open field than the CON mice (22.38 ± 4.65 vs 33.44 ± 4.44). C, D: The P3d mice and CON group spent similar amounts of time in the open and closed arms of the elevated plus maze (57.63 ± 24.94 vs 59.92 ± 14.98 and 192.69 ± 31.66 vs 205.06 ± 48.99, respectively). E, F: The immobility times (90.91 ± 22.03 vs 88.09 ± 33.62) and sucrose preference rates (84.30 ± 6.63 vs 81.55 ± 8.71) of the two groups were similar. n = 10 in each group, $^{***}P < 0.001$.