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Research report

Protective effect of the orientin on noise-induced cognitive impairments in mice

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HIGHLIGHTS

- Orientin alleviates the noise-induced cognitive impairments in mice.
- Orientin attenuates the noise-induced oxidative stress in the hippocampus and prefrontal cortex.
- Orientin improves neurotransmission and increases synapse-associated proteins in the noise-exposed mice.

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ABSTRACT

There is increasing evidence that chronic noise stress impairs cognition and induces oxidative stress in the brain. Recently, orientin, a phenolic compound abundant in some fruits, millet, and herbs, has been shown to have antioxidant properties. This study investigated the potential effects of orientin against chronic noise-induced cognitive decline and its underlying mechanisms. A moderate-intensity noise exposure model was used to investigate the effects of orientin on behavior and biochemical alterations in mice. After 3 weeks of the noise exposure, the mice were treated with orientin (20 mg/kg and 40 mg/kg, oral gavage) for 3 weeks. The chronic noise exposure impaired the learning and memory in mice in the Morris water maze and step-through tests. The noise exposure also decreased exploration and interest in a novel environment in the open field test. The administration of orientin significantly reversed noise-induced alterations in these behavior tests. Moreover, the orientin treatment significantly improved the noise-induced alteration of serum corticosterone and catecholamine levels and oxidative stress in the hippocampus and prefrontal cortex. Furthermore, the orientin treatment ameliorated the noise-induced decrease in brain-derived neurotrophic factor and synapse-associated proteins (synaptophysin and postsynaptic density protein 95) in the hippocampus and prefrontal cortex. Thus, orientin exerts protective effects on noise-induced cognitive decline in mice, specifically by improving central oxidative stress, neurotransmission, and increases synapse-associated proteins. Therefore, supplementation with orientin-enriched food or fruit could be beneficial as a preventive strategy for chronic noise-induced cognitive decline.

1. Introduction

Noise, defined as 'unwanted sound' is perceived as an environmental stressor and annoyance. With the development of urbanization and industrialization, noise pollution has become a risk factor for neurodegenerative diseases, depression and cognitive decline. Exposure to environmental noise can induce hearing deficit in the auditory system and sleep disturbance [1]. Recently, increasing animal and clinical evidence has shown that chronic noise exposure has obvious effects on cognitive impairment, such as declined memory and learning. For example, working memory was impaired after chronic noise stress in rats with reduced dendritic count in the hippocampus and prefrontal cortex [2]. Noise exposure during pregnancy impaired spatial learning ability and decreased neurogenesis in the hippocampus in rat pups [3]. In

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addition, a large cross-national and cross-sectional clinical study has demonstrated that chronic aircraft noise impaired cognitive development in children, specifically reading comprehension [4].

The physiological responses to chronic stress include the activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympatho-adrenomedullary system (SAM), through which the levels of corticosterone and catecholamine are altered [5,6]. In a continuously open auditory system, noise-induced stress can cause the significant release of hypothalamic hormones such as the corticotrophin-releasing hormone and the adrenocorticotropic hormone, which increase the activity of the HPA-axis and the release of corticosterone from the adrenal cortex [7]. It is known that high levels of corticosterone, induced by the hyperactivity of the HPA axis, impair cognition, including learning, memory, and spatial recognition [8]. Furthermore, catecholamines such as norepinephrine (NE) and dopamine (DA) are essential monoamines for learning and memory through their ability to regulate synaptic plasticity [9,10]. The increased level of serum catecholamines such as norepinephrine (NE) and dopamine (DA), is considered to be an immediate response in combating the stress induced by the activation of the SAM system [11]. Moreover, increasing evidence shows that the activation of the oxidative stress process by chronic stress may cause lipid peroxidation, reduced antioxidant enzyme activity, and increased monoamine catabolism, which are all related to cognitive decline [12]. Chronic exposure to low frequency noise at moderate levels increased the levels of oxidative stress in mice, while attenuating oxidative stress inhibited cognitive impairment [13,14]. These findings strongly suggest that corticosterone, catecholamine and oxidative stress are closely associated with noise stress induced cognitive impairment.

The hippocampus and prefrontal cortex are important brain regions responsible for enhancing cognition. Studies in rodents have showed that chronic noise impairs the neurotransmitter signaling system in the hippocampus and prefrontal cortex [15], which in turn impairs cognitive function. Brain-derived neurotrophic factor (BDNF) in the hippocampus and prefrontal cortex plays a critical role in synaptic plasticity and cognition [16,17]. For example, the effect of exercise enhancing cognitive function was blocked by inhibiting BDNF action in the hippocampus [17]. Recently, synaptophysin (SYN) and post-synaptic density 95 (PSD-95) biomarkers in synaptic reconstruction have been reported to be regulated by BDNF to facilitate regeneration of neurons and axons [18–20]. Growing evidence suggests that neurotrophic factors and synaptic proteins in the hippocampus and prefrontal cortex may function as attractive therapeutic targets for neuropsychiatric diseases.

Orientin (luteolin-8-C-glucoside) is a phenolic compound found abundantly in millet and the juice and peel of passionfruit [21,22]. It is also abundant in bamboo leaves, which have a long history of nutritional and medical applications in Asia [23]. Several recent studies have demonstrated that orientin exerts a variety of pharmacological effects, including antioxidant, anti-inflammatory, and neuroprotective effects [24,25]. For example, orientin (20 mg/kg and 40 mg/kg, intragastric administration) has shown significant antioxidant properties in improving the neuronal ultrastructure in the hippocampus of D-galactose-aged mice [26]. Importantly, our previous study have shown orientin (20 mg/kg and 40 mg/kg, oral gavage) alleviated the chronic unpredictable mild stress (CUMS)-induced depression-like behavior and increased the brain-derived neurotrophic factor and synapse-associated proteins [27]. However, the protective effect of orientin on noise-induced cognitive impairments and the mechanisms of cognitive improvement are yet to be reported. This study aimed to evaluate the protective effect of orientin on noise-induced cognitive impairment in mice by examining behavior tests. In addition, this study also determined the neuroendocrine changes (corticosterone and catecholamine) and alterations in anti-oxidative status and synaptic plasticity in the hippocampus and prefrontal cortex which are associated with noise.

2. Methods and materials

2.1. Animals

Adult male Kunming mice (18–22 g) were provided by Laboratory Animal Center, Xuzhou Medical College, Xuzhou, Jiangsu, China. The mice were housed with ad libitum access to food and water under controlled temperature ($22 \pm 2\,^{\circ}C$) and humidity ($50 \pm 10\%$) and maintained on a 12-h light/dark cycle for 1 week of adaptation. All procedures were approved by the Animal Ethics Committee, Xuzhou Medical College, China, and complied with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

2.2. Noise stress procedure

The continuous noise used in this study was generated by a noise generator (type DG1032Z, Beijing puyuan, China). The amplitude of the noise was 80 dB SPL, and the range of noise frequency was from 10 to 10,000 Hz [28]. The noise level was measured with a sound level meter (type WS-1361, Wensn, Dongwan, Guangdong province). The noise exposure was performed for 2 h continuously and randomly per day for six weeks.

2.3. Drug and treatments

The mice were randomized into five groups ($n = 14$ per group): control group (without noise stress procedure); noise group (exposure to noise stress procedure); noise + orientin-L group (exposure to noise stress procedure and low dosage of orientin 20 mg/kg); noise + orientin-H group (exposure to noise stress procedure and high dosage of orientin 40 mg/kg); orientin-H group (without noise stress procedure and high dosage of orientin 40 mg/kg). After three weeks of the noise stress procedure, the orientin was administered orally (gavage daily) for 3 weeks. Both the control group and the noise group received the same volume of normal saline. In this study, the orientin (purity, 99.8%, WT, 464) used was purchased from Extrasynthese (Genay, France).

2.4. Behavioral tests

2.4.1. Morris water maze test

As previously described [29], the Morris water maze test was performed in a circular pool filled with water at room temperature (diameter, 120 cm; height, 60 cm; water temperature, $24 \pm 1\,^{\circ}C$). An escape platform (10 cm in diameter) was hidden 1.5 cm below the surface of water in the center of one quadrant. The pool was virtually divided into four quadrants, i.e., NE, SE, SW, and NW. The mice received four consecutive daily training trials. At the beginning of each trial, the mice were released at one of the four possible starting points facing the wall, and allowed to swim freely until they reached the platform. The time it took them to reach the hidden platform (escape latency) was recorded. If a mouse did not find the escape platform within 90 s, it was given a latency score of 90 s.

On the probe trial performed on the fifth day. The mice were placed and released opposite the site where the platform had been located. The probe trial consisted of a 90 s free swim in the pool without the platform. The percentage of time spent in the target quadrant indicates the degree of memory consolidation.

2.4.2. Open-field test

The locomotor and exploratory activities were assessed by the open-field test as previously described [30]. The apparatus