

The Anti-obesity Agent d-norpseudoephedrine Protects Against Rotenone-induced Parkinson's Disease in Mice

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ABSTRACT

The effect of the ephedrine derivative D-norpseudoephedrine on rotenone-induced Parkinson's disease in mice was studied. Mice received subcutaneous injections of rotenone (1.5 mg/kg, every other day for two weeks) and were treated with the vehicle, L-dopa (25 mg/kg) or pseudoephedrine at doses of 1.8, 5.4 and 10.8 mg/kg once daily orally. Brain levels of malondialdehyde (MDA), reduced glutathione (GSH) and nitric oxide (NO) were determined and histopathological study of the brain was done. Motor testing included stair, wire hanging and wood walking tests. Results indicated that compared with vehicle controls, rotenone caused significant increases in brain MDA and NO along with GSH depletion. Rotenone impaired neuromuscular strength, and motor balance and coordination. There were also marked decrease in size and number of substantia nigra pigmented cells and deeply stained neurons and karyorrhexis in the cerebral cortex and hippocampus. Treatment with pseudoephedrine reduced brain MDA, NO and increased GSH levels and improved motor performance. Furthermore, pseudoephedrine prevented substantia nigra dopaminergic cell death and neurodegeneration in the cortex and hippocampus brain regions in a dose-dependent manner. These data suggest that pseudoephedrine might prove of benefit adjunctive therapy of Parkinson's disease.

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1. Introduction

Parkinson's disease (PD) is a chronic and progressive motor disorder and the second most common age-related neurodegenerative disease after Alzheimer's disease. The majority of PD cases are sporadic, occurring with median age at onset at 60 years and often referred to as "idiopathic PD" (Pankratz and Foroud, 2007). The disease occurs in about 1% of individuals over the age of 65 years and in up to 3% among persons 80 years of age and older (Alves et al., 2008). The cardinal symptoms are those of disturbed motor activity manifested by slowness, reduced amplitude, and impaired initiation of voluntary movements (bradykinesia/akinesia), and decrease of spontaneous or associated movements, muscular stiffness or rigidity, postural abnormalities and resting tremor (Berardelli et al., 2001). These result from a preferential and progressive loss of dopamine-producing neurons of the substantia nigra pars compacta (SNc) and striatum of the midbrain basal ganglia (Hughes et al., 1992) and the subsequent consequent disruption of the basal ganglia circuitry that control motor movement via connections with thalamocortical and brain stem motor

systems (Santens et al., 2003). The exact cause of idiopathic PD is still unknown but is largely thought to involve exposure to environmental toxin coupled with genetic factors (Wirdefeldt et al., 2011). In this context, a number of epidemiological studies implicated pesticide, herbicide exposure with an increase in the risk for developing PD (Ritz et al., 2016). In animal studies, rotenone, a naturally occurring pesticide was shown to cause motor impairment, nigrostriatal cell loss and α -synuclein inclusions similar to what is found in PD (Sherer et al., 2003).

The mechanisms underlying the death of SNc dopaminergic neurons are not entirely understood but there is strong evidence to suggest an important role for oxidative stress where markers of lipid peroxidation, DNA oxidation, and protein oxidation besides glutathione depletion have been found in the substantia nigra of PD patients, post-mortem (Nagatsu and Sawada, 2007). The SNc in PD appear to be exposed to inappropriately high levels of reactive oxygen species (ROS) beyond their antioxidant capacity. Sources of ROS include auto-oxidation of dopamine or oxidative metabolism of dopamine by the enzyme monoamine oxidase (Hermida-Ameijeiras et al., 2004), increased SNc content of the redox-active transition metal iron undergoing cell damaging redox-cycling reactions (Dexter et al., 1989).

The treatment of PD is directed towards correcting the biochemical deficit by administering levodopa (L-dopa), the precursor of dopamine, which results in alleviating the motor dysfunction. However, after several years of L-dopa treatment, complications such as wearing off phenomenon and dyskinesia arise, necessitating the introduction of other drugs eg., dopamine receptor agonists, monoamine oxidase-B inhibitors and catechol-O-methyltransferase inhibitors. Nevertheless, the continued death of dopaminergic neurons over the time medications, diminish the ability of these drugs to control symptoms (Abdel-Salam, 2015). This emphasizes the search for neuroprotective or neuroregenerative therapies.

D-norpseudoephedrine (PSE) is commonly used as oral decongestant (Eccles et al., 2005) and appetite suppressant for the treatment of obesity (Hauner et al., 2017). The drug which is structurally related to the potent psychostimulant amphetamine, increases dopamine release in the striatum and nucleus accumbens and results in the activation of D1 dopamine receptors (Kumarnsit et al., 1999). D-norpseudoephedrine is also known as cathine, and together with cathinone constitutes the active ingredients of leaves of "Khat" (Wagner et al., 1982). In humans, cathinone is biotransformed to d-norpseudoephedrine (Guantai and Maitai, 1983). Cathinone and cathine are thus considered to be natural amphetamines, although possessing fewer addictive properties (Kalix, 1990). Previous studies have shown that low doses of amphetamine were able to protect against rotenone-induced substantia nigra dopaminergic neurodegeneration (Abdel-Salam et al., 2020). Due to its similarity in structure with amphetamine, it possible that PSE may also exert neuroprotective effect.

The present study therefore aimed to elucidate the effect of PSE in brain neurodegeneration induced by rotenone injection in mice. The modulatory effect of PSE and the standard anti-parkinsonian drug L-dopa on oxidative stress biomarkers, motor impairments and histopathological changes caused by rotenone were examined.

2. Materials and Methods

2.1. Animals

Swiss male albino mice, weighing 25-26 g were obtained from the breeding colony maintained at the animal house of National Research Center, Cairo, Egypt. Animal procedures were performed in accordance with the ethics committee of the National Research Centre and followed the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

2.2. Drugs and chemicals

Rotenone was obtained from Sigma-Aldrich (St Louis, MO, USA). D-norpseudoephedrine (Mirapro N) was obtained from October Pharma, Egypt. Rotenone was freshly prepared in 100% dimethyl sulfoxide. D-norpseudoephedrine was dissolved in saline obtain the necessary doses. All

the used chemicals and reagents in the present study were of analytical grade and obtained from Sigma-Aldrich. The doses of norpseudoephedrine were selected based on the human dose after conversion to that of mice according to the Paget and Barnes conversion tables (Paget and Barnes, 1964).

2.3. Experimental design

Mice were randomly divided into 6 groups (6 animals each).

Group 1 received the vehicle (DEMSO) three times a week.

Group 2 received subcutaneous injection of rotenone (1.5 mg/kg) every other day. Group 3 received rotenone every other day along with L-dopa 26 mg/kg orally daily.

Group 4 received rotenone every other day along with pseudoephedrine 1.8 mg/kg orally daily.

Group 5 received rotenone every other day along with pseudoephedrine 5.4 mg/kg orally daily.

Group 6 received rotenone every other day along with pseudoephedrine 10.8 mg/kg orally daily.

Treatment were continued for two weeks, then behavioral tests were done 24 hrs after last injection of rotenone, and at the end of the day, mice were euthanized by cervical dislocation and each brain was quickly removed, washed with ice-cold phosphate-buffered saline (PBS, pH 7.4), dissected on ice cold plate, weighed, and stored at -80°C . For the biochemical analyses, the tissues were homogenized in 0.1 M phosphate-buffered saline at pH 7.4 to give a final concentration of 10 % w/v. Homogenization was performed using a homogenizer (ULTRA-TURAX, IKA T10 basic, Germany) at speed 5000 rpm for 30 seconds.

2.4. Biochemical assays

2.4.1. Determination of lipid peroxidation

Lipid peroxidation was measured in brain homogenates by determining malondialdehyde (MDA) according to Nair and Turne (1984). In this assay 2-thiobarbituric acid reacts with MDA at 25°C to yield a red colored complex with a peak absorbance at 532 nm.

2.4.2. Determination of reduced glutathione

Reduced glutathione was determined in brain homogenates according to Ellman (1959). In this assay, Ellman's reagent (DTNB; 5, 5'-dithiobis (2-nitrobenzoic acid)) reacts with the free thiol group of GSH to form 2-nitro-s-mercaptobenzoic acid. The chromophore has yellow color and is determined with spectrophotometer at 412 nm.

2.4.3. Determination of nitric oxide

Nitric oxide production was determined by measuring nitrite in the supernatant with the Griess reagent. Nitrate is converted to nitrite with by the enzyme nitrate reductase. Nitrite then reacts with the Griess reagent to form a purple azo compound, and its absorbance is measured at 540 nm with spectrophotometer (Archer, 1993).

2.5. Behavioral testing

2.5.1. Wire hanging test

Wire hanging test is used to assess grip strength. Mice were placed on a steel wire (25 cm long, 0.2 cm in diameter) hanging by their forelimbs 25 cm above the bench for a maximum of 3 minutes. The time each mouse spent suspended from the wire was recorded for three trials (Crawley, 2017).

2.5.2. Wood walking test

To assess motor coordination and balance, mice were made to cross over a wooden stick (~1 m in length, 1 cm in width and elevated 30 cm from the ground) and the time each mouse spent to reach the end is recorded (Rogers, 1997).

2.5.3. Stair test

In order to assess skilled reaching, mice were placed at the bottom of a stair (30 cm in length), placed at an angle of 55° above the bench, and the latency to climb the stair is recorded for each mouse (Baird et al., 2001).

2.6. Statistical analysis

The experimental data are expressed as mean \pm SE. Differences between vehicle control and treatment groups were tested using one-way ANOVA followed by Tukey's multiple comparisons test. Statistical analysis was performed using GraphPad Prism 6 for Windows (GraphPad Prism Software Inc., San Diego, CA, USA) was used. Statistical significance was considered at a probability value of less than 0.05.

2.7. Histopathology

Brain sections were fixed in freshly prepared 10% neutral buffered formalin, processed routinely, and embedded in paraffin. Paraffin sections 5 μ m thick were prepared and stained with hematoxylin and eosin for histopathological examination. Images were examined and photographed under a digital camera (Microscope Digital Camera DP70, Tokyo, Japan), and processed using Adobe Photoshop version 8.0 (San Jose, CA, USA).

3. Results

Test the effectiveness of a professional intervention program based on the techniques of rational-emotional therapy in amending the irrational thoughts related to the pressures of life for forced retirees. A set of sub-goals emanates from this goal:

3.1. Biochemical results

3.1.1. Lipid peroxidation

In mice treated with only rotenone, the level of MDA increased by 72.3% (31.69 ± 0.58 vs. 18.39 ± 0.95 nmol/g. tissue) compared with the vehicle group. Following treatment with PSE at 5.4 and 10.8 mg/kg, MDA levels significantly decreased by 35.5% and 38.3% (from 31.69 ± 0.58 in the rotenone only group to 20.43 ± 0.44 and 19.54 ± 0.80 nmol/g. tissue in the rotenone/PSE- treated groups). On the other hand, treatment with L-dopa resulted in 28.5% decrease in MDA level compared to the rotenone control (22.65 ± 0.91 vs. 31.69 ± 0.58 nmol/g. tissue).

3.1.2. Nitric oxide

Compared with mice receiving the vehicle, mice that were treated with rotenone alone showed significantly increased level of nitric oxide by 114.9% (48.93 ± 1.13 vs. 22.77 ± 1.57 μ mol/g. tissue). In rotenone/PSE-treated groups, the level of nitric oxide significantly decreased after treatment with PSE at 5.4 and 10.8 mg/kg by 25.3% and 36.8%, respectively (from 48.93 ± 1.13 to 36.53 ± 1.22 and 30.92 ± 1.54 μ mol/g. tissue). Meanwhile, a significant decrease in nitric oxide by 30.3% was observed in rotenone/L-dopa-treated group compared to rotenone control (34.09 ± 1.85 vs. 48.93 ± 1.13 μ mol/g. tissue).

3.1.3. Reduced glutathione

Rotenone treatment reduced the brain reduced glutathione content by 51.4% compared with that of the vehicle-treated control (1.59 ± 0.06 vs. 3.27 ± 0.15 μ mol/g. tissue). PSE significantly attenuated the rotenone-induced decrease in reduced glutathione in a dose-dependent manner. In rotenone/PSE-treated groups, the level of reduced glutathione increased by 40.9, 74.8 and 93.1%. Values are 2.24 ± 0.08 , 2.78 ± 0.09 and 3.07 ± 0.06 for 1.8, 5.4 and 10.8 mg/kg PSE vs. rotenone control value of 1.59 ± 0.06 μ mol/g. tissue. Moreover, mice treated with L-dopa exhibited significantly increased brain reduced glutathione by 64.8% compared with the rotenone control group (2.62 ± 0.05 vs. 1.59 ± 0.06 μ mol/g. tissue).

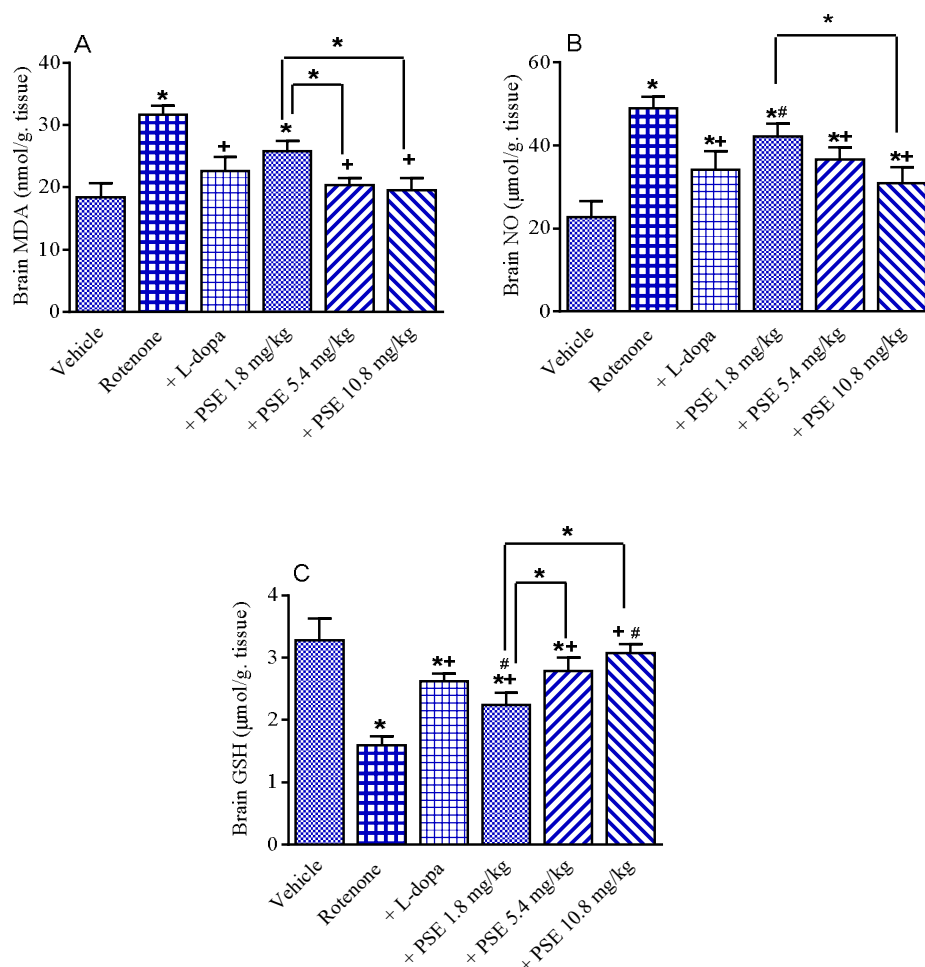


Fig. 1. Effect of norpseudoephedrine (PSE) and L-dopa on brain oxidative stress in rotenone-treated mice. Values represent means \pm SEM. *: $P < 0.05$ vs. vehicle and between different groups as indicated in the graph. +: $P < 0.05$ vs. rotenone control. #: $P < 0.05$ vs. L-dopa-treated group.

3.2. Behavioral results

3.2.1. Wire hanging test

Rotenone treatment significantly decreased the time mice spent hanging suspended from a steel rod by 67.5% compared to the vehicle control group, indicating impairment in motor strength (4.91 ± 0.43 vs. 15.12 ± 0.57 sec). In rotenone/PSE-treated groups there was significant increase in the time spent by mice holding the wire by 136.2%, 217.5% and 234.6%, respectively compared to rotenone control (11.60 ± 0.42 , 15.59 ± 0.64 , 16.34 ± 2.17 vs. 4.91 ± 0.43 sec). The latency before falling also increased by 126.1% after treatment with L-dopa (11.10 ± 0.31 vs. vs. 4.91 ± 0.43 sec).

3.2.2. Wood walking test

Rotenone-treated mice were significantly slower to traverse a wooden stick compared to their vehicle control (37.8% increase in time; 10.54 ± 0.55 vs. 7.65 ± 0.29 sec). In rotenone/PSE-treated groups, mice took shorter time to traverse the stick by 31.1%, 43.1% and 52.4%, respectively compared to the rotenone control group (7.26 ± 0.37 , 6.0 ± 0.38 , 5.02 ± 0.4 vs. 10.54 ± 0.55 sec). In comparison, mice treated with L-dopa exhibited 48.2% shorter time to traverse the stick compared to rotenone-only group (5.46 ± 0.25 vs. 10.54 ± 0.55 sec).

3.2.3. Stair test

The time spent by mice to ascend the stair was significantly increased by rotenone by 44.2 % (15.05 ± 0.47 vs. 10.44 ± 0.30 sec). Mice treated with rotenone/PSE displayed shorter time by 20.7%, 40.2% and 41.3% when compared to the rotenone only group (11.93 ± 0.56 , 9.0 ± 0.57 , 8.84 ± 0.35 vs. 15.05 ± 0.47 sec). Meanwhile, treatment with L-dopa resulted in significant shortening of time to ascend by 47.4% compared to rotenone control (7.92 ± 0.41 vs. 15.05 ± 0.47 sec).

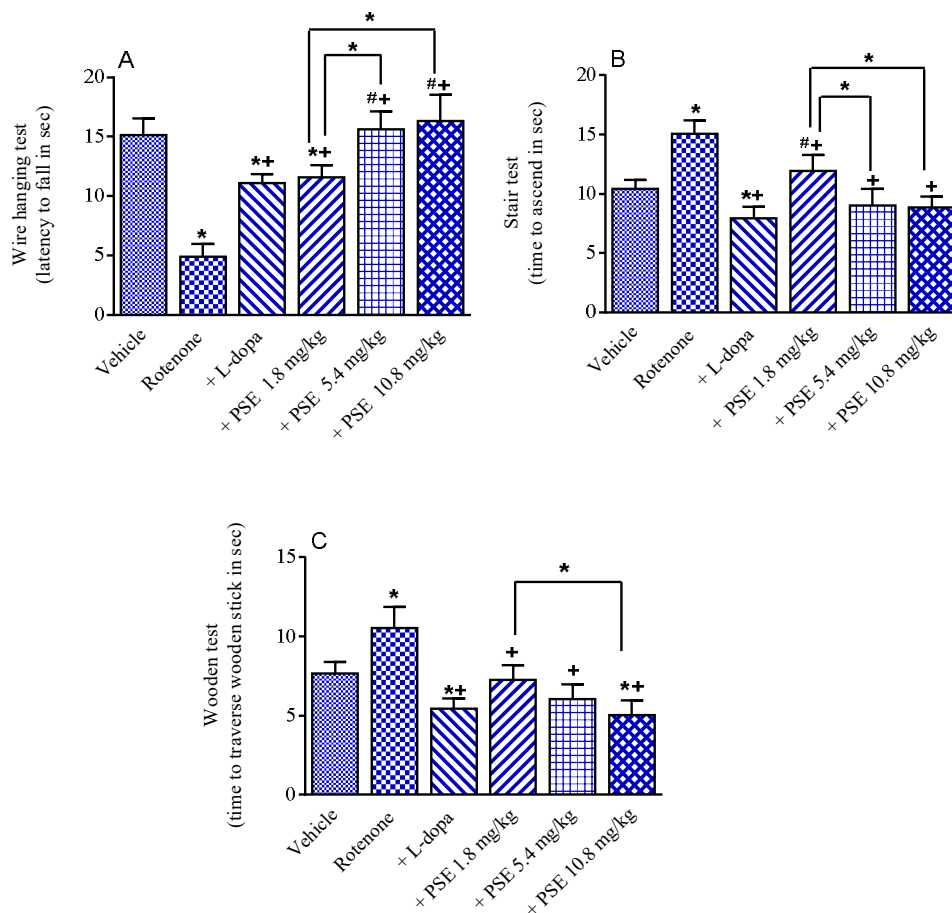


Fig. 2. Effect of norepseudoephedrine (PSE) or L-dopa on motor performance in mice treated with rotenone. Values represent means \pm SEM. *: $P < 0.05$ vs. vehicle and between different groups as indicated in the graph. +: $P < 0.05$ vs. rotenone control. #: $P < 0.05$ vs. L-dopa-treated group.

3.3. Histopathological results

We determined the effect of PSE on the neurodegeneration in brain after treatment with rotenone. As shown in Fig. 3, rotenone caused marked decrease in size and number of pigmented cells in the substantia nigra compared with vehicle control. Mice that received PSE at 5.4 and 10.8 mg/kg showed dose-related increase of the number and size of neurons. The cerebral cortex and hippocampus of mice that received rotenone showed many neurons that were deeply stained. Mice treated with PSE at 10.8 mg/kg showed marked amelioration of the damaging effects of rotenone (Figs. 4 & 5). Additionally, a neuroprotective effect for L-dopa was evident in the examined brain regions (Figs. 3,4 &5).

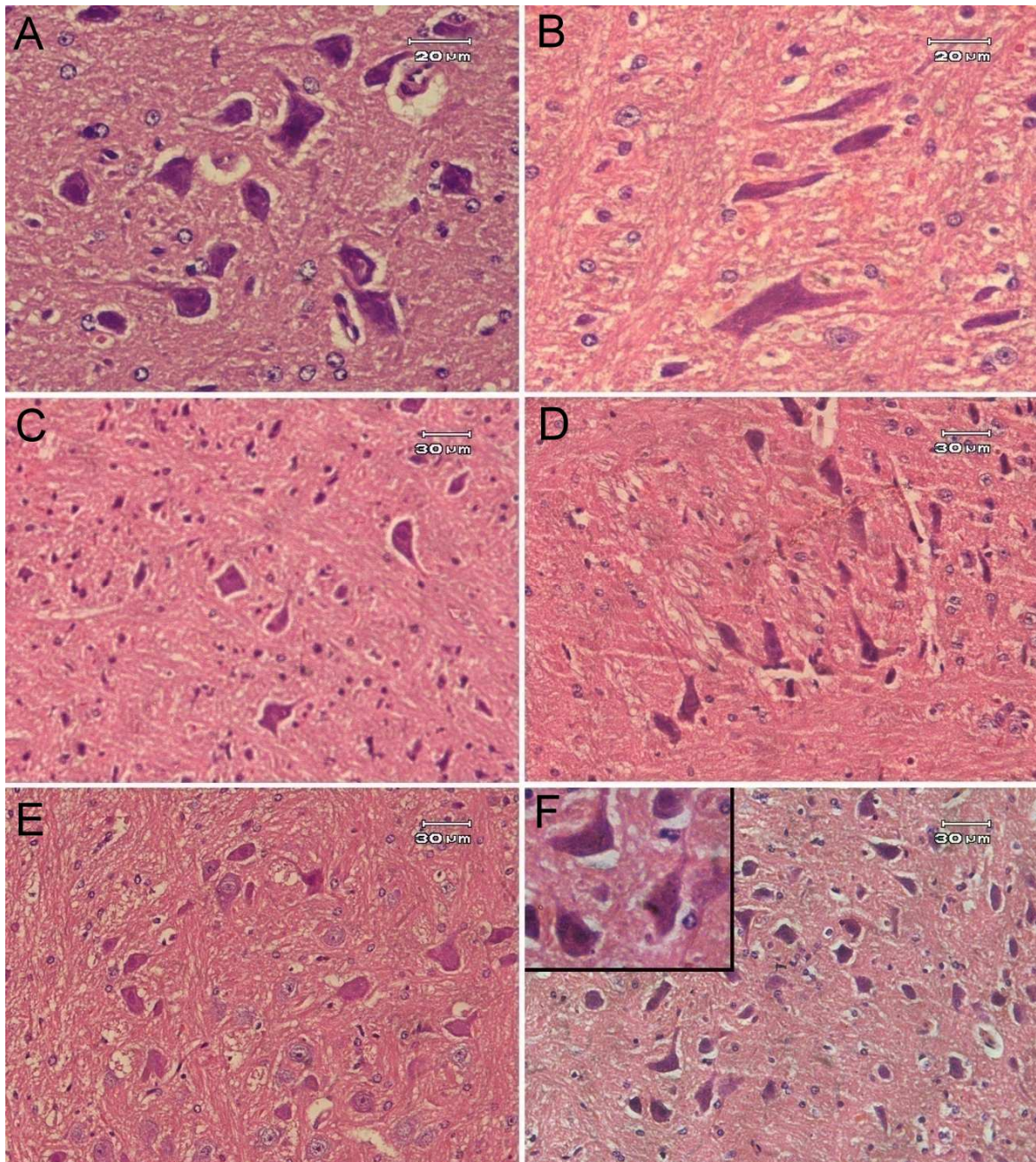


Fig. 3. Representative photomicrographs of Hx & E stained sections of the substantia nigra area after treatment with: **(A)** Vehicle: showing the normal structure of the pigmented neurons in this area. **(B)** Rotenone: showing marked decrease in size and number of pigmented cells. **(C)** Rotenone + L-dopa: showing decrease of pigmented neurons in number, but many of them regain their normal size. **(D)** Rotenone + PSE 1.8 mg/kg showing noticeable decrease of the size of pigmented cells. **(E)** Rotenone + PSE 5.4 mg/kg showing slight increase of the number and size of neurons, but the pigmentation intensity is less than normal. **(F)** Rotenone + PSE 10.8 mg/kg showing marked increase of the number and size of neurons.

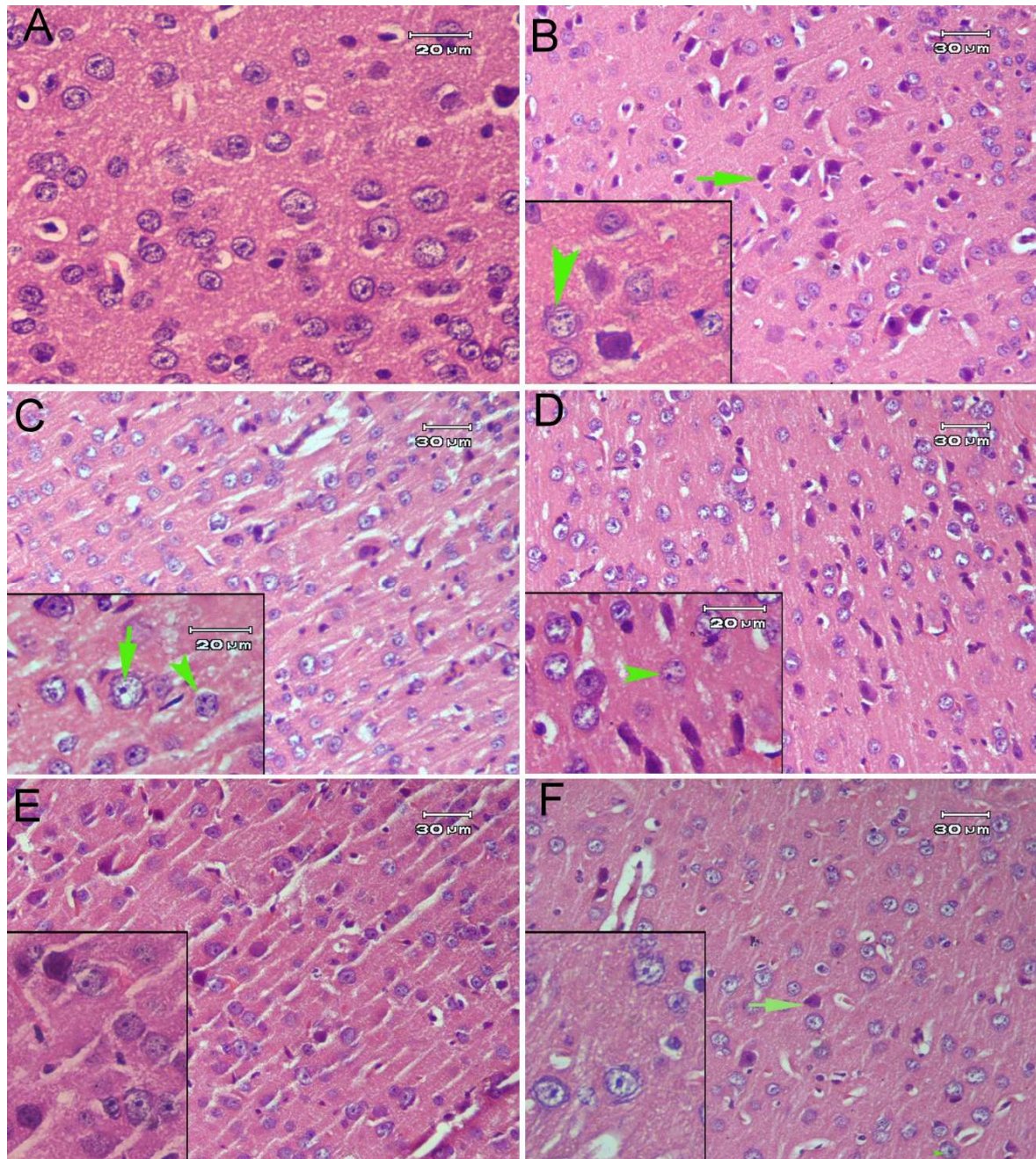


Fig. 4. Representative photomicrographs of Hx & E stained sections of the cerebral cortex tissue from mice treated with: **(A)** Vehicle: showing the normal structure of this tissue. **(B)** Rotenone showing many deeply stained neurons (arrow) and karyorrhexis (arrowhead) in many other neurons (in the highly magnified part of the figure). **(C)** Rotenone + L-dopa: showing marked decrease of deeply stained neurons, but neurons with karyorrhexis are still noticed (arrowhead). Most of neurons appear normal (arrow). **(D)** Rotenone + PSE 1.8 mg/kg showing high number of dark, abnormal shaped neurons are observed. Neurons with fragmented chromatin are also seen (arrowhead). **(E)** Rotenone + PSE 5.4 mg/kg showing marked decrease of affected cells. **(F)** Rotenone + PSE 10.8 mg/kg showing most of neurons appear normal. Only a few neurons appear darkly stained (arrow).

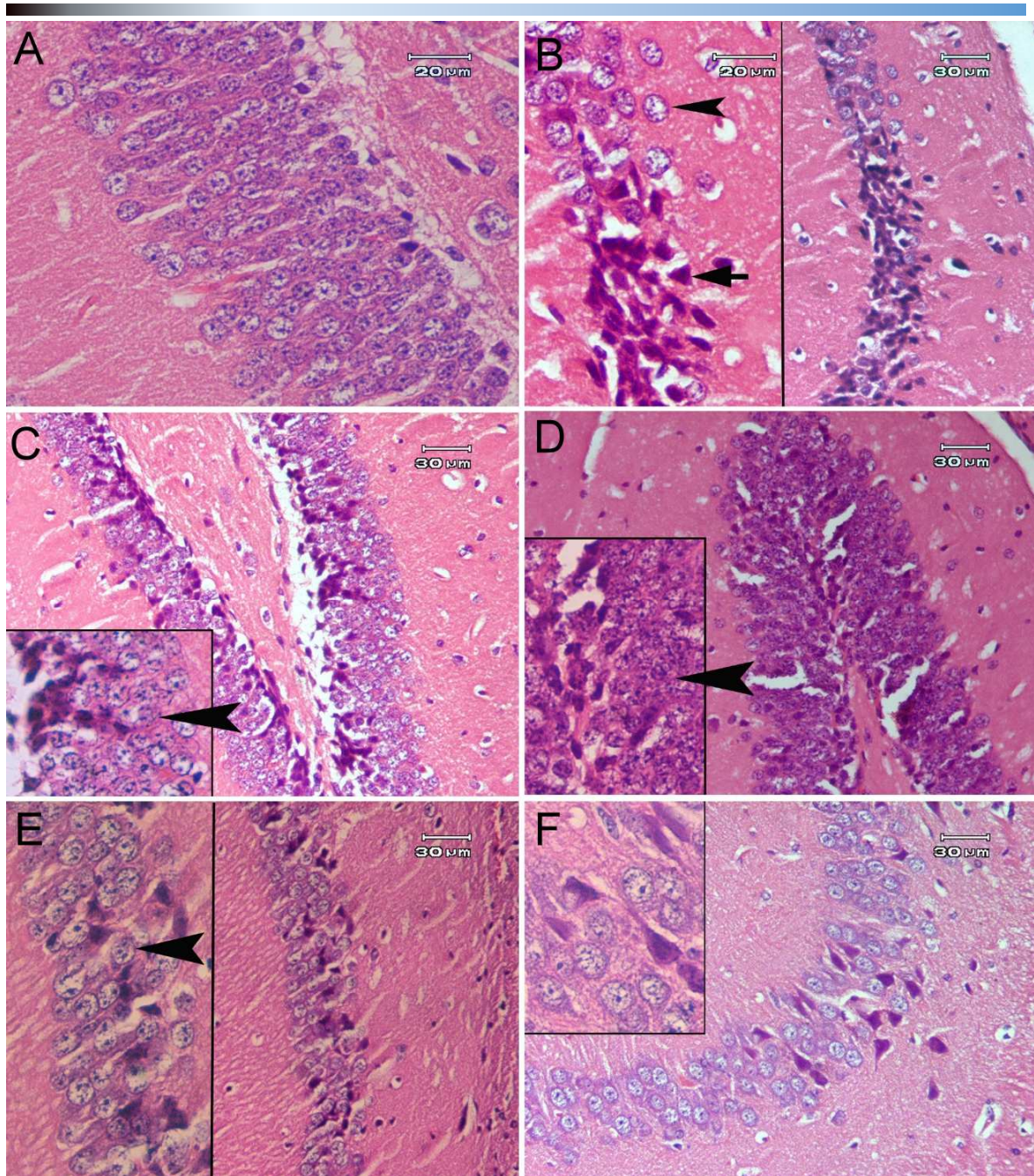


Fig. 5. Representative photomicrographs of Hx & E stained sections of the hippocampus area from mice treated with: **(A)** Vehicle: showing the normal structure of this tissue. **(B)** Rotenone showing many deeply stained neurons (arrow) and karyorrhexis (arrowhead) in some other neurons. A marked decrease of the granular cell layer thickness is observed. **(C)** Rotenone + L-dopa: showing decrease of deeply stained neurons. Neurons with karyorrhexis are also noticed (arrowhead). **(D)** Rotenone + PSE 1.8 mg/kg showing some deeply stained neurons. Many neurons show fragmented chromatin (arrowhead). **(E)** Rotenone + PSE 5.4 mg/kg showing slight decrease of affected cells, although, the karyorrhectic cells (arrowhead) are more pronounced than the dark cells. **(F)** Rotenone + PSE 10.8 mg/kg showing marked structural amelioration of the damage with regaining of the normal thickness of the granular cell layer. Only a few dark cells and neurons with karyorrhexis are observed.

4. Discussion

The present study provided the first evidence that low doses of norpseudoephedrine (NSP) can rescue pigmented dopamine cells in SN and protect against the development of neurodegeneration in other brain regions in the rotenone mouse model of PD. Moreover, NSP administration mitigated oxidative stress, as indicated by decreased levels of malondialdehyde, a biomarker of lipid peroxidation, nitric oxide and increased levels of reduced glutathione. The drug markedly improved the impairment in motor strength and coordination which are the most important problems in PD.

Oxidative stress has been implicated in brain damage and neuronal apoptosis caused by rotenone. The pesticide was shown to cause the increased production of intracellular ROS, lipid peroxidation, protein carbonylation, decrease the level of GSH, and induce apoptotic cell death in vitro (Sherer et al., 2003; Testa et al., 2005) and following systemic administration in rodents (Abdel-Salam et al., 2014). Rotenone being highly lipophilic is capable of readily crossing the blood brain barrier and causes inhibition of mitochondrial complex I or NADH-ubiquinone oxidoreductase, resulting in the increased generation of superoxide (Li et al., 2003) or hydrogen peroxide (Michelini et al., 2015). Rotenone also activates microglia cells to release superoxide (Gao et al., 2003) or hypochlorous acid (Chang et al., 2011). Rotenone neurotoxicity and apoptosis were prevented by antioxidants such as *N*-acetylcysteine, vitamin C and vitamin E (Sherer et al., 2003; Testa et al., 2005; Abdel-Salam et al., 2019). The ability of low doses of NSP to protect against rotenone neurotoxicity may involve an antioxidant effect. We also found that treatment with L-dopa was associated with significant decrease in lipid peroxidation along with increased levels of GSH, indicating the presence of lower levels of oxidants in the brain of rats treated with the drug.

High levels of nitric oxide have been shown to mediate neurotoxicity and induce apoptotic cell death. Normally, low concentrations of nitric oxide are produced by neuronal and endothelial isoforms of nitric oxide synthase (nNOS & eNOS). In contrast, increased expression of inducible NOS by activated microglia and inflammatory cells during inflammatory or toxic conditions will result in the release of greater amounts of nitric oxide that are damaging to cells. These neurotoxic effects are mediated by peroxynitrite (ONOO-) radical generated by the reaction of nitric oxide with superoxide. Peroxynitrite radical can result in oxidation and nitration of tyrosine residues in proteins, oxidation of free thiols, lipid peroxidation and DNA base oxidation (Pacher et al., 2007). The brains of rotenone-treated animals showed increased levels of nitric oxide and iNOS expression in substantia nigra and striatum (Abdel-Salam et al., 2014). Excessive production of nitric oxide plays a crucial role in the development of rotenone-induced neuronal injury. This is because the pharmacological inhibition of nNOS and iNOS protected against rotenone-induced dopaminergic cell death (He et al., 2003; Gao et al., 2015). The findings in the present study indicate that NSP significantly attenuated the raised nitric oxide levels in the brain of rotenone-treated animals. Norpseudoephedrine may be neuroprotective through an inhibitory effect on nitric oxide release.

Norpseudoephedrine is a commonly used nasal decongestant (Eccles et al., 2005) and an appetite-suppressive drug in the short term management of obesity (Hauner et al., 2017). In man, orally given NSP is readily and completely absorbed, not substantially metabolized, having $t_{1/2}$ of 6h and mainly excreted through the kidneys (Kanfer et al., 1993). Norpseudoephedrine is a stereoisomer of ephedrine, the alkaloid isolated from *Ephedra* species. It also has sympathomimetic activity, increasing blood pressure and heart rate but with lower potency compared to ephedrine (Drew et al., 1978). Moreover, NSP or cathine is one of the main active constituents of the fresh leaves of the “khat” (*Catha edulis*) shrub which has stimulant amphetamine-like effect. The other active ingredient or cathinone [S (-) alpha-aminopropiophenone] is metabolized to NSP in man (Guantai and Maitai, 1983). It is conceivable therefore that some of the effects of “Khat” in man involves NSP. In a recent study, ephedrine was shown to neuroprotective effects in which the drug given at 5 and 10 mg/kg decreased protein expression of nuclear factor kappa B, infarct size, neuronal apoptosis and improved neurologic outcome after brain ischaemia in rats (Shi et al., 2020). The drug also decreased ROS and lipid peroxides and increased superoxide dismutase in endotoxin-stimulated BV2 microglia cells in vitro (Li et al., 2021).

Studies in rats suggested that NSP increases the release of dopamine in the striatum and nucleus accumbens. The drug induces Fos-like immunoreactivity in nucleus accumbens and striatum that is mediated predominantly via the D1 receptors being inhibited by D1 specific antagonist (Kumarnsit et al., 1999). The increase in c-Fos expression in the nucleus accumbens and striatum by NSP (40 mg/kg, i.p.) was reduced after chronic treatment with either amphetamine or NSP indicating the presence of cross tolerance (Ruksee et al., 2008). The drug which resembles amphetamine in structure is used in the illicit manufacture of methamphetamine (World Drug Report, 2019) and like amphetamine inhibited [3H] dopamine uptake in synaptosomal preparations (Ruksee et al., 2008) [41]. Neuroprotective effects of low doses of amphetamine (2 mg/kg) have been reported in stroke model in rats (Hurwitz et al., 1991) and Parkinson's disease model in mice (Abdel-Salam et al., 2020).

Similar to ephedrine, NSP has β -phenylethylamine core structure. β -phenylethylamine which belongs to trace amines occurs naturally in the body and in diet eg., cocoa and chocolate (Broadley, 2010). β -phenylethylamine activates trace amine-associated receptor 1 (TAAR1) and significantly inhibited uptake and induced efflux of [3H] dopamine and [3H] serotonin in striatal synaptosomes of rhesus monkeys and wild-type mice (Xie and Miller, 2008). Notably, it has been suggested that the usefulness of the monoamine oxidase-B inhibitor selegiline in PD may be due to increasing β -PEA in the brain by preventing its metabolism (Janssen et al., 1999). It is possible therefore that the beneficial effects of NSP, particularly the improved motor function in the present study involves at least in part stimulation of dopamine receptors or involve other brain monoamine neurotransmitters.

5. Conclusion

In summary, our findings indicate that NSP, a commonly used drug for common cold and body weight reduction, was capable of preventing neuronal loss and motor deterioration in the rotenone model of PD in mice. The exact mechanism by which NSP protect neurons is not clear but may possibly involve antioxidant effect or modulation of brain monoamines.

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Conflict of interest

The authors declare no conflicts of interest.

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