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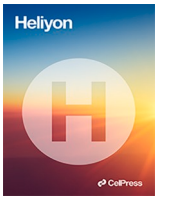

Abscisic acid ameliorates motor disabilities in 6-OHDA-induced mice model of Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is characterized by a myriad of symptoms, encompassing both motor disabilities and cognitive impairments. Recent research has shown that abscisic acid (ABA) is a phytohormone found in various brain regions of several mammals and exhibits neuroprotective properties. To investigate the effects of ABA on cognitive and motor disorders, a mouse model of PD was utilized. The administration of 6-hydroxydopamine (6-OHDA) to the lateral ventricles was conducted, with ABA (10 and 15 μg/mouse, i. c.v.) being administered for one week after the 6-OHDA injection for 4 days. Motor and cognitive performance were evaluated through the use of open field, rotarod, wire grip, and shuttle box tests. The results indicated that cognitive function and motor disorders were significantly impaired in 6-OHDA-treated animals. However, in mice treated with 6-OHDA, ABA (15 μg/mouse) significantly reversed balance and muscle strength deficits. It should be noted that the administration of ABA did not significantly improve cognitive impairment or rearing in Parkinsonism mice. Therefore, the findings suggest that ABA plays a crucial role in protecting mice from motor disabilities caused by 6-OHDA.

1. Introduction

It has been observed that Parkinson's disease (PD) is highly prevalent among individuals aged 60 and above, with a percentage exceeding 2%. This renders PD as one of the most commonly occurring disorders associated with age. The motor symptoms linked with this neurodegenerative disease include tremor, rigidity, bradykinesia, slowness of motion, poor gait functioning, and postural instability, to name a few [1]. In addition to motor dysfunction, PD patients also experience a broad spectrum of non-motor symptoms, including sleep disturbance, cognitive impairment, and other related conditions [2,3].

An association has been established between PD-related motor and cognitive impairments and an imbalance in excitatory and inhibitory neurotransmitter systems [4–6]. The primary cause of this neurodegenerative disorder is the demise or impairment of dopamine (DA)-secreting neurons in the substantia nigra pars compacta (SNc), according to multiple studies. The striatum, which is involved in various brain functions, such as motor learning and memory [7], receives inhibitory dopaminergic inputs from the substantia nigra. After dopaminergic denervation of the nigrostriatal pathway, there is an increase in subthalamic nucleus glutamatergic activity [8,9]. Hyperactivity of the glutamate neurotransmitter, which mediates synaptic transmission in stratum motor circuits, can impair neurotransmission [10]. Consequently, it appears that reducing the activity of excitation neurotransmitter systems can ameliorate PD symptoms.

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Abscisic acid (ABA), a plant hormone, has been demonstrated to be synthesized and secreted in animal tissues and cells in response to both normal and abnormal stimuli. In particular, Le Page-Degivry et al. (1986) have observed that the concentration of ABA in the brains of pigs and rats is higher than that in other tissues [11]. In light of the recent realization that ABA is produced by various animals, it is crucial for future studies to consider both its benefits and drawbacks. One study, nonetheless, has concluded that ABA does not induce significant toxicity in animal cells [12]. Notably, animal investigations have indicated that this phytohormone exhibits anti-inflammatory, anti-oxidative, and anti-apoptotic effects [13–17]. In both *in vitro* and *in vivo* studies, it has been demonstrated that ABA can alleviate oxidative stress [16–18].

Recent investigations have documented the neuroprotective properties of this particular substance on the nervous systems of animals. The administration of ABA has been shown to mitigate the occurrence of learning and memory deficits [19,20] anxiety-like behaviors [19] and, depression [21] in rats. Furthermore, ABA has the potential to enhance cognitive impairments in a rat model of high-fat diet-induced neuroinflammation [22,23] Alzheimer's [24,25] and, diabetes [13,26]. It is worth noting that ABA has been recognized to have protective effects against neurotoxicity induced by 6-hydroxy dopamine (6-OHDA) [16].

Given the presence of ABA in the brain [11,27] and the established evidence of its neuroprotective effects [19,20,28,29], the objective of the present study was to investigate the plausible beneficial effects of ABA central administration on motor and cognitive disorders in male mice with 6-OHDA-induced hemiparkinsonism.

2. Materials and methods

2.1. Animals

Male Swiss mice (weighing between 25 and 35 g) were selected for this investigation. These rodents were housed in controlled condition, where they were subjected to a 12-h light/dark cycle. Throughout the experiment, the ambient temperature was maintained at a consistent $22 \pm 2^{\circ}$ Celsius. The animals were provided with ad libitum access to both food and water. All experimental procedures were granted ethical approval by the Animal Research Ethics Committee of the Kerman Neuroscience Research Center, under Ethics Code IR. KMU.REC.1400.002.

2.2. Experimental design

A concise depiction of the experimental design timeline is presented in Fig. 1. Following a 30-min duration post the last ABA injection, behavioral tests were evaluated with sequential 15-min rest intervals among each assay in the subsequent order: open field test, rotarod, wire grip, and passive avoidance task. The mice were randomly allocated into several experimental groups, each consisting of 8 animals: Control group (Cont) which underwent no surgery and received no injection; Sham-operated group (Sham) which was cannulated and administered vehicle (DMSO); ABA-treated group (ABA) which received 10 and 15 μg/mouse ABA; 6OHDA-treated group (6OHDA) which received 40 μg in 2 μl saline containing 0.05% ascorbic acid (to prevent oxidation); 6OHDA plus ABA-treated group (6OHDA + ABA) which received ABA at the dose of 10 and 15 μg/mouse one week after 6OHDA injection.

2.3. Surgery and microinjection

Under anesthesia induced by a combination of ketamine and xylazine, with ketamine administered at 90 mg/kg and xylazine at 10 mg/kg intraperitoneally (i.p.), the animals were secured in a stereotaxic apparatus. Subsequently, the guide cannula was bilaterally inserted into the cerebral lateral ventricles at the specified coordinates of AP = −0.3 mm, ML = ±1.0 mm, and DV = −2.5 mm relative to the bregma. Dental cement was utilized to affix the implanted cannula to the skull surface, and the inlet of the cannula was sealed

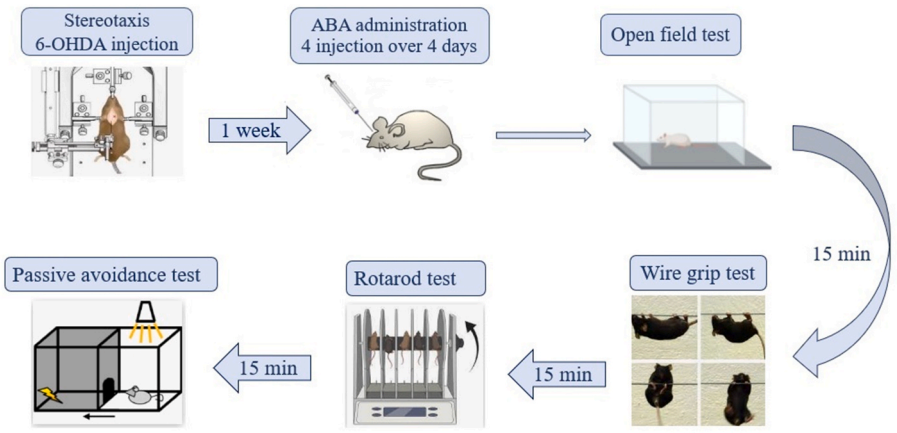

Fig. 1. The experimental design and study timeline.

with a stylet. Desipramine was administered intraperitoneally at a dose of 25 mg/kg, 30 min prior to the injection of 6-OHDA (hydrochloride salt; Sigma-Aldrich Co., LLC, USA) in order to inhibit noradrenaline reuptake. The administration of 6-OHDA was carried out by bilateral injection into the cerebral ventricle. In the same manner, sham-operated mice received 2 μl of a vehicle into the cerebral ventricle. Subsequently, a one week recovery period was allowed. Following this, (±)-cis, *trans*-ABA (Sigma-Aldrich, USA) was dissolved in a sterile saline solution (0.9% w/v sodium chloride) with dimethyl sulfoxide (DMSO) at a ratio of 2:1 (v/v) and delivered into the lateral ventricles for four consecutive days. Both drugs and their vehicles were administered using a 27-gauge internal cannula, which was connected via polyethylene tubing to a Hamilton syringe. The injection needle was left in place for an additional 1 min before being slowly withdrawn.

2.4. Open field test

The experimental paradigm employed was an open-field, characterized by a square arena (90 × 90 × 45 [H] cm) with floor demarcated into equal squares, facilitating the identification of central and peripheral regions. Upon gentle placement of the mice in the central area of the arena, the ensuing behavioral parameters were assessed, including total distance moved (TDM, cm), velocity (cm/s), and frequency of rearing and grooming over a period of 5 min. Analysis was performed offline using Ethovision7.1 (Noldus Information Technology, Netherland). Between sessions, the apparatus was meticulously cleaned with 70% ethanol and dried [30,31].

2.5. Rotarod test

The assessment of motor coordination and balance skills was carried out using the accelerating rotating rod test (manufactured by Hugo Sachs Electronik in Germany). Prior to the experiment, the animals underwent a training period of 24 h on the rotarod. The rotarod was set to accelerate from a minimum to a maximum speed, ranging from 10 to 60 rpm/min. During the experiment, animals were given three trials, each with a maximum time limit of 300 s and a 15-min rest interval. To determine motor coordination and balance, the average time spent on the rod during the three trials was recorded [32].

2.6. Wire grip test

In order to evaluate the muscular strength and balance of the test subjects, a wire grip examination was employed. This examination involved suspending the mice by both forepaws from an 80 cm long, 7 mm diameter horizontal steel wire, and allowing them to grasp it. Subsequently, the latency to fall was recorded with a stopwatch, after the subjects were given three trials each, separated by a 15 min rest interval [33].

2.7. Passive avoidance test

Passive avoidance learning and memory were evaluated utilizing a shuttle box apparatus, comprising of a lighted chamber and a dark chamber. The two chambers were divided by a grid door, and electric shocks were dispensed by a separate stimulator to the grid floor of the apparatus. The animals were introduced into the lighted area of the maze, and after a 10-s interlude, the door was opened, thereby allowing the animal to traverse to the dark chamber, without electric shock, for duration of 30 s. One hour following acclimation, the acquisition phase was executed, whereby the animal was directed to the dark compartment and upon entering, the animal received an electrical shock (0.5 mA, 50 Hz, for 1 s) via the stainless steel floor. The aforementioned component was reiterated up to a maximum of five instances, each separated by 15-min intervals, until the animal's capacity to avoid the dark compartment was attained, and the number of shocks necessary for such learning was documented. The memory related to passive avoidance was evaluated after a 24-h period following the learning stage. The subject mouse was situated within the illuminated compartment (at which point the entrance was sealed). Following a 10-s interval, the door was opened, and the duration of time taken to enter the dark chamber (referred to as the step-through latency; STL) was noted for a duration of 300 s [34].

2.8. Statistical analysis

The statistical analysis and figure production in this study were conducted using Graph Pad Prism 8. The data were presented as mean ± SEM. The criterion for statistical significance was set at $P < 0.05$. Non-parametric analysis was performed if the data were not significant, while parametric analysis was conducted if they were significant. The analysis of normally distributed data involved a one-way ANOVA, followed by the Tukey post hoc analysis for multiple comparisons between other groups. On the other hand, non-normally distributed data were presented as median and interquartile range and were analyzed using a Kruskal-Wallis test. Finally, pairwise comparisons between groups were conducted using Dunn's multiple comparisons test.

3. Results

3.1. Effect of 6-OHDA and 6-OHDA plus ABA on explorative and anxiety-related behaviors

Fig. 2 depicts significant differences amongst the experimental groups in their TDM [$F(5, 42) = 5.068$, $P = 0.001$], velocity [$F(4, 42) = 11.73$, $P = 0.001$] and rearing [$F(5, 42) = 6.757$, $P = 0.001$, Fig. 2A, B, C]. However, no significant difference was observed in

grooming frequency between the experimental groups [F (5, 42) = 1.510; P = 0.2072] (Fig. 2D). The 6-OHDA-injected animals showed a significant decrease in TDM ($P < 0.01$), velocity ($P < 0.001$) and rearing number ($P < 0.05$) compared to the Cont group. Conversely, treatment with 15 μg ABA resulted in a significant increase in TDM ($P < 0.05$, Fig. 2A) and velocity ($P < 0.001$, Fig. 2B) in contrast to the 6-OHDA group. In addition, Fig. 2C indicates that there was no significant difference in rearing numbers between 6-OHDA- and 6-OHDA plus ABA-treated mice.

3.2. Effect of 6-OHDA and 6-OHDA plus ABA on balance and muscle strength

The results displayed in Fig. 3 reveal significant differences among the experimental groups with respect to their muscle strength [F (5, 42) = 27.84; P = 0.001] during the wire grip test and balance function [F (5, 42) = 102.5; P = 0.001] during the rotarod test. The 6-OHDA group exhibited a decline in the time taken to fall during three consecutive trials in comparison to the Cont animals ($P < 0.001$) in wire grip test. Conversely, the 6-OHDA plus 15 μg ABA-treated mice demonstrated a significant increase in the time taken to fall as compared to the 6-OHDA group ($P < 0.001$, as shown in Fig. 3A). The mice in the 6-OHDA group also showed a decline in the time spent on the rod during motor learning and balance function in comparison to the Cont group ($P < 0.001$). The microinjection of 15 μg ABA proved to be effective in counteracting the observed effect of 6-OHDA ($P < 0.05$, as presented in Fig. 3B).

3.3. Effect of 6-OHDA and 6-OHDA plus ABA on passive avoidance learning and memory

The statistical analysis conducted on the data revealed significant differences among the experimental groups in terms of the number of shocks [H (5, 42) = 14.48; P = 0.0001] and STL [H (5, 42) = 7.345; P = 0.0004]. The outcomes demonstrated that the 6-OHDA group required a considerably higher amount of shocks to learn the task in comparison to the Cont animals ($P < 0.001$, Fig. 4A). Moreover, STL significantly diminished in the 6-OHDA-injected animals as compared to the Cont group ($P < 0.001$, Fig. 4B). Nonetheless, the administration of ABA did not have any effect on these consequences of 6-OHDA in the passive avoidance test.

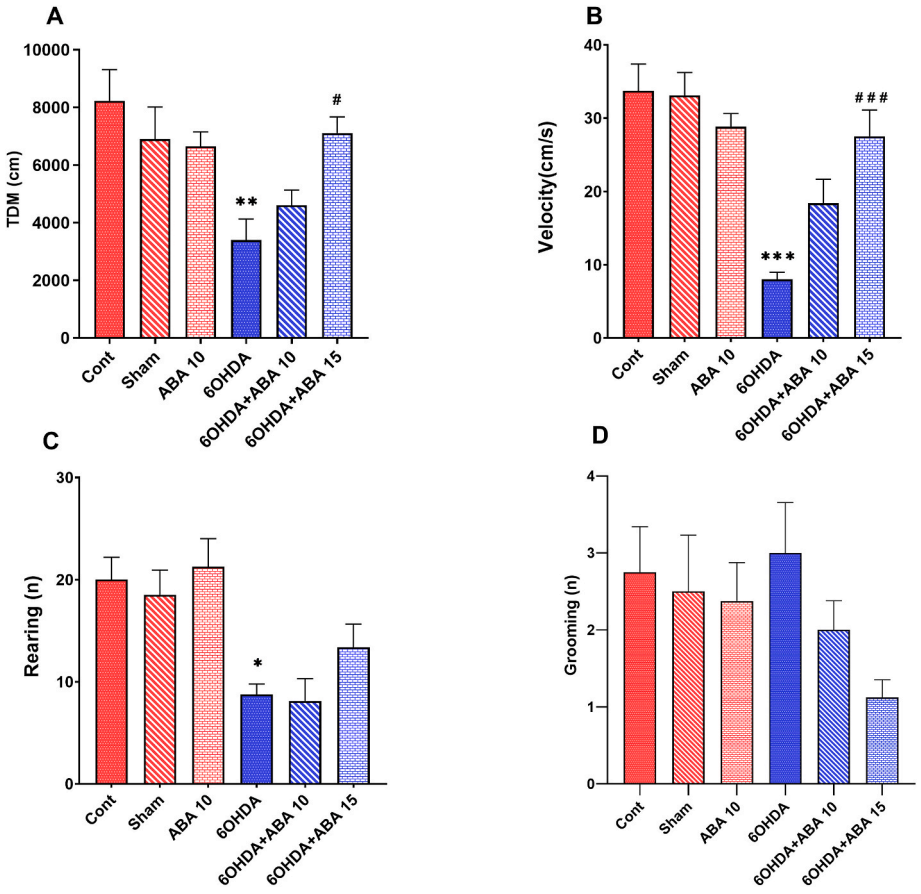

Fig. 2. The impact of ABA administration at 10 and 15 μg/mouse doses on the changes in exploratory and anxiety-like behaviors that are triggered by 6-OHDA. TDM (A), velocity (B), rearing (C), and grooming number (D). Data presented as mean ± SEM. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ versus Cont group; $^{\#}P < 0.05$ and $^{\#\#\#}P < 0.001$ versus 6-OHDA group.

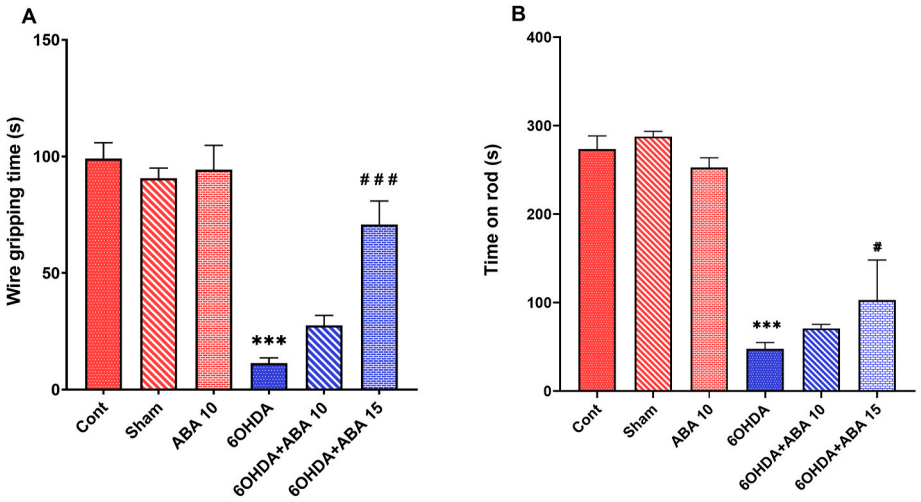

Fig. 3. The impact of ABA administration, with dosage of 10 and 15 μg/mouse, on muscle strength and balance function subsequent to 6-OHDA administration. Wire grip test (A), rotarod (B). Data presented as mean ± SEM. ***P < 0.001 versus Cont group; $^{\#}$P < 0.05 and $^{\#\#\#}$P < 0.001 versus 6-OHDA group.

4. Discussion

The objective of the current study was to investigate the potential impact of ABA on mice affected by cognitive and motor deficits resulting from 6-OHDA. The findings indicated that a central injection of ABA (15 μg/mouse) could restore balance and muscle strength in 6-OHDA-injected mice. However, the cognitive impairments induced by 6-OHDA remained unaffected despite the administration of ABA. It is widely accepted that an imbalance of free radicals and antioxidants significantly influences dopaminergic cell death in PD. The susceptibility of dopamine-rich brain regions to oxidative stress is attributed to the restricted antioxidant capacity of dopaminergic neurons, in addition to the generation of reactive oxygen species through dopamine auto-oxidation and metabolism [35–38]. The process of autoxidation of 6-OHDA by molecular oxygen or monoamine oxidase in the brain has been found to result in the destruction of dopaminergic neurons [39,40]. However, given that 6-OHDA is incapable of permeating the blood-brain barrier, the method of its introduction into the brains of experimental animals necessitates the use of stereotaxic surgery. Furthermore, one of the drawbacks of this model is its inability to induce Lewy bodies, which are one of the markers of Parkinson's disease.

An increased risk of PD has been associated with deficiencies in antioxidants such as vitamins A, C, E, and niacin [41]. Additionally, a decline in antioxidant enzyme activity has been observed in patients with PD [42]. Therefore, antioxidants are believed to have the potential to mitigate or halt the progression of neurodegenerative processes in PD.

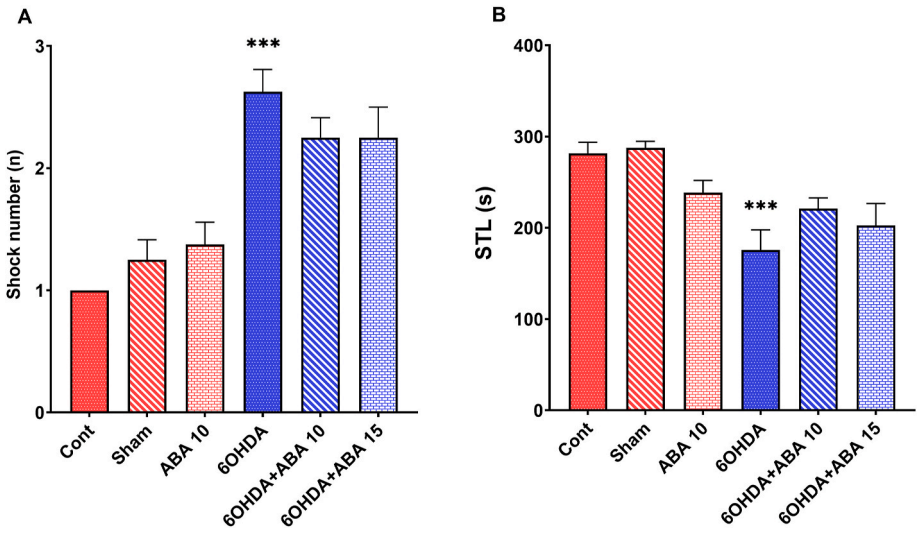

Fig. 4. Effect of ABA (10 and 15 μg/mouse) on passive avoidance after 6-OHDA administration. Number of shock (A), STL (B). ***P < 0.001 versus Cont group.

It is a widely recognized fact that ABA, a significant plant hormone, regulates various physiological processes, increases the activities of antioxidant enzymes, and amplifies gene expression in plants that code for antioxidants [43,44]. In response to environmental challenges, ABA plays a crucial role in regulating plant growth and survival. Recent studies have demonstrated that the antioxidant properties of this phytohormone in animals can have positive impacts. Based on the research conducted by Soti and colleagues, ABA can elevate antioxidant capacity, leading to favorable effects on body weight and feeding habits, while reducing MDA and H2O2 levels and increasing catalase and peroxidase activity in the diencephalon [17]. Furthermore, ABA effectively mitigates myocardium damage caused by isoproterenol by enhancing antioxidant capacity and regulating NO release in rats [18]. It has been demonstrated that ABA has anti-atherosclerosis [[45], anti-inflammatory [13,15], anti-nociceptive [46], and anti-cancer [47] properties. PD has been identified as being predominantly caused by oxidative stress and mitochondrial dysfunction [2,3]. In the context of maize seedlings, ABA has been shown to protect mitochondria from oxidative damage after chilling injury through the increased presence of antioxidant enzymes [48]. Prior research has indicated the generation of ROS as a result of 6-OHDA, leading to neuronal injury and mitochondrial damage [49,50]. Interestingly, Rafiepour et al. have reported that ABA can mitigate 6-OHDA-induced cell damage and changes in mitochondrial membrane potential in the SH-SY5Y cell line, serving as an *in vitro* model of PD [16].

Recent research has shown that ABA is produced in various regions of the brain, including the hypothalamus, hippocampus, cortex, and cerebellum, and is involved in the neurophysiological processes of mammals [20,27]. In addition, it has been reported that ABA can modulate emotions and alleviate symptoms associated with depression and anxiety, as well as the behaviors linked to these conditions [19,27].

The utilization of ABA in cognitive processes among rodents has been the subject of numerous studies. Both oral and central administration of ABA have been found to enhance spatial learning and memory, as evidenced by various research sources [19,20]. Moreover, ABA has been proven to reduce cognitive impairment in rats with neuroinflammation induced by a high-fat diet [28]. In rats, ABA has the potential to alleviate cognitive impairments caused by Alzheimer's [25] and diabetes [51].

An imbalance between the excitation and inhibition of striatal neuronal circuits leads to three primary manifestations in PD, namely tremor, stiffness, and akinesia [4,5,52]. The depletion of dopamine in the striatum is the primary pathogenic characteristic of PD [53]. Thus, dopamine replacement therapies are deemed as the standard treatment for PD's motor symptoms [54]. The extended usage of dopaminergic drugs has been found to induce involuntary movements [55]. Alongside dopamine depletion, glutamate neurotransmitters also contribute to the pathogenesis of PD [56].

The development and maintenance of motor fluctuations and dyskinesias induced by levodopa are modulated by numerous glutamate receptors present in dopaminergic neurons situated in the substantia nigra [57,58]. It has been found that antagonists of glutamate receptors possess neuroprotective properties that mitigate the loss of dopaminergic cells in the substantia nigra [59]. In addition, inhibition of *N*-methyl-D-aspartate (NMDA) receptors has been shown to terminate levodopa-induced dyskinesias in rats with Parkinson's disease through the research conducted by Papa and colleagues [57]. Furthermore, the NMDA receptor antagonist, Memantine, has been reported to have an impact on glutamatergic neuronal transmission, thereby improving attention and episodic memory in patients with PD [60]. Nevertheless, the utilization of glutamate antagonists is restricted due to the development of ataxia and lack of coordination [61].

The compound Phaseic acid, which shares similarities with ABA, has been demonstrated to act as an antagonist of the NMDA receptors, effectively blocking the NMDA glutamate receptors following ischemic brain injury. Similar to memantine, Phaseic acid inhibits glutamate receptors without competition. Thus, Phaseic acid or its analog may function as a glutamate receptor inhibitor in the mouse brain [62]. It is worth noting that the effects of ABA may endure for some time, given its half-life. However, since the duration of our evaluation was brief, this factor warrants consideration in future investigations.

Taken collectively, the results of this study propose that central ABA injections may aid in alleviating muscular weakness and balance-related deficiencies in mice induced by 6-OHDA. Notably, ABA treatment did not result in cognitive improvement in PD-affected mice.

Author contribution statement

Mohammad Shabani: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Monavereh Soti; Hoda Ranjbar: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Reyhaneh Naderi: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare no competing and financial interests exist.

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