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Research Report

The role of the central histaminergic receptors in the exercise-induced improvements of the spatial learning and memory in rats

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ABSTRACT

While it is well known that exercise can improve cognitive performance, the underlying mechanisms are not fully understood. There is now evidence that histamine can modulate learning and memory in different types of behavioral tasks. The present study was designed to examine the possible role of central histamine H_1 and H_2 receptors in forced treadmill running-induced enhancement of learning and memory in rats. For this purpose the animals received intracerebroventricularly chlorpheniramine (H_1 receptor blocker) and cimetidine (H_2 receptor blocker) before each day of fifteen consecutive days of exercise. Then their learning and memory were tested on the water maze task using a four-trial-per-day for 4 consecutive days. A probe trial was performed after the last training day. Our data showed that cimetidine reversed the exercise-induced improvement in learning and memory in rats; however, this was not the case regarding chlorpheniramine. Our findings indicate that central histamine H_2 receptors play an important role in mediating the beneficial effects of forced exercise on learning and memory.

1. Introduction

Extensive research indicates that physical exercise can improve cognitive functions in humans and experimental animals (Cotman and Berchtold, 2002; Erickson and Kramer, 2009). Notably, exercise enhances learning and memory (Kramer et al., 1999). A number of mechanisms have been suggested as the mediators of the beneficial effects of the exercise on learning and memory, some examples of which include: the hypothalamic–pituitary–adrenal (HPA) axis activations,

Abbreviations: NMDA, N-methyl-D-aspartate; HPA, Hypothalamic–pituitary–adrenal; CPA, Chlorpheniramine; CIM, Cimetidine; ICV, Intracerebroventricular; LTP, Long-term potentiation

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and such receptors activity as, brain derived neurotropic factor (Chen and Russo-Neustadt, 2009); insulin-like growth factor I (Ding et al., 2006); vascular endothelial growth factor (Fabel et al., 2003), and N-methyl-D-aspartate (NMDA) (Hajisoltani et al., 2011). Other studies also have investigated the role of the central biogenic amine systems in the exercise-induced enhancement of learning and memory through the noradrenergic and serotonergic systems (Ebrahimi et al., 2010).

Histamine as an important neurotransmitter is present in the neurons of the central histaminergic system (Garção et al., 2009). This biogenic monoamine, via three histamines (H_1, H_2, and H_3) and NMDA receptors in the brain, is involved in many behavioral and neurobiological functions such as circadian rhythm (Burns et al., 2003); anxiety (Faganello and Mattioli, 2007); pain perception (Izadi Mobarakeh et al., 2003); locomotor activity modulation (Alvarez et al., 1994), and the regulation of appetite (Montoro et al., 2006). Numerous studies suggest that the manipulation of the central histaminergic system affects behavioral responses during several learning and memory processes (Kohler et al., 2011). However, the results are often contradictory and because of the opposite effects that the activation of the different histamine-receptor subtypes has on memory due to the variability of cellular action, the final course of action of histamine on cognitive behavior is not predictable (Kohler et al., 2011). Additionally, the contribution of histamine and its receptors in mediating the effects of exercise on cognitive functions is not clear yet. At the same time, it is evident that the histaminergic neurons are activated at high level during attention and physical activity (Brown et al., 2002). In light of this, we were encouraged to examine the hypothesis that the central histaminergic system may play an important role in mediating the effects of exercise on cognitive behavior. This hypothesis is supported by the observation that the central histaminergic system closely interacts with other systems that are the mediators of the beneficial effects of the exercise on learning and memory. Researches indicate the histaminergic system interacts with and excites the serotoninergic (Brown et al., 2002) and noradrenergic neurons (Korotkowa et al., 2005). Moreover, it has been shown that the histamine activates the HPA axis resulting in glucocorticoid production which is required for the voluntary exercise-induced enhancement of learning and memory (Hajisoltani et al., 2011). These reports support the view that histaminergic system through its receptors may modulate the effects of exercise on learning and memory.

In this study, we examined the effects of centrally injection of H_1 and H_2 receptor blockers (Chlorpheniramine and Cimetidine) on treadmill exercise-induced improvement of learning and memory in rats.

2. Results

Experiment 1: Acquisition data of the experimental groups during 4 days of training in the water maze are depicted in Fig. 1. A two-way ANOVA revealed a significant main effects of groups ($F_{3,88}=4.82$, $P=0.023$) and days ($F_{3,88}=3.75$, $P=0.038$) on the escape latencies. The comparisons of groups showed that the escape latencies of TE-SAL group were significantly lower than that of SED-SAL group on the 2nd, 3rd and 4th days ($P<0.05$ for the 2nd and 3rd days, and $P<0.01$ for the 4th day, respectively). The escape latency of TE-CPA group was significantly longer than that of TE-SAL group in 2nd day ($P<0.05$), 3rd day and 4th day ($P<0.01$ for both days). It was observed that escape latencies of SED-CPA are longer than that of SED-SAL group on the 3rd and 4th days ($P<0.05$ for these two days).

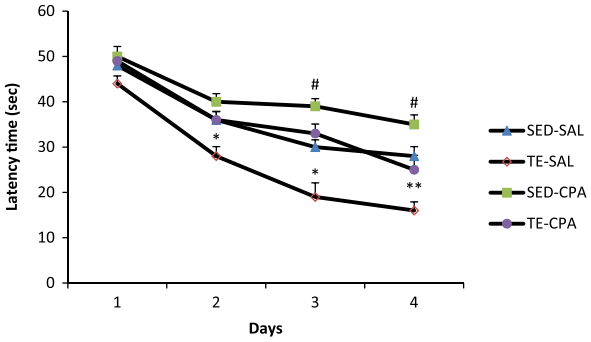

Fig. 1 – Effect of blocking the histamine H1 receptors by CPA during exercise on learning acquisition as measured by the MWM task.* represents the significant difference between treadmill exercise-saline (TE-SAL) with sedentary-saline (SED-SAL) groups. # represents the significant difference between TE-SAL and exercise-chlorpheniramine (TE-CPA) groups. Data are expressed as the mean±S.E.M. * $P<0.05$, ** $P<0.01$, # $P<0.05$.

Fig. 2 shows the data from memory retention test. A two-way ANOVA on the mean escape latency data indicated a significant effects of exercise ($F_{1,22}=3.95$, $P=0.031$), CPA ($F_{1,22}=2.85$, $P=0.043$), and a significant interaction between exercise and CPA ($F_{1,22}=4.01$, $P=0.029$) (Fig. 2A). Post hoc comparisons indicated that the mean escape latency of TE-SAL group is significantly lower than that of SED-SAL, SED-CPA and TE-CPA groups ($P<0.05$ in all cases). The mean escape latency of SED-CPA group was longer than that of SED-SAL group ($P<0.05$). The differences in the mean escape latencies between the TE-SAL and TE-CPA groups were significant (Fig. 2A).

Analysis of data from mean time spent in zones by a two-way ANOVA showed a significant groups × zones effect ($F_{3,44}=3.05$, $P=0.04$). Between groups comparisons indicated that the TE-SAL group spent more time in the target zone than the SED-SAL group ($P<0.05$) (Fig. 2B). The SED-CPA group spent significantly less time in the target zone than did the SED-SAL group ($P<0.05$) (Fig. 2B). Difference between TE-SAL and TE-CPA groups on their time spent in the target zone was not statisticaly significant (Fig. 2B).

Experiment 2: Acquisition data of the experimental groups during 5 days training in the water maze are showed in Fig. 3. A two-way ANOVA on the escape latencies showed significant groups ($F_{3,92}=2.56$, $P=0.044$) and days effects ($F_{3,92}=5.16$, $P=0.029$). Between group comparisons showed that the escape latencies of TE-SAL group were significantly lower than that of SED-SAL group on the 2nd, 3rd and 4th days ($P<0.05$ for all days). The escape latency of TE-CIM group was significantly longer than that of TE-SAL group in 3rd and 4th days ($P<0.05$ for all days). No significant differences were found between groups of SED-SAL and SED-CIM on any day.

Data from memory retention test are shown in Fig. 4. Analysis of data on the mean escape latencies by ANOVA