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Original article

Environmental stimulation influence the cognition of developing mice by inducing changes in oxidative and apoptosis status

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Abstract

Environment condition has been shown to play an important role in brain development. The present study examined the effects of enriched and impoverished environment on both spatial and emotional learning and memory of young mice and explored the underlying mechanisms. 3-week-old mice were housed in enriched environment ($n = 10$, 10 mice in a large cage with toys and a running wheel), or standard environment ($n = 10$, 10 mice in a large cage without objects), or impoverished environment ($n = 10$, single mice in a small cage without objects) for 6 weeks. Then, the spatial and emotional cognition of mice were evaluated by the water maze and step-down inhibitory avoidance test, respectively. To explore the underlying mechanisms, oxidation measurement in hippocampus and medial-temporal lobe cortex (MTLC) and apoptosis examination in hippocampus were performed. Results showed that compared with standard environment group, enriched and impoverished mice exhibited high and low performance levels in behavior tests, respectively. The oxidative status of hippocampus and MTLC were decreased in enriched group but increased in impoverished group. Moreover, changes in apoptosis of hippocampus in these two groups showed the same tendency with oxidative status. These results suggest that environment condition can simultaneously influence spatial and emotional learning and memory, which may result from inducing changes in the oxidative and apoptosis status in associated brain regions. Here, we firstly report using young mice to examine the oxidative status as a primary and direct factor to explore the mechanism of effects of different environment on both spatial and emotional cognition.

Keywords: Environment; Cognition; Oxidation; Apoptosis

1. Introduction

Environmental stimulation has been considered as an important factor affecting brain development of human and animals. Lack of environmental stimulation during the critical period of brain development can have long term behavioral, neuroanatomical, neuroendocrinological and neurochemical consequences [1,2]. As early as 1940s, researches concerning the effects of environmental stimulation on brain functions have been carried out [3]. Till now, a host of studies have focused on it. As to cognitive function in which we were interested, those previous studies showed that enriched environment (EE) could improve spatial learning [4,5], enhance long-term memory [6,7] and prevent cognitive deficits induced by stress or disease [2,8,9]. In comparison with the effects of EE on cognition, impoverished environment (IE) produced completely opposite effects [10,11].

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However, the major focus of previous research work has only been on spatial cognition, and whether the complexity effects of environment can influence multiple (i.e., spatial and emotional) aspects of cognition simultaneously, or are just linked to particular (i.e., spatial) aspect has not been addressed. During young period, the mammalian nervous undergoes rapid and progressive structural and functional maturation, and may be more susceptible to environment factors. Thus, in the present study, we investigated the effects of different housing conditions on both emotional and spatial learning and memory of developing mice.

The learning and memory ability are coordinated by different brain regions, especially hippocampus [12]. Previous studies carried out on animals indicated that the effects of environment on learning and memory were related to structural and functional changes in hippocampus, such as synaptic and spine density [7], neurogenesis [13,14] and long-term potentiation [15]. But, the clear mechanisms responsible for the effects of environment on learning and memory are not well understood. As we know, the oxidative stress is an imbalance between the activity of free radicals generation and scavenging system, which can cause oxidative damage directly to critical biological molecules and organisms [16,17]. Moreover, it was found recently that the activity of superoxide dismutase (SOD) was significant increased after the combined treatment, enriched living condition and antioxidant diet [18]. It is then conceivable that there is a mechanism of action of environment through the modulation of oxidative status to change morphological structure of hippocampus to cause learning and memory impairment. So, in the present study, we housed mice in different conditions, and then tested their spatial and emotional learning and memory ability and oxidative and apoptosis status in hippocampus. Besides, medial-temporal lobe cortex (MTLC) has complex association with hippocampus and it also involves in modulation of learning and memory function [19,20]. Therefore, the oxidative status in MTLC of mice reared in different conditions was also examined.

2. Materials and methods

All experiments were conducted with the approval of the Institutional Animal Care and Use Committee of Central China Normal University, Wuhan, Hubei, China.

2.1. Animals and groups

A total of 30 healthy Kunming mice (*Mus musculus*, Km, 9-12 g, 3 weeks old, purchased from the Centers for Disease Control and Prevention of Hubei province of China) were included in the present study. Mice were housed on natural light cycles with free access to food and water. The ambient temperature was maintained at 20–25 °C. Total mice were divided into three groups ($n = 10$): EE group: 10 mice were reared in a large cage ($100 \times 50 \times 45$ cm) containing a variety of stimuli, i.e., running wheels, tunnels, plastic coloured toys, shelters (a house-shaped toy), balls and other small constructions. Throughout the enrichment period, the plastic coloured toys, balls and constructions changed once a week. Standard environment (SE) group: mice were also reared in a large cage ($100 \times 50 \times 45$ cm) but no stimuli. IE group: mice were housed singly in individual cages ($40 \times 26 \times 18$ cm) without any stimuli. Animals were kept in the respective conditions until learning and memory tests were carried out 6 weeks later.

2.2. Learning and memory tests

2.2.1. Morris water maze tests

The spatial cognition ability of mice was tests by Morris water maze tests and analyzed using the Anymaze system (Stoelting, Wood Dale, IL, USA). The water maze apparatus consisted of a metal circular pool (60 cm high, 100 cm in diameter), in which a circular Plexiglas platform (diameter 5 cm, height 15 cm) was hidden 1-2 cm below the surface of the water (26 ± 2 °C). The mice were gently released into water and allowed to swim around to find the platform in southwest quadrant of pool. On reaching the platform, each mouse was allowed to stay there for 30 s. If a mouse failed to locate the platform within 180 s, it was guided to the platform and allowed to remain on it for 30 s. Training totally lasted 6 days (1 trial/day). The first 5 trials started from northeast pool quadrant and the final training trial from northwest (as interruption of learning and memory before). 24 h after the final training trial on day 6, the mice were given another 180 s trial which started from northeast quadrant to test their spatial memory. Latencies to find the hidden platform during the whole treatment period were recorded with a computerized tracking system as indicators except the interrupted training trial on day 6.

2.2.2. Step-down inhibitory avoidance tests

The step-down inhibitory avoidance tests were used for assessing the emotional cognition of mice as described before [21]. The experimental device is a $11 \times 11 \times 30$ cm electronic avoidance-response chamber, made of Plexiglas on its three sides and hard black plastic on the other. The chamber has a bottom of parallel stainless steel bars (0.4 cm in diameter), with a 0.6 cm space between adjacent bars. A rubber platform (3 cm high, 3 cm in diameter of its top surface) was fixedly placed at a corner on the bottom of the chamber, providing mice a shelter from the electronic attack. At the beginning of tests, the mice were given 5 min in the