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Research report

Studies on the animal model of post-stroke depression and application of antipsychotic aripiprazole

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HIGHLIGHTS

- Chronic mild stress after stroke showed neuronal loss and declined neurogenesis.
- Chronic mild stress after stroke produced neuronal loss at lesion and exofocal sites.
- Neurodegeneration by chronic mild stress is involved in a process of depression.
- Aripiprazole treatment is effective in ameliorating characteristics of depression.

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ABSTRACT

We investigated the question of whether an animal model of post-stroke depression in ischemic stroke can be developed by additional chronic mild stress (CMS) procedures. Behavioral and histopathological analysis was performed for examination of the depressive disorders in CMS, left middle cerebral artery occlusion (MCAO) and CMS after MCAO (MCAO + CMS) in mice. In all depressant screening tests involving open field, sucrose preference, forced swim and Morris water maze test, MCAO + CMS mice showed more significant depressive behaviors than MCAO mice. MCAO + CMS mice also showed distinct deficits in forced swim and Morris water maze test compared with CMS. In the histopathological analysis, prominent atrophic changes were seen in the striatum and midbrain of MCAO treated mice compared with CMS. MCAO + CMS mice showed a decrease of proliferative and differentiated neuronal cells in the striatum and hippocampus with dopaminergic neuronal injuries in the midbrain as compared with CMS and MCAO alone treated mice. Treatment of MCAO + CMS mice with aripiprazole resulted in reduction of all depressive behaviors examined, particularly in the Morris water maze test. Recovered dopaminergic neuronal injuries in the midbrain and enhanced neurogenesis in the hippocampus were also demonstrated. Our results suggest that CMS after ischemic stroke can lead to severe depressive-like behavior compared with CMS or MCAO alone treated mice via neurodegeneration in the primary lesion and secondary extrafocal sites and degradation of neurogenesis, and these behavioral and histopathological changes are reversed by treatment with aripiprazole. Thus adjunct therapy with an antipsychotic may exert its antidepressant effects via neuroprotection and neurogenesis in CMS-treated ischemic mice.

1. Introduction

Depression, a debilitating mental disorder characterized by negative mood, diminished interest or pleasure in activities, etc., is very common after stroke events [1]. More than one-third of stroke survivors suffer from common mood symptoms including anxiety and feelings of despair as well as anhedonia [1,2]. Vascular depression is poorly defined, but its hypothesis proposed that cerebrovascular diseases are associated with increased risk for some depressive syndromes. Ischemic depression is considered a subtype of vascular depression [3].

Underlying mechanisms of post-stroke depression are associated in part with neuronal loss and impaired neurogenesis in

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the ischemic lesion and secondary degenerative changes [2,4]. Although there are a number of established risk factors for development of depression after brain ischemia, including physical disability and cognitive impairment, personal circumstances also have a major impact on mental health [1,5]. Social stress such as isolation after stroke is recognized as a major risk factor in both histological and behavioral analysis that can potentially improve post-stroke depression [6–8].

Previous studies have investigated the influence of chronic mild stress (CMS) after middle cerebral artery occlusion (MCAO) on depressive-like behavior in animal models. Chronic mild stressors after stroke induce a broad spectrum of core depressive-like symptoms that seem to be regarded as synthetic effects of MCAO and CMS [9,10]. Exposure to chronic stress after stroke can result in atrophy or degeneration in brain regions including inhibition of neurogenesis [11–14]. Stroke entails neurodegeneration in the lesion site and penumbra as well as in remote brain areas that contribute to mood symptoms [4]. Thus CMS may strongly influence stroke damage and recovery, however, the mechanisms involved in its effects on expression of post-stroke depression remain unknown.

Aripiprazole, an atypical antipsychotic drug, is approved as an adjunct therapy for major depressive disorder with a drug from the group of selective serotonin reuptake inhibitors (SSRIs) and its adjunctive therapy could be effective for complex post-stroke emotional disorders with a beneficial effect on cognitive function [15,16]. Antidepressants, particularly SSRIs, exert beneficial effects on brain structure extending far beyond mood effects [17,18]. In addition, CMS may strongly enhance stroke damage contributing to clinical symptoms of depression in the experimental model, and aripiprazole treatment may have potential in treatment of post-stroke depression as an add-on therapy via neuroprotection and neurogenesis against summative neuronal injury by CMS [15].

To validate these hypotheses, we first compared their ability to induce depressive-like behaviors in three experimental models, CMS, MCAO, and MCAO + CMS, and then determined histopathological interaction of stroke and chronic mild stress on depressive phenotypes. Next we investigated effects of antipsychotic aripiprazole on the behavioral and histopathological changes of the brain in chronic mild stress-treated ischemic mice.

2. Materials and methods

2.1. Animal

Male C57BL/6 mice aged 10 weeks were obtained from Dooyeol Biotech (Seoul, Korea). The mice were housed at 22 °C under alternating 12 h cycles of dark and light, and were fed a commercial diet and allowed tap water ad libitum throughout the study. All experiments were approved by the Pusan National University Animal Care and Use Committee in accordance with the National Institutes of Health Guidelines.

2.2. Chronic mild stress

The CMS procedure was applied from Willner et al. with slight modification [19]. The chronic mild stress regimen included a total of 7 different stressors, which were arranged day and night in order for 17 consecutive days as follows: food and water deprivation (20 h), water deprivation (18 h), 45° cage tilt (17 h), overnight illumination (36 h), soiled cage (21 h), swimming in 4 °C water (5 min), and paired caging (2 h).

2.3. Focal cerebral ischemia

Focal cerebral ischemia was induced by occluding the middle cerebral artery (MCA) using the intraluminal filament technique. A fiber-optic probe was affixed to the skull over the middle cerebral artery for measurement of regional cerebral blood flow using a PeriFlux Laser Doppler System 5000 (Perimed, Stockholm, Sweden). Left MCAO model was induced by a silicon-coated 4-0 monofilament in the internal carotid artery and the monofilament was advanced to occlude the MCA. The filament was withdrawn 30 min after occlusion and reperfusion was confirmed using laser Doppler. All groups were kept in adjacent cages in the same area and the MCAO mice did not receive any stress and also had free access to food and water. MCAO + CMS mice underwent the CMS procedure from 2 days after MCAO.

2.4. Drug administration

Aripiprazole was administered orally into the mice from 2 days after MCAO during the CMS process (successive 17 d) using a sonde. Aripiprazole was dissolved at concentration of 3, 10, and 30 mg/kg body weight in distilled water.

2.5. Bromodeoxyuridine labeling

Bromodeoxyuridine (BrdU), a synthetic thymidine analog, becomes incorporated into a cell's DNA when the cell is dividing during the S-phase of the cell cycle. For labeling of proliferating cells, all animals were injected with BrdU (50 mg/kg, i.p.) to successive 5 days after MCAO.

2.6. Behavioral experiments

The open field, sucrose preference, and forced swim test were performed from the 2nd week after MCAO to the 6th week once a week. Morris water maze tests were performed during successive 4 days at 6th week after MCAO.

2.6.1. Open filed test

The open-field apparatus consisted of a black box (30 cm × 30 cm × 40 cm). After 10 min of adaptation in a black box, measurement was performed for 30 min as the total distance traveled by placing the mice. Results of the experiment were recorded using SMART 2.5.18 (Panlab S.L.U., Barcelona, Spain).

2.6.2. Sucrose preference test

Mice were deprived of food and water for 20 h after habituation of 1% sucrose solution (AMRESCO Inc., Solon, OH, USA) for 24 h. Subsequently, their preference for 1% sucrose solution and water was measured for 1 h by weighing the whole bottle with solution or water.

2.6.3. Forced swim test

One day before the test, mice were exposed in a glass cylinder (15 cm in height × 10 cm diameter) of 25 °C water for 5 min. On the test day, behavior was recorded using a digital camera (E8400, Nicon Corporation, Japan) for 5 min and scored until immobile time in a cylinder.

2.6.4. Morris water maze test

Mice trained on the Morris water maze for 4 days (5 trials per day) before MCAO. The tank had a diameter of 100 cm, an altitude of 50 cm. The platform was placed 0.5 cm beneath the surface of the water. Each trial was performed for 90 s or until the mouse arrives on the platform. Results of the experiment were recorded using SMART 2.5.18 (Panlab, S.L.U.).