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ORIGINAL RESEARCH

Preventive and therapeutic effect of treadmill running on chronic stress-induced memory deficit in rats

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Summary Previous results indicated that stress impairs learning and memory. In this research, the effects of preventive, therapeutic and regular continually running activity on chronic stress-induced memory deficit in rats were investigated. 70 male rats were randomly divided into seven groups as follows: Control, Sham, Stress—Rest, Rest—Stress, Stress—Exercise, Exercise—Stress and Exercise—Stress & Exercise groups. Chronic restraint stress was applied 6 h/day for 21days and treadmill running 1 h/day. Memory function was evaluated by the passive avoidance test. The results revealed that running activities had therapeutic effect on mid and long-term memory deficit and preventive effects on short and mid-term memory deficit in stressed rats. Regular continually running activity improved mid and long-term memory compared to Exercise—Stress group. The beneficial effects of exercise were time-dependent in stress conditions. Finally, data corresponded to the possibility that treadmill running had a more important role on treatment rather than on prevention on memory impairment induced by stress.

Introduction

Exposure to stressors causes an array of biochemical, physiological and behavioral changes in the brain (Martí et al., 1994). It has previously been reported that chronic stress impairs neuronal plasticity (Krishnan and Nestler, 2008), learning (Radahmadi et al., 2013b) and memory processes (Bowman et al., 2003) via glucocorticoids (Heffelfinger and Newcomer, 2001). Also, it could affect the onset or degree of cognitive dysfunction and psychopathology disorders (Krishnan and Nestler, 2008). In this regard, stress acts via different mechanisms such as, cell damage of, DNA, genes, changes of various receptors and their mRNA levels (e.g. receptors of glucocorticoids,

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glutamate and GABA), synaptic transmission, and neurotransmitters, inhibition of LTP and many other mechanisms that can directly affect brain functions on learning and memory (Calabrese et al., 2012; Fontella et al., 2005; Harvey et al., 2004; Liu et al., 1996; Popoli et al., 2012; Schwendt and Jezova, 2000).

In contrast, previous studies indicated that physical activity has beneficial and neuroprotective effects on brain function. Exercise leads to changes at neuronal activity, synaptic structure and the synthesis of neurotransmitters which are important in memory processing (Shen et al., 2001). It has been documented that some kinds of physical activities improve passive avoidance memory and spatial learning (Alaei et al., 2006; Chen and Shen, 2002; Huang et al., 2006). However, the relationship between physical activity and cognitive function remains unclear. Since humans cannot spend much time during the day for exercise (Radak et al., 2006), treadmill running is more similar to human exercise training. Therefore, treadmill running was used in this experiment because it has the feature that allows animals to run only for a limited time per day. There are few studies that have systematically investigated the association between physical activity and stress effect on cognitive function. Some researchers demonstrated that running activity reversed harmful stress effects. It enhanced learning and memory in the open field and Morris water tasks and improved object recognition memory in the temporal order task (Grace et al., 2009; Zheng et al., 2006). We previously reported that although treadmill running alone has beneficial effects on learning and memory consolidation, that when synchronized with stress there are no significant protective effects on chronic stress-induced memory deficit (Radahmadi et al., 2013a,b). Based on this information, the aim of this study was to investigate the effects of long-term treadmill running (before, after and continual) on chronic stress-induced memory deficit by the passive avoidance task. The best time for exercise on improvement of memory impairment in stressed rats was investigated. Also, the effect of time depending on exercise on memory in stressed rats to prevent the onset or degree of psychopathology disorders is established.

Materials and methods

Experimental animals

Experiments were performed on 70 male Wistar rats, with an initial weight of 250—300 g obtained from Jondishapour Institute, Ahvaz, Iran. All the experimental protocols were approved by the Ethics Committee of the Isfahan University of Medical Science (Isfahan, Iran), followed by the "Principles of laboratory animal care" and carried out in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). Five rats were housed in each cage, under light-controlled condition (12-h light/dark; lights on 07:00—19:00 h) in a room with a temperature of 22 ± 2 °C and humidity (55 ± 10%). Food and water were available ad libitum, except during the stressing procedure. In addition, to prevent any human interactions, only one person was responsible for handling the rats. Also, environmental factors (such as cage size, colony grouping, room humidity, and background noise levels) were completely similar in all groups. All behavioral experiments (passive avoidance test) were carried out at 13:00—14:00 h. The experiment lasted for 42 days and passive avoidance test was performed after 21 days in all groups (Fig. 1). Rats were randomly divided into seven groups (n = 10 in each group) as follows:

1 Control group (Co); rats were transported to the laboratory room and handled similarly to the experimental animals throughout the study period with no special treatment.
2 Sham group (Sh); rats were put on the treadmill without running for 1 h/day for 21 days.
3 Stress before rest group (S—R); chronic restraint stress was applied 6 h/day for 21 days, then the rats remained undisturbed in the cage for 21 days (they had a recovery period).
4 Stress after rest group (R—S); rats had no special treatment for 21 days, and then chronic restraint stress was applied 6 h/day for 21 days.
5 Exercise—Stress group (E—S); rats were exercised for 21 days before applying 21 days stress.
6 Stress—Exercise group (S—E), rats were under stress for 21 days then exercised for 21 days.
7 Exercise—Stress & Exercise (E—SE); rats were exercised continually (before and associated with stress), exercise for 21 days, and then the rats had 21 days stress and exercise together to investigate continuous exercise effects.

All experiments were performed during the light period of the circadian cycle.

Experimental procedures

Stress paradigms

In the current study, rats were placed in Plexiglas cylindrical restrainers and fitted tightly there for 6 h/day

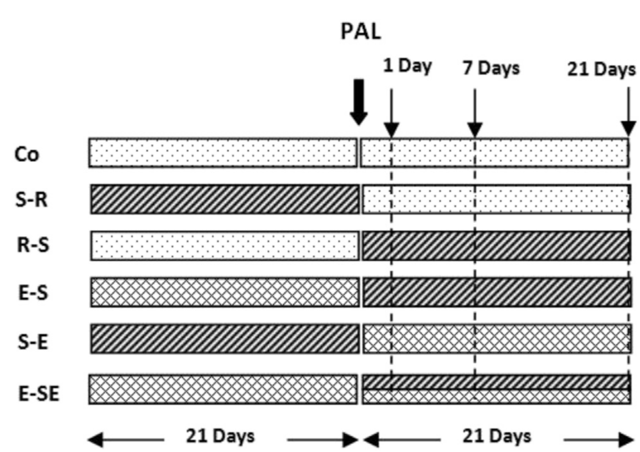

Figure 1 Schematic diagram of different groups. Co: Control (Rest—Rest) group; S—R: Stress—Rest group; R—S: Rest—Stress; E—S: Exercise—stress group; S—E: Stress—Exercise group; E—SE: Exercise—Stress & Exercise group.