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Effect of castration on the susceptibility of male rats to the sleep deprivation-induced impairment of behavioral and synaptic plasticity

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ABSTRACT

In both human and animal studies, the effect of sleep deficiency on cognitive performances has mostly been studied during adulthood in males, but very little data exist concerning the effects of poor sleep in gonadal hormones-depleted status, such as aging or gonadectomized (GDX) male animal models. The present study investigated the potential modulatory effects of the endogenous male sex hormones on the 48 h REM sleep deprivation (SD)-induced cognitive and synaptic impairments by comparing the gonadally intact with castrated male rats, a rodent model of androgen-deprived male animals. The multiple platform method was used for inducing REM-SD and spatial performances were evaluated using Morris water maze (MWM) task. Early long-term potentiation (E-LTP) was measured in area CA1 of the hippocampus and PCR and western blotting assays were employed to assess brain derived neurotrophic factor (BDNF) gene and protein expression in the hippocampus. To reveal any influence of sleep loss on stress level, we also evaluated the plasma corticosterone levels of animals. Regardless of reproductive status, REM-SD significantly disrupted short-term memory and LTP, as well as hippocampal BDNF expression. The corticosterone levels were not significantly changed following REM-SD neither in intact nor in GDX male rats. These findings suggest that depletion of male sex steroid hormones by castration does not lead to any heightened sensitivity of male animals to the deleterious effects of 48 h REM-SD on cognitive and synaptic performances.

1. Introduction

The average amount of sleep per 24 h has declined by 1.5 h over the past century, a figure that seems to continue to increase (Rajaratnam & Arendt, 2001). A great body of evidence from both human and rodent studies suggests that sleep has a remarkable role in certain types of learning and memory (Diekelmann & Born, 2010). It was primarily believed that sleep after a learning task (post-training sleep) contributes to the consolidation of new information into long-term memory (Stickgold & Walker, 2007). Accordingly, sleep deprivation (SD) following a learning task causes subsequent memory deficits in both humans (Stickgold, James, et al., 2000) and rodents (Smith, Conway, et al., 1998). However, as post-training sleep, sleep prior to learning (pre-training sleep) can also improve memory consolidation by promoting the capability of related neuronal systems to process new information and encode new memories (Stickgold & Walker, 2007). Human studies show that total SD for a single night disrupts different kinds of subsequent memory (Van Der Werf, Altena, et al., 2009; Yoo, Hu, et al., 2007). Numerous animal studies also show that one to five days of SD before training task can lead to impairment in subsequent behavioral efficiency (Alvarenga, Patti, et al., 2008; Hagewoud, Havekes, et al., 2010; McDermott, LaHoste, et al., 2003; Ruskin & Lahoste, 2008; Ruskin, Liu, et al., 2004; Silva, Chehin, et al., 2004; Tiba, Oliveira, et al., 2008). In parallel with these alterations in cognitive performances, a lot of cellular

Abbreviations: REM, rapid eye movement; GDX, gonadectomized; SD, sleep deprivation; MWM, Morris water maze; WP, wide platform; LTP, long-term potentiation; BDNF, brain derived neurotrophic factor; fEPSPs, field excitatory post synaptic potentials; PPF, paired-pulse facilitation.

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and molecular correlates of membrane excitability and synaptic plasticity within the hippocampus have been shown to be affected by SD (Guzman-Marin, Ying, et al., 2006; McDermott et al., 2003; Ravassard, Pachoud, et al., 2009).

The effects of sleep deficiency on cognitive functions have frequently been investigated during adulthood in both human and animal studies but very few reports exist concerning the effects of poor sleep in gonadal hormones-depleted status (eg, androgen deprivation therapy, aging, gonadectomized animal models, or postmenopausal women). The effect of sleep loss on physical (Goldman, Stone, et al., 2007) and cognitive performances (Blackwell, Yaffe, et al., 2006) of postmenopausal women has been explored, but to our knowledge, to date no study has examined the effects of poor sleep on cognitive functions of androgen-depleted status. A few available studies regarding the effects of SD in elderly subjects suggest that the aged men may be more susceptible to the negative effects of sleep loss on cognitive performances (Webb, 1985; Webb & Levy, 1982).

Robust evidence suggests the potential neurotrophic and neuroprotective effects of sex steroid hormones in the nervous system (Pike, Carroll, et al., 2009; Pike, Nguyen, et al., 2008). Testosterone levels are decreased in aged men (Nankin & Calkins, 1987) and it has been shown to have protective potentials against a variety of neuronal insults, brain injuries in experimental models, as well as cognitive and neurodegenerative disorders (Bialek, Zaremba, et al., 2004; Cherrier, Matsumoto, et al., 2005a, 2005b; Roglio, Bianchi, et al., 2007). Accordingly, it is plausible that the stronger effects of SD at older age might be the consequence of lower levels of testosterone. Therefore, in light of the fact that chronic SD is a common problem in industrialized societies (National Sleep Fundation, 2005) and that age-related testosterone depletion in men may result in the increased susceptibility to the negative effects of sleep loss, it is important to fully understand the responsivity of androgen-depleted subjects to the impairing effects of SD on cognitive performances. In the present study, we compared the gonadally intact male with gonadectomized (GDX) rats to examine any potential protective effects of endogenous male sex steroid hormones against the 48 h REM-sleep deprivation-induced cognitive and synaptic modulations.

Brain-derived neurotropic factor (BDNF), as the second member of neurotrophin family, has been shown to strongly affect synaptic plasticity, as well as learning and memory processes (Cunha, Brambilla, et al., 2010). Several lines of evidence suggest that BDNF is a potential mediator for the central effects of gonadal steroid hormones (Rasika, Alvarez-Buylla, et al., 1999; Scharfman & MacLusky, 2006). There has been, therefore, a long history of studies showing the extensive similarities between the actions of sex steroids and BDNF in the CNS (Scharfman & Maclusky, 2005; Yang & Arnold, 2000).

Along these lines of evidence, in this study, we first aimed to compare the extent of the effects of 48 h REM-SD on cognitive functions between intact and GDX male rats in Morris water maze (MWM) and then to determine the possible cellular and molecular mechanisms responsible for REM-sleep deprivation-induced modulations of memory performances, we investigated the synaptic efficacy by measuring long-term potentiation (LTP) and BDNF expression in the hippocampus of the experimental groups.

2. Experimental protocols

2.1. Animals

Adult male Sprague-Dawley rats, (200–250 g, 10–12 weeks of age) were purchased from the colony maintained by Kerman Neuroscience Research Center Animal Facility. Animals were kept in groups of four in the Plexiglas cages with free access to food and water and housed in a climate-controlled room (23 °C ± 1 °C) on a 24-h light-dark cycle (lights-on 07:00–19:00 h). In this study, three sets of intact male and GDX animals were submitted to SD (narrow platform), wide platform (WP; sham groups), or maintained in home cages as controls for behavioral, electrophysiological, and molecular experiments. All experimental protocols and animal handling procedures were in accordance with the Animal Ethics Committee of Kerman Neuroscience Research Center (EC/KNRC/89/46).

2.2. Gonadectomy

Bilateral gonadectomy was carried out under general anesthesia (60 mg/kg ketamine and 10 mg/kg xylazine). All the gonadectomized rats were at the same ages as the gonadally intact animals and entered in the experiments four weeks after the surgery to insure that all gonadally synthesized steroids had been cleared from circulation.

2.3. REM sleep deprivation

REM sleep deprivation was induced as described previously (Hajali, Sheibani, et al., 2012, 2015; Joukar, Ghorbani-Shahrbabaki, et al., 2013). In this study, animals were sleep deprived for 48 h using the multiple platforms model. It started and ended somewhere in the beginning of the light phase and the room was maintained under controlled temperature (23 ± 1 °C) and a light–dark cycle (lights on 07:00–19:00 h). The procedure involves placing 4 rats from a same group in a water tank (90 cm × 50 cm × 50 cm) containing 10 round platforms (7 cm diameter, 10 cm height, rising 2 cm above the water level) arranged in two lines and spaced 10 cm away from each other (edge to edge), in which the animals can move around freely by leaping from one platform to the another. Loss of the muscle tone at the beginning of each REM (paradoxical) sleep episode causes rats to touch the water, thus being awakened. To test the possible effects of the chamber atmosphere on the stress level of sleep deprived animals, we also utilized a wide platform (WP, sham group) (15 cm in diameter) version, which allowed the rats to sleep comfortably. During the SD period, the animals had free access to water bottles and chow pellets attaching from a grill located on the top of the chamber. The water in the tank was refreshed daily throughout this period. This protocol involves repeated awakenings, which predominantly, but not exclusively, affects the REM stage of sleep which has been confirmed by the electroencephalogram (EEG) recording in the previous studies (Machado, Hipolide, et al., 2004; Ravassard et al., 2009). Machado et al have shown that animals in the small platforms display 100% and 31% reduction of REM and non-REM sleep respectively, compared to the home cage control group (Machado et al., 2004). Ravassard et al reported that compared to WP group, REM sleep was suppressed by 60%, but non-REM sleep was increased by 10% in the small platforms group (Ravassard et al., 2009). As the animals can move freely within such multiplatform chambers, it has been reported that they will experience less immobilization stress compared to the single version of platform technique. Moreover, this paradigm allows rats from the same cages and groups to be deprived of sleep at the same time thus, remaining socially connected and some probable separation stress associated with the single flowerpot model is avoided. (Machado et al., 2004; Suchecki & Tufik, 2000).

2.4. Spatial learning and memory in Morris water maze (MWM)

The MWM was a black circular metal tank (160 cm diameter and 80 cm height) filled with 40 cm of water maintained at room temperature (21 °C ± 1 °C). The pool was geographically divided