Physiology and Pharmacology 26 (2022) 30-38
Original Article

The impact of sesamol and exercise on striatal TNF-α level, motor behavior, aversive memory and oxidative stress status in 6-hydroxydopamine-lesioned rats

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ABSTRACT

Introduction: Neuroinflammation and oxidative stress play critical roles in the pathophysiology of Parkinson's disease (PD), and neuroprotective agents could be helpful to slow down the dopaminergic neurodegeneration. Neuroprotective and antioxidant properties of exercise and sesamol have been previously reported. The current research evaluated the influences of sesamol and exercise on memory and motor impairments, oxidative stress and inflammatory markers in an experimental model of PD.

Methods: 6-hydroxydopamine (6-OHDA) was microinjected into the medial forebrain bundle of male rats. Treatment with sesamol (50mg/kg) or treadmill exercise was performed for 7 weeks. Behavioral and biochemical assessments were performed at the end of 6th week after 6-OHDA injection.

Results: Net number of rotations and tumor necrosis factor (TNF)-α level was significantly enhanced in 6-OHDA group in comparison with sham group. Also, step-through latency was decreased in this group along with increased lipid peroxidation and decreased total thiol levels in the hippocampus. Moreover, sesamol and exercise, alone or in combination, improved rotational behavior, which was accompanied by decreased striatal TNF-α level. However, sesamol and/or treadmill exercise had no effect on aversive memory, although exercise enhanced hippocampal total thiol level.

Conclusion: Beneficial properties of sesamol and treadmill exercise for amelioration of motor impairments might be due to their anti-inflammatory activities.

Keywords:
Sesamol
6-OHDA
Exercise
Motor activity
Memory
Oxidative stress

Introduction

Parkinson's disease (PD) is distinguished by motor deficits such as bradykinesia and resting tremor as a result of damage and death of dopaminergic nigrostriatal neurons (Shulman et al., 2011). Patients with PD also develop non-motor impairments including poor memo-

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Received 19 December 2020; Revised from 7 April 2021; Accepted 10 April 2021

Citation: Shahidani S, Rajaei Z, Alaei H, Mohammadzadeh S. The impact of sesamol and exercise on striatal TNF-α level, motor behavior, aversive memory and oxidative stress status in 6-hydroxydopamine-lesioned rats. Physiology and Pharmacology 2022; 26: 30-38. http://dx.doi.org/10.52547/phypha.26.1.6

ry performance, anxiety, depression and sleep disorders (Getz and Levin, 2017). Multiple factors such as neuroinflammation (Qian et al., 2010) and oxidative stress (Subramaniam and Chesselet, 2013) play roles in the etiology of PD. Oxidative stress is considered as a key factor in the onset of PD. Dopamine auto-oxidation and metabolism appears to be the source of reactive oxygen species (ROS) and H2O2 (Schapira, 2008). Excessive production of ROS can result in neuronal damage by attack on membrane polyunsaturated fatty acids and production of lipid peroxidation in substantia nigra (Dexter and Jenner, 2013). Moreover, alterations in major antioxidant enzymes levels such as glutathione indicate that oxidative stress is engaged in the pathophysiology of PD (Zaman et al., 2021; Bjørklund et al., 2021).

Substantial evidences also indicate that neuroinflammation have a crucial role in the pathogenesis of PD (Lee et al., 2009). In this disease, microglia and astroglia cells are activated under the influence of various proinflammatory initiators such as α-synuclein and cytokines (Lee et al., 2010; Long-Smith et al., 2009), thus the density of activated microglia is enhanced in the substantia nigra and striatum. Subsequently, the level of inflammatory cytokines such as tumor necrosis factor (TNF)-α is enhanced in the brain and blood of patients of PD (Pieper et al., 2008; Long-Smith et al., 2009). TNF-α also activates microglial cells in the midbrain and enhances inflammatory responses, ROS and nitric oxide radicals which damage dopaminergic neurons (Niranjan, 2014).

Nowadays, most drugs used for PD treatment do not prevent the degeneration of nigrostriatal dopaminergic neurons. Thus, application of neuroprotective agents to cease or postpone the process of neurodegeneration is recommended.

Sesamol is known as the main active constituent of sesame seed oil. Sesamol possesses several pharmacological activities, including antioxidant (Parihar et al., 2006), neuroprotective (Kuhad and Chopra, 2008), anti-inflammatory (Chopra et al., 2010) and hepatoprotective (Hsu et al., 2007) effects. It was shown that sesamol inhibits the effects of ultraviolet radiation and brain lipid peroxidation level in rat (Prasad et al., 2005). In addition, sesamol reduces ROS production and so reduces mitochondrial damage and apoptosis in the rotenone model of PD (Sonia Angeline et al., 2013). Sesamol also decreases lipid peroxidation and increases antioxidants level in the serum upon intrastriatal injection of 6-hydroxydopamine (6-OHDA) (Khadira Sereen et al., 2017). However, the effect of sesamol on motor and memory impairments through inflammatory and oxidative stress mechanisms have not been previously reported in a 6-OHDA model of PD.

Additionally, among non-pharmacological approaches, physical exercise has been shown to possess neuroprotective properties in neurodegenerative disorders including Alzheimer's disease (Um et al., 2008). Exercise was shown to improve balance, gait, posture and life quality in patients with PD (Goodwin et al., 2008). Also, physical training enhanced antioxidant enzymes and brain-derived neurotrophic factor level (BDNF) in the central nervous system (Aguiar et al., 2008; Macêdo et al., 2017). Although several evidences suggest the neuroprotective properties of exercise on PD (Tajiri et al., 2010), there is still some controversy regarding this issue (Aguiar et al., 2014). For instance, several studies reported that training in MPTP mouse model of PD does not inhibit mitochondrial dysfunction or damage of dopaminergic nigrostriatal neurons (Aguiar et al., 2014). In our recent research, we reported anti-inflammatory and antioxidant properties of exercise in PD (Shahidani et al., 2019; Hamzehloei et al., 2019).

The present study evaluated the impact of sesamol, alone and combined with exercise, in an experimental model of PD, by assessment of motor behavior, aversive memory, striatal TNF-α level and hippocampal oxidative stress markers.

Materials and methods

Animals

Male Wistar rats (250-300g) were used in the current study. Animals were kept in a room at a controlled temperature under a 12h light/dark cycle. They had access to food and water *ad libitum*. All experimental protocols were approved by Ethics Committee for Animal Experimentation (IR.MUI.REC.1395.3.676).

Experimental design

Rats were classified to 5 groups (n=8): 1) sham-operated group; 2) 6-OHDA-lesioned group; 3) sesamol group; 4) exercise group and 5) sesamol+exercise group. Groups 2-5 received microinjection of 16μg 6-OHDA in 4μl ascorbate-saline into the left medial forebrain bundle (MFB). Treadmill exercise and/or sesamol injection (50mg/kg, IP) was begun one week before surgery and

continued for 6 weeks post-surgery.

In order to induce PD, animals were anesthetized with chloral hydrate (450mg/kg) and located in the stereotaxic instrument (Stoelting, USA). Then, the 6-OHDA was microinjected into the left MFB at a 1µl/min rate according to the following coordinates: ML: -1.8mm, AP: 3.6mm, DV: −8.2mm (Paxinos and Watson, 2005). A same volume of the ascorbate-saline was microinjected to the brain in the sham-operated group.

Physical exercise

Rats in exercise groups were accustomed to running on a five-lane motorized treadmill at a speed of 10m/min for 5min/day for one week. Then, the exercise groups performed a running program at the speed of 17m/min for 40min/day for 7 weeks (Shahidani et al., 2019).

Aversive memory

Aversive memory was evaluated by a shuttle box at the end of week 6 post-surgery (days 39, 40). The instrument is composed of light and dark chambers, connected by a guillotine door. On acquisition phase, each rat was located in the light chamber for one minute. After entering to the dark chamber, a 0.5mA electric shock was delivered to the rat feet for 3s. On retention phase which was performed 24h later, the rat was again located in the light chamber and the latency to enter the dark chamber was measured with a cut-off time of 300s (Haddadi et al., 2018).

Rotational behavior

Apomorphine (2mg/kg, IP) was injected to rats at the end of the 6th week post-surgery to diagnose hemiparkinsonian rats by rotational behavior. Each rat was accustomed to a plexiglass container (28×28×50cm) for 10min. About 1min after apomorphine injection, the ipsilateral and contralateral rotations was measured for 30min in a quiet space. Net number of rotations was determined as the difference between the ipsilateral and contralateral rotations (Hosseini et al., 2016).

Preparation of tissue homogenate

Rats were euthanized after the end of the behavioural tests on day 42. Then, the entire hippocampus and striatum was collected, weighed and homogenized with NaCl solution 10 times (w/v).

Cytokine levels

The striatal homogenates were centrifugated at 3000rpm for 5min to remove participation. Then, TNF-α level in the supernatants was measured by an ELISA kit (ebioscience Co, USA). Data were presented as pg/ml.

TBARS levels

Thiobarbituric acid reactive substances (TBARS) was measured to estimate lipid peroxidation level in the hippocampus. To determine, trichloroacetic acid, thiobarbituric acid and hydrochloric acid was added to the homogenate. It was then incubated at 100°C for 45min. After centrifuging at 1000g for 10min, the absorbance of samples was read at 535nm. The level of TBARS was estimated by: $C(M) = A/1.65\times10^5$ (Haddadi et al., 2018).

Total thiol concentration

DTNB (2,2′-dinitro-5,5′-dithiodibenzoic acid) was used as a reagent to estimate total thiol groups in the hippocampus. The protocol was done as described before (Haddadi et al., 2018).

Statistical analyses

Data were presented as the mean±SEM. The results were analyzed by one-way analysis of variance (ANOVA) followed by the LSD *post hoc* test. $P<0.05$ was considered significant.

Results

Rotational behaviour

Net number of rotations following apomorphine injection was increased in 6-OHDA group in comparison with sham group at the end of the experiment ($P<0.001$, Figure 1). Moreover, treatment with sesamol ($P<0.05$), exercise ($P<0.05$) and sesamol along with exercise ($P<0.05$) attenuated rotations in comparison with 6-OHDA group (Figure 1).

Aversive memory

The latencies in 6-OHDA group was shorter than sham group ($P<0.05$, Figure 2). In addition, sesamol and exercise (alone and in combination) did not significantly change the latencies in comparison with 6-OHDA group (Figure 2).

TNF-α level

Striatal TNF-α levels was increased in 6-OHDA group

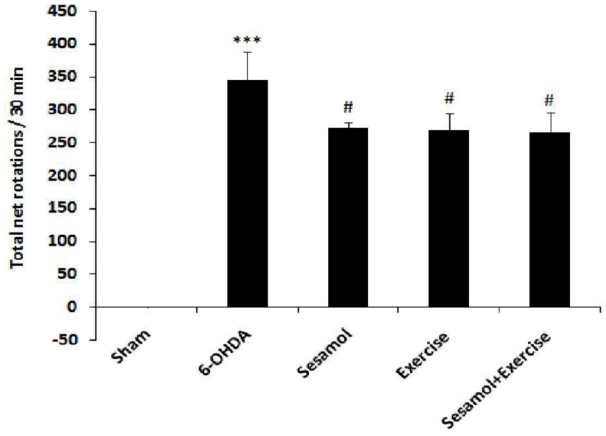

FIGURE 1. Effects of sesamol (50mg/kg) and exercise on net number of rotations in experimental groups upon a period of 30min. Data are expressed as mean±SEM. $^{***}P<0.001$ vs sham group; $^{\#}P<0.05$ vs 6-OHDA group.

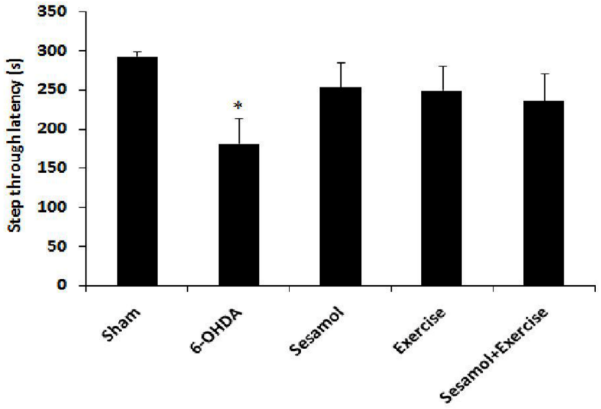

FIGURE 2. Effects of sesamol (50mg/kg) and exercise on latency to enter the dark chamber in experimental groups. Data are expressed as mean±SEM. $^{*}P<0.05$ vs sham group.

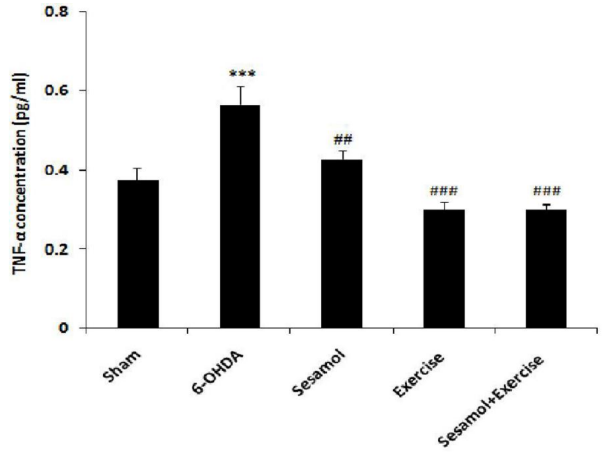

FIGURE 3. Effects of sesamol (50mg/kg) and exercise on striatal TNF-α level in experimental groups. Data are expressed as mean±SEM. $^{***}P<0.001$ vs sham group; $^{\#\#}P<0.01$ and $^{\#\#\#}P<0.001$ vs 6-OHDA group.

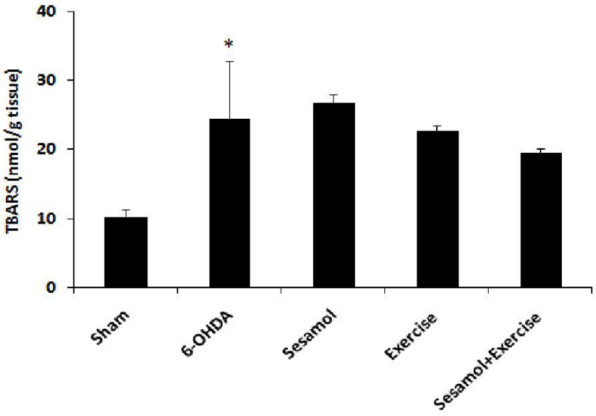

FIGURE 4. Effects of sesamol (50mg/kg) and exercise on hippocampal TBARS levels in experimental groups. Data are expressed as mean±SEM. $^{*}P<0.05$ vs sham group.

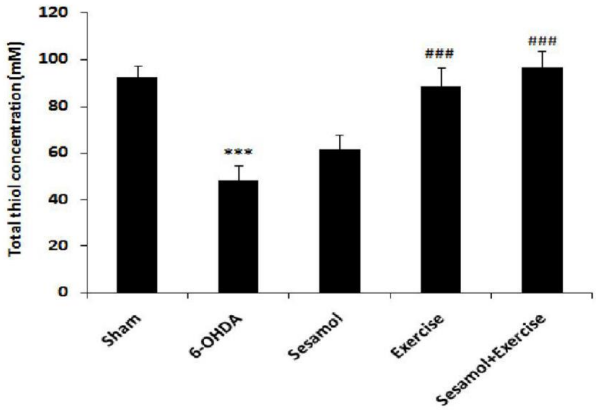

FIGURE 5. Effects of sesamol (50mg/kg) and exercise on hippocampal total thiol level in experimental groups. Data are expressed as mean±SEM. $^{***}P<0.001$ vs sham group; $^{\#\#\#}P<0.001$ vs 6-OHDA group.

in comparison with sham group (P<0.001, Figure 3). Furthermore, sesamol (P<0.01), exercise (P<0.001) and sesamol along with exercise (P<0.001) decreased striatal TNF-α levels in comparison with 6-OHDA (Figure 3).

Lipid peroxidation level

Hippocampal TBARS levels was increased in 6-OHDA rats in comparison with the sham group (P<0.05, Figure 4). Furthermore, treatment with sesamol and exercise (alone and in combination), had no effect on increased TBARS levels in the hippocampus (Figure 4).

Total thiol level

Hippocampal total thiol level was decreased in 6-OHDA group in comparison with sham group (P<0.001, Figure 5). Sesamol alone had no effect on total thiol level. However, physical exercise alone (P<0.001) and along with sesamol (P<0.001) enhanced total thiol level in comparison with 6-OHDA group (Figure 5).

Discussion

Our findings revealed that 6-OHDA injection into MFB induced significant impairments in motor behavior and aversive memory six weeks after injection. Also, 6-OHDA significantly increased striatal TNF-α and hippocampal TBARS levels, while reduced total thiol level. Furthermore, chronic treatment of sesamol and exercise attenuated apomorphine-stimulated rotational behavior by decreasing TNF-α level in the striatum. However, treatment with sesamol and treadmill exercise had modest effect on aversive memory.

The 6-OHDA injection induces oxidative stress which leads to damage of dopaminergic neurons in the substantia nigra and subsequently causes motor and non-motor impairments as seen in patients of PD (Campos et al., 2013). The 6-OHDA has a pro-oxidant function and produces ROS in the extracellular space (Hanrott et al., 2006). Excess formation of free radicals and consequent oxidative stress enhances lipid peroxidation level, DNA oxidation products, modification of proteins, and consequently neuronal destruction and death. Several evidences also suggest that 6-OHDA lesion leads to neuroinflammation (Cicchetti et al., 2002) and increases brain inflammatory cytokines in PD (Nagatsu and Sawada, 2005). In our study, 6-OHDA injection into MFB enhanced striatal TNF-α level. In accordance with these results, some evidences have revealed that proinflammatory cytokines level, especially TNF-α, is enhanced in the substantia nigra and striatum of patients with PD, leading to neuronal loss (Hirsch and Hunot, 2009).

Unilateral injection of 6-OHDA causes unilateral injury to the dopaminergic nigrostriatal pathway, leading to up-regulation of dopamine receptors on the lesioned-side. This makes a motor asymmetry which is evaluated by apomorphine as rotations (Schwarting and Huston, 1997). Evaluation of rotational behavior is a suitable method for assessing the imbalances of dopamine in striatums of the hemiparkinsonian rats (Mokry, 1995). According to our results, treatment with sesamol decreased the rotations in comparison with 6-OHDA group rats. The results also showed that sesamol decreased TNF-α level in the striatum. Conclusively, the beneficial impact of sesamol on motor impairment might be partly attributed to the anti-inflammatory properties of sesamol. To the best of our knowledge, this is the first study that reports the positive influence of sesamol on motor deficit by decreasing TNF-α level in a 6-OHDA PD model. In this context, it was previously reported that treatment with sesamol enhanced dopamine level in the striatum upon intrastriatal injection of 6-OHDA along with decreased TBARS levels and increased antioxidants level in the serum (Khadira Sereen et al., 2017); however, motor activity was not assessed in that study. The effects of sesamol on Huntington's disease model has been also reported by Kumar and colleagues (2009). They showed that pretreatment with sesamol improved locomotor activity and attenuated oxidative damage in the striatum and cortex of 3-nitropropionic acid-lesioned rats.

Our findings also revealed that exercise decreased TNFα level in the striatum. In this context, another study showed that exercise decreased the amounts of striatal TNF-α and interleukin-1β in a 6-OHDA PD model in mice (Tuon et al., 2015). Our data also demonstrated that exercise for 7 weeks ameliorated rotations in rats. This result is in line with another study that reported physical training reduced amphetamine-induced rotations in 6-OHDA-treated rats (Tajiri et al., 2010). Other mechanisms might be involved in mediating the impact of exercise on PD. It was shown that exercise training decreased TBARS level and increased total thiol level in the striatum of rats exposed to 6-OHDA (Hamzehloei

et al., 2019). The effect of exercise on increased levels of BDNF and glial cell-derived neurotrophic factor in the striatum has also been reported (Tajiri et al. 2010; Speck et al., 2019). Shi and colleagues (2019) have shown the influence of exercise on striatal glutamate levels and glutamatergic transmission through metabotropic glutamate receptors in hemiparkinsonian rats. Present data also revealed that treatment with sesamol combined with treadmill exercise ameliorated rotational behaviour. Improvement of rotational behaviour could be due to anti-inflammatory properties of sesamol and treadmill exercise.

Patients with PD also develop cognitive impairments and a large majority of PD patients develop dementia with progression of the disease (Lang and Lozano, 1998). Cognitive deficits have also been demonstrated in experimental models of PD and it was shown that oxidative stress plays a key role in memory impairment (Rajaei et al., 2016). Experimental evidences also indicated that 6-OHDA-induced oxidative stress is involved in neuronal injury via protein oxidation, lipid peroxidation and DNA damage. In our research, microinjection of 6-OHDA also led to aversive memory impairment by increasing the TBARS level as well as decreasing total thiol level in the hippocampus. Behavioural analysis also showed that sesamol and/or exercise did not significantly enhance latencies in passive avoidance test in 6-OHDA-lesioned rats. However, there was a tendency toward an increase in latencies in three treatment groups, suggesting that sesamol or exercise could have a modest memory-enhancing effect in this model. In this context, it has been reported that sesamol improves cognitive dysfunction via restoration of oxidative defense of the hippocampus in 3-nitropropionic acid model of Huntington's disease (Kumar et al., 2010). A recent study also demonstrated that treatment of aging mice with sesamol as dietary supplementation for 12 weeks improved aging-associated cognitive impairments by suppression of malondialdehyde production and enhancement of antioxidant enzymes in the hippocampus of mice (Ren et al., 2020). Zhang and colleagues (2021) have also reported that sesamol alleviates chronic intermittent hypoxia-induced learning and memory deficits via increased the activity of superoxide dismutase and decreased level of malondialdehyde in the hippocampus. In contrast with these studies, present findings showed that treatment with sesamol had no effect on oxidative stress status in the hippocampus. The reason for this difference could be associated with the type of disease, dosage of sesamol and the duration of treatment with sesamol.

In the present study, exercise training for 7 weeks significantly enhanced hippocampal total thiol level in hemiparkinsonian rats. Thus, the modest impact of exercise on memory performance might be due to its antioxidant activity in the hippocampus. In confirmation of this, Macêdo and colleagues (2017) demonstrated that treadmill exercise improved memory and enhanced antioxidant enzymes activity in the hippocampus of healthy rats. Other mechanisms responsible for exercise effects on memory function could be through its effects on neurogenesis and BDNF level in the hippocampus. In this regard, it was shown that treadmill exercise for 4 weeks improved long-term memory impairment and enhanced the number of BrdU/NeuN positive cells as well as BDNF level in the hippocampus of MPTP mice (Sung, 2015).

Conclusion

Conclusively, the results indicated that chronic treatment with sesamol and physical exercise for 7 weeks improved rotational behavior in 6-OHDA-lesioned rats. This might be partly attributed to anti-inflammatory properties of sesamol and physical exercise in the 6-OHDA model of PD. More neurochemical and histological studies is needed to prove full neuroprotective effects of sesamol and exercise on Parkinson's disease.

Acknowledgment

This study was supported by a grant from the Council of Research, Isfahan University of Medical Sciences.

Conflict of interest

None.

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