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Research report

Amantadine preserves dopamine level and attenuates depression-like behavior induced by traumatic brain injury in rats

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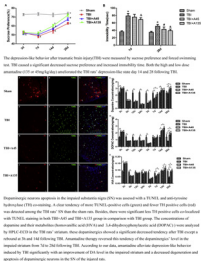
HIGHLIGHTS

- Amantadine ameliorated the depression-like behavior caused by traumatic brain injury (TBI).
- Amantadine reduced the neuronal degeneration in the impaired substantia nigra (SN) instead of the striatum.
- Amantadine alleviated the dopaminergic neuronal apoptosis following TBI in the SN.
- Amantadine reversed the decrease of dopamine in the striatum induced by TBI.

GRAPHICAL ABSTRACT



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ABSTRACT

Traumatic brain injury (TBI) often results in multiple neuropsychiatric sequelae, including cognitive, emotional, and behavioral problems. Among them, depression is a common psychiatric symptom, and links to poorer recovery. Amantadine, as an antiparkinsonian, increases dopamine release, and blocks dopamine reuptake, but has recently received attention for its effectiveness as an antidepressant. In the present study, we first induced a post-TBI depression rat model to probe the efficacy of amantadine therapy in reducing post-TBI depression. The DA concentration in the striatum of the injured rats, as well as the degeneration and apoptosis of dopaminergic neurons in the substantia nigra (SN), were checked along with the depression-like behavior. The results showed that amantadine therapy could significantly ameliorate the depression-like behavior, improving the DA level in the striatum and decreasing the degeneration and apoptosis of dopaminergic neurons in the SN. The results indicated that the anti-depression effect may result from the increase of extracellular DA concentration in the striatum and/or the indirect neuroprotection on the dopaminergic neurons in the SN. We conclude that DA plays a critical role in post-TBI depression, and that amantadine shows its potential value in anti-depression treatment for TBI.

Abbreviations: DA, dopamine; TBI, traumatic brain injury; SN, substantia nigra; NMDA, N-methyl-D-aspartate; FJC, Fluoro-Jade C; HVA, homovanillic acid; DOAPC, 3, 4-dihydroxyphenylacetic acid; HPLD-ECD, high-performance liquid chromatography-eletochemical; TH, tyrosine hydroxylase; TUNEL, terminal deoxynucleotidyl-mediated deoxyuridine triphosphate nick end labeling stain.

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1. Introduction

Traumatic brain injury (TBI) is one of the major causes of morbidity and mortality among the persons less than 45 years old worldwide [1,2]. Accumulated reports indicate that a significant range of psychiatric disorders occur after TBI contributing to disability [3,4]. Post-TBI depression, one of the most common post-traumatic psychiatric sequelae, has become a chronic public health issue [5,6]. However, the etiological factors leading to post-TBI depression remain unknown [7]. The general consensus is that post-TBI depression could be the result of a complex interaction of neurological, psychological and social factors [8].

Dopamine (DA) plays a critical role in the brain's reward mechanism [9], in major depressions caused by Parkinson's disease (PD) [10], and in several anti-depression therapies [11]. Furthermore, Penmatsa et al. [12] has elucidated the anti-depression mechanism of DA transport by identifying its X-ray structure. It has been shown that the dopaminergic neurons in the substantia nigra (SN) project to the striatum maintaining DA homeostasis [13]. Increasing data suggested that a deficit of dopaminergic function in the limbic circuitry and striatum could be involved in the underlying mechanism of depression [14,15]. And TBI may damage the nigrostriatal pathway, block the dopaminergic synaptic transmission in varying degrees, and reduce the dopaminergic activity of the central nervous system (CNS) [16,17]. The mechanism for post-TBI depression remains unclear. We hypothesize that the sustained-low level of dopamine in the striatum leads to post-TBI depression.

Amantadine hydrochloride, a weak N-methyl-D-aspartate (NMDA) antagonist, increases dopamine synthesis and blocks dopamine reuptake, which is widely used in the treatment of Parkinson's disease (PD). Additionally, some reports argued that amantadine can suppress microglial activation and neuroinflammation [18,19]. Recent studies documented how amantadine has been used extensively in clinical application for patients with post-traumatic disorders of consciousness and dysfunction [20,21]. Besides, the anti-depressive function of the NMDA receptor antagonist has been noted in recent studies [22,23]. In particular, amantadine has shown a mild anti-depressive effect when used alone, but has proved an effective adjunctive treatment when combined with other anti-depressants in both human and animal models [24]. This evidence indicates that amantadine may act as an effective drug to treat post-TBI depression.

Given the lack of studies into the potential use of amantadine on post-TBI depression as an exogenous dopaminergic supplement, it is necessary to utilize animal experiments to elucidate its anti-depressive effect before its clinical application. Thus, in the present study, we report on amantadine therapy on post-TBI depression in a rat model.

2. Materials and methods

2.1. Animal

Adult male Sprague-Dawley rats weighing 250–280 g were purchased from the Animal Center of the Third Military Medical University. All animal experiments were performed in accordance with the China Animal Welfare Legislation and were approved by the Third Military Medical University Committee on Ethics in the Care and Use of Laboratory Animals. The animals were housed in a temperature- and humidity-controlled environment with food and water ad libitum in a 12-h light/dark cycle. The animals were acclimatized for more than 1 week before surgical procedures. In our experiment, the rats were randomly grouped as follows: sham-operated (Sham), vehicle-treated TBI (TBI), low dose amantadine-treated TBI (TBI + A45), and high dose amantadine-treated TBI (TBI + A135). Amantadine hydrochloride (Sigma, USA) was dissolved in sterile saline and administered intraperitoneally every 8 h (45 or 135 mg/kg/day respectively for TBI + A45 and TBI + A135 group) for 28 days following TBI. The first injection was administered at 60 min after surgery. Specific doses and dosing schedules were verified to bracket human exposure to 100 mg BID dosing according to the previous report [18]. Equal volumes of sterile saline were i.p. injected into the rats of the TBI group at the same intervals for 28 days. To ensure that the results would not be influenced by the motor deficits caused by TBI, rats were excluded if physical signs of motor deficits, such as forelimb flexion, decreased resistance to push, and circling, were observed during our experiment.

2.2. TBI model

We conducted the TBI procedure on the basis of a modification of the method of Feeney et al. [25]. The rats were anesthetized with a pentobarbital (50 mg/kg) intraperitoneal injection. After depilation and disinfection, the heads were mounted on a stereotaxic frame. The scalp was opened by a midline incision, and a right parietal craniotomy (4.5 mm in diameter, 3 mm posterior and 2.5 mm lateral to the bregma) was performed with a dental drill, without laceration of the dura. A 30 g stainless steel rod with a small pillar (4.5 mm in diameter, 5 mm in height) was dropped on the exposed dura from a height of 20 cm at a spot 4 mm rightward and posterior to the bregma. A gelatin sponge was used for hemostasis, and the rats in the sham group only underwent the craniotomy. All procedures were carried out under aseptic conditions. The rats were returned to the feeding room for anesthesia recovery.

2.3. Magnetic resonance imaging

Serial and T2-weighed were performed on each group at 0, 7, 14, and 28 days after TBI ($n = 6$) with a Bruker 7.0T MR scanner (Bruker Analytik GmbH, Karlsruhe, Germany). The rats were anesthetized with isoflurane at 2% in ambient air during each imaging study. Contiguous coronal slices, centered 1.5 mm posterior to the bregma, were imaged with a resolution matrix = 256 × 256, field of view (FOV) = 30 mm × 30 mm, slice number = 16, slice thickness = 1 mm. Relaxation time TR = 2.0 s, and echo time TE = 12 ms. A single technician ran all the image acquisition without knowledge of the nature of the groupings. Contusion volumes were calculated using an Image J software package (ImageJ v.1.36, US National Institutes of Health, Bethesda, MD).

2.4. Sucrose preference test

After TBI, a sucrose preference test was employed to quantify symptoms of anhedonia which is indicative of the depression-like behavior. The animals were trained to consume a 1% sucrose solution prior to the operation. Before each test, they were deprived of food and water for 20 h. The animals were then allowed water and the 1% sucrose solution for 1 h. Bottle positions were switched at 0.5 h after the start of the test. The sucrose preference was calculated with the following formula described by Willner et al. [26]: sucrose preference (%) = (sucrose intake/total fluid intake) × 100%. All behavioral testing was conducted during the 12-h light cycle.

2.5. Forced swimming test

A forced swimming test was conducted to assess a depressive-like state on days 7 and 28 after surgery as described by Cryan et al. [27]. Rats were individually placed in a transparent cylinder (25 cm diameter, 60 cm tall) filled with water (25 ± 1 °C) to a depth of 40 cm for 15 min on day 1, in order to familiarize them with