

Treadmill exercise improves impaired spatial memory function in partial androgen deficiency rat model

Dear Editor- in-chief

Elderly men have a relative deficiency of testosterone compared with younger men (i.e., partial androgen deficiency of the aged male (PADAM)). In the cognitive impairment in elderly men, testosterone levels may be significantly associated with memory and visuospatial function (Warren, 2008). Androgen receptors are expressed in CA1 of rat hippocampus and mediate the effects of testosterone on learning and memory (Harooni et al., 2007). These evidences from both human and animal studies suggest that testosterone exerts causal effects of adult spatial behavior.

Exercise alter specific aspects of delayed long-term memory in young adults (Coles and Tomporowski, 2008), and enhanced spatial memory formation in Wister male rats (Khabour et al., 2009). Little is known about the effect of exercise on performance in healthy partial androgen deficiency.

In this report, we examined whether exercise improved spatial long-term memory in gonadectomized (GND) rat using a win-shift strategy.

The animal procedures were reviewed and approved by the Animal Research Committee of Gifu Women's University and the Japanese Government Animal Protection and Management Law. Male Sprague-Dawley rats weighing 350 ± 10 g were obtained from Charles River Japan Inc. (Tokyo, Japan) at 8 weeks of age. The rats were housed in standard cages and fed with standard laboratory chow and tap water ad libitum. The rats were assigned randomly to three different groups: GND sedentary ($n = 6$), GND-exercise ($n = 6$), and the sham-operated ($n = 6$). Bilateral gonadectomy was performed under thiopental anesthesia, and all animals were killed by decapitation. The sham rats (Sham) were subjected to the same general surgical procedure, except that the testes were not excised. Brain dissections of the hippocampus were performed according to a previously described method (Hasegawa and Mochizuki, 2009).

The radial arm maze consisted of eight arms, extending radially from a central area (Brain Science Idea. Co. Ltd., Tokyo). The GND and Sham rats were housed for 1 month and subjected to a win-shift task according to previous described methods (Espina-Marchant et al., 2006). Before win-shift task, there was a six days habituation period. The trial continued until all the baits had been consumed or until 5 min had elapsed. For the training phase, only 4 arms of the maze were loaded with the bait, while the other 4 arms were blocked. The rat was placed in the central platform and required to enter into any of the 4 non-blocked arms to retrieve the bait for a maximal period of 5 min. Then the rat was return to the home cage for 5 min. For test phase, the rat was again placed in the

maze with all arms opened, but baits only placed in the arms that were previously blocked during training phase. The number of long-term memory errors (entering an arm without bait for test phase already visited) was counted. Results are expressed as the mean \pm SEM. The significance of differences for analyzing data of the maze was determined by nonparametric U Mann-Whitney test.

Figure 1 illustrates the maze performance in the GND rats. Castration caused significant long-term memory deficits ($p < 0.05$). The results confirm androgen necessary for spatial memory function. In older or elderly men, hypogonadism condition, testosterone levels may be significantly associated with memory (Warren et al., 2008). These results suggested that testosterone plays a pivotal role in the expression of aggressive behavior.

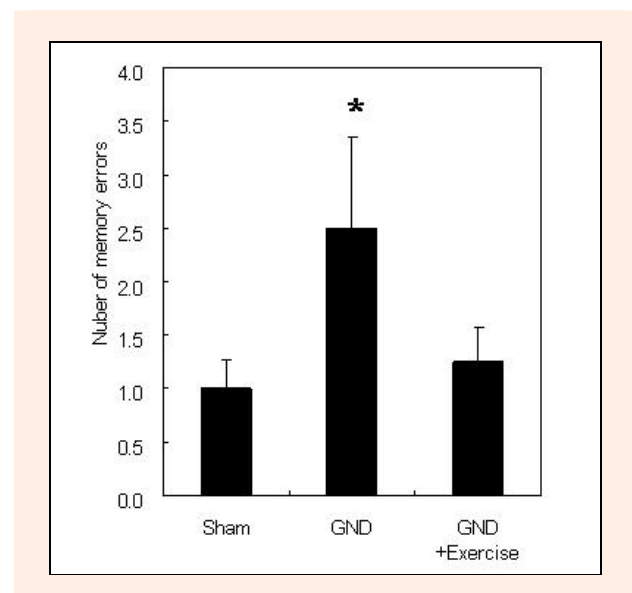


Figure 1. Effects of exercise on long-term memory functions in GND rats.

GND and Sham rats were housed for 1 month and subjected to a long-term memory function with delay. Results are presented as the mean \pm SEM of six experiments. GND significantly impaired long-term memory ($p < 0.05$ by nonparametric U Mann-Whitney test). Exercise altered specific aspects of delayed long-term memory.

In the present experiment, we investigated the effects of exercise in GND rats. Exercise training consisted of continuous running on a motor-driven rodent treadmill for 30 min in trained group. Rats were made to run from 10 min/day at 13 m/min, 6°slope for a week, up to 60 min/day the last 15 days. Exercise improved the delayed long-term memory impairment by GND (Figure 1). Voluntary exercise enhanced short-term, intermediate-term and long-term memory formation (Khabour et al., 2009). These results suggested that exercise enhanced spatial memory formation in PADM.

Hippocampal testosterone and estradiol were measured by a commercial EIA kit (Cayman Chemical Co., USA). The protein content was determined using BCA protein assay reagent (Pierce, IL, USA). Results are expressed as the mean \pm SEM. Student's *t*-test was used for two-group statistical comparison. In the present experiment, the mean level of hippocampal testosterone in the GND and exercised GND rats were 10.36 ± 0.45 pg mg^{-1} protein ($n = 6$) and 14.45 ± 0.04 pg $\cdot \text{mg}^{-1}$ protein ($n=6$), respectively. The mean level of estradiol in the GND and exercised GND rats were 10.36 ± 0.45 pg $\cdot \text{mg}^{-1}$ protein ($n = 6$) and 14.45 ± 0.04 pg $\cdot \text{mg}^{-1}$ protein ($n = 6$), respectively. These results showed that exercise significantly increased hippocampal testosterone and estradiol content in the GND rats ($p < 0.01$). The hippocampus is essentially involved in learning and memory (Harooni et al., 2007). Testosterone upregulate hippocampal neurogenesis in adult male rodent (Galea et al., 2008), and testosterone in CA1 region is as a neuromodulator (Mohaddes et al., 2009). Estradiol affects different brain regions involved in working memory, reference memory and conditioned place preference (Galea et al., 2008).

These results suggested that treadmill exercise improved the spatial memory impairment in androgen-deficient rats by increase of testosterone and estradiol content in the hippocampus and exercise improved spatial memory function.

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