

Fluoxetine Improves the Effect of Levodopa on 6-Hydroxy Dopamine-Induced Motor Impairments in Rats

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ABSTRACT

Purpose: Long term L-DOPA therapy in Parkinson's disease is associated with troublesome motor fluctuations such as L-DOPA induced dyskinesia and wearing off effect. Our recent study showed that activation of 5-HT_{1A} receptors could improve the anti-cataleptic effect of L-DOPA in parkinsonian rats. In this study we investigated the effect of fluoxetine on anti-parkinsonian effect of L-DOPA in 6-hydroxydopamine (6-OHDA)-lesioned rats. **Methods:** Catalepsy and motor incoordination were induced by unilateral injection of 6-OHDA (8µg/2µl/rat) into the central region of the substantia nigra pars compacta (SNc). After 3 weeks as a recovery period, these rats injected intraperitoneally (i.p.) L-DOPA (15 mg/kg) twice daily for 20 consecutive days, and anti-parkinsonian effect of L-DOPA was investigated by bar-test and rotarod on days 5, 10, 15 and 20. **Results:** The results showed that L-DOPA is able to improve motor coordination in rotarod only until day 15 and these effects of L-DOPA were abolished on the day 20. On day 21, rats were co-injected with fluoxetine (0.1, 0.5 and 1mg/kg, i.p.) and L-DOPA (15 mg/kg, i.p.). Fluoxetine increased anti-cataleptic effect of L-DOPA at the dose of 1 mg/kg, while fluoxetine had not any impact on the effect of L-DOPA in rotarod test. The effect of fluoxetine (1 mg/kg, i.p.) on anti-cataleptic effect of L-DOPA (15 mg/kg, i.p.) was reversed by 1-(2-methoxyphenyl)-4-(4-phthalimidobutyl) piperazine hydrobromide (NAN-190; 0.5 mg/kg, i.p.), as a 5-HT_{1A} receptor antagonist. **Conclusion:** According to the results, it may be concluded that fluoxetine improves 6-OHDA-induced catalepsy and motor imbalance in L-DOPA-treated rats through activation of 5-HT_{1A}. Further studies should be designed to clarify the precise mechanism of interaction between 5-HT_{1A} and dopaminergic neurons.

Introduction

Parkinson's disease (PD) is considered as a movement and neurodegenerative disorder.^{1,2} Nearly 1% of populations over 60 years old are affected by this disease.³ The main cause of this disease is the degeneration of nigrostriatal pathway, leading to reduction of dopamine levels in the striatum⁴ that subsequently induces motor dysfunctions, such as muscle rigidity, akinesia, tremor at rest and bradykinesia.⁵⁻⁶ Replacement therapy with L-3,4-dihydroxyphenylalanine (L-DOPA) commonly is used for treatment of PD motor symptoms.⁷⁻⁸ This strategy is effective in the early stages of disease, but long-term use of L-DOPA causes motor fluctuations such as L-DOPA-induced dyskinesia (LID)^{7,9} and wearing off phenomenon.⁷ The mechanism(s) underlying of these motor disorders are weakly understood and there are

not comprehensive data about these mechanisms. It has been shown that following destruction of dopaminergic neurons by 6-OHDA in rats, hyperinnervation of serotonergic (5-HT) fibers occurs within the affected area.¹⁰ It seems these serotonergic neurons are able to compensate some effects of lost dopaminergic neurons.¹¹ In normal conditions, dopaminergic neurons are able to convert L-DOPA to dopamine. Accordingly this process is mediated by aromatic amino acid decarboxylase (AADC) and mono amine vesicular transporter 2 (VAMT 2) that are responsible for synthesis of dopamine from L-DOPA and loading of dopamine from intra-neural space into vesicles within the dopaminergic neurons, respectively.^{1,12} Serotonergic neurons possess both essential components, AADC and VAMT 2, for processing of L-

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DOPA to dopamine.¹³⁻¹⁴ Existence of these components enables 5-HT neurons to decarboxylate L-DOPA to dopamine as well as its loading into vesicles.¹⁴ In serotonergic neurons dopamine is co-stored with serotonin in the same vesicles and is known as a false transmitter.¹⁵

Dopamine is released from dopaminergic neurons in a physiological level,¹³ while it is released from serotonergic neurons in an activity dependent fashion.^{13,16} This paradigm results in fluctuation of striatal dopamine levels.¹⁴ It is therefore plausible that in PD dopamine receptors are faced to fluctuated levels of dopamine.¹⁷ All components of basal ganglia receive serotonergic neurons from dorsal raphe nucleus.¹⁸ Hence it seems that serotonergic system has an axial role in regulation of normal movement.⁶ 5-HT_{1A} receptors are found throughout the basal ganglia.⁶ It has been reported that activation of these receptors may exert anti-parkinsonian effect.² Studies have shown that stimulation of these receptors results in improving of dyskinesia.¹³ Anti-cataleptic effect of 5-HT_{1A} agonists in rodent model of PD has been shown.^{6,19} We have shown that fluoxetine attenuates catalepsy in 6-OHDA-lesioned rats.²⁰ Furthermore, activation of 5-HT_{1A} receptors could improve anti-cataleptic effect of L-DOPA in hemiparkinsonian rats.¹² However there is not any report about effect of fluoxetine on anti-cataleptic and motor-balance improving effect of L-DOPA in 6-OHDA-lesioned rats. This study was designed to investigate effect of fluoxetine and L-DOPA co-treatment on 6-OHDA-induced motor impairments in rats.

Materials and Methods

Chemicals

All chemicals were purchased from Sigma Chemical Co. (USA). L-DOPA and Carbidopa were donated by Ramopharmin Co, Iran. Solutions were made freshly on the days of experimentation by dissolving drugs in physiological saline (0.9% NaCl). The drugs were injected intraperitoneally (i.p.) except for 6-hydroxydopamine (6-OHDA) which was injected into substantia nigra pars compacta (SNc). Movement disorders were assessed by bar test and rotarod 5, 60, 120 and 180 min after drug administration.

Animals

The experiments were carried out on male Wistar rats weighing between 200-220 g. Animals were housed in standard polypropylene cages, four per cage, under a 12:12 light/dark program and at a temperature of 25 ± 2°C, with free access to food and water. Animals were acclimated to the testing conditions 2 days before the behavioral investigations were done. All of the procedures were carried out under the ethical guidelines of Tabriz University of Medical Sciences for the care and use of laboratory animals.

Surgical procedures

The animals were anesthetized by intraperitoneal injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). After they were deeply anaesthetized, rats were fixed in a stereotaxic frame in the flat skin positions. Scalp hairs of the rats were completely shaved with a standard electric shaving machine, swabbed with 70% ethanol and a central incision made to reveal skull. A 0.7 millimeter bar hole was drilled and 23 gauge sterile stainless steel cannula, as a guide cannula inserted for subsequent injection of 6-OHDA in to SNc. The coordinates for this position were determined according to the rat brain in stereotaxic coordinates:²¹ anteroposterior from bregma (AP) = -5 mm, mediolateral from the midline (ML) = -2.2 mm and dorsoventral from the skull (DV) = -8.8 mm. Desipramine (25 mg/kg) was injected intraperitoneally 30 min before intra-nigral injection of 6-OHDA to avoid degeneration of noradrenergic neurons.²² Then 6-OHDA (8 µg/ per rat in 2 µl saline with 0.02 % ascorbic acid) was infused by infusion pump at the flow rate of 0.2 µl/minute into the left substantia nigra. At the end of injection, guide cannula was kept for an additional 2 min and then slowly was withdrawn. All of these procedures were repeated in Sham-operated animals but they were received only 2 µl vehicle of 6-OHDA (0.9% saline containing 0.2% (w/v) ascorbic acid). After three weeks as a recovery period, only the rats that showed marked immobilization in bare test and motor imbalance in rotarod test were subjected to further experimentation. Then parkinsonian rats were randomly allocated to equal groups and were treated with L-DOPA (15 mg/kg, i.p.) twice daily (9 AM, 9 PM) for 20 days. Peripheral metabolism of L-DOPA was inhibited by concomitant administration of carbidopa (1.5 mg/kg, i.p.).

Motor impairment study

Catalepsy was assessed by using of standard wooden bar test mean. Anterior limbs of rat gently extended on 9 cm high bar (0.9 cm in diameter). Elapsed time for each rat in this imposed posture was considered as a bar test time. The end point of catalepsy was designated to occur when both front paws were removed from the bar or if the animal moved its head in an exploratory manner. The cut-off time of the test was 720 seconds. Assessment of motor imbalance was done by a rotarod apparatus. Rat was placed on the rotarod (18 RPM) and the latency to fall off the rotarod was recorded. Animals staying during 720 s were taken from the rotarod and their retention time on rotarod considered 720 s. All observations were made between 9 AM and 4 PM by an observer who was blind to the entity of treatments.

Statistical analysis

Statistical analysis of each data set was calculated by use of SigmaStat software. Data were expressed as the mean + SEM, and were analyzed by one-way ANOVA

in each experiment. In the case of significant variation ($p < 0.05$), the values were compared by Tukey test.

Results

The effect of intra-SNc-injection of 6-OHDA on motor-balance

The effect of intra-SNc injection of 6-OHDA on motor-balance was evaluated by rotarod test. The duration of time to fall from rotating rod was evaluated in three groups of rats: normal, sham-operated and 6-OHDA (8

$\mu\text{g}/2 \mu\text{l}/\text{rat}$)-lesioned groups. 6-OHDA (8 $\mu\text{g}/2 \mu\text{l}/\text{rat}$) induced motor imbalance ($P < 0.001$) in comparison with normal and sham operated groups (Figure 1). The results of intra-SNc injection of 6-OHDA on bar test (as a standard catalepsy test) have been shown in our previous studies (12, 22) in which it induced marked catalepsy ($P < 0.001$) when compared with normal and sham operated groups. Therefore, the results have not been shown in this paper.

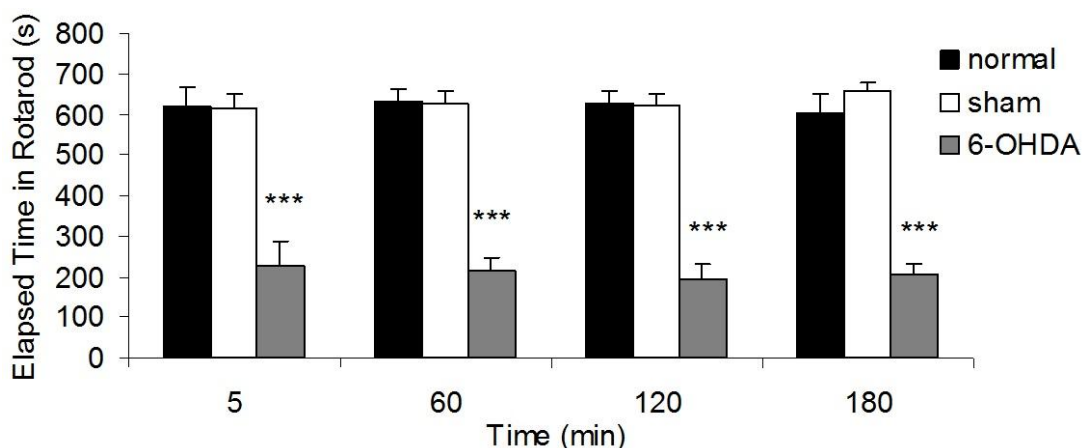


Figure 1. The results of rotarod test in control, Sham-operated and 6-OHDA (8 $\mu\text{g}/2\mu\text{l}/\text{rat}$)-lesioned rats. Each bar presents the mean \pm SEM of elapsed time (s), $n = 8$ rats for each group; *** $p < 0.001$ when compared with normal and sham operated groups.

The effect of chronic administration of L-DOPA on motor-balance

The effect of chronic injection of L-DOPA (15 mg/kg, i.p.) and its vehicle on motor-balance was investigated in 6-OHDA-lesioned rats for 20 consecutive days (Figure 2). In these groups, motor-balance was assessed by rotarod on days 5, 10, 15 and 20. L-DOPA significantly increased retention time on rotarod ($p < 0.001$, $p < 0.01$ and $p < 0.05$) at days 5, 10 and 15, whereas its motor-balance improving effect was decreased at day 20. The results of same treatments on bar test are accessible in our previous paper.^{12,22} In that study we showed that L-DOPA could induce anti-cataleptic effect only until day 15.

The effect of fluoxetine on anti-cataleptic and motor-balance improving effect of L-DOPA

Three groups of animals that were pre-treated with L-DOPA (15 mg/kg twice daily, i.p.), received three different doses of fluoxetine (0.1, 0.5 and 1 mg/kg, i.p.) on day 21. The results showed that fluoxetine improved the anti-cataleptic effect of L-DOPA at the doses of 0.5 and 1 mg/kg ($p < 0.05$ and 0.01) (Figure 3, panel A), while it did not improve the effect of L-DOPA in rotarod test (Figure 3, panel B).

The effect of NAN-190 co-treatment with fluoxetine on anti-cataleptic effect of L-DOPA

On day 21, the effect co-administration of NAN-190 (1mg/kg, i.p.) with fluoxetine (0.5 mg/kg, i.p.) was

investigated in rats pre-treated with L-DOPA (15 mg/kg twice daily, i.p.). As it has been shown in Figure 4, the catalepsy-improving effect of fluoxetine was halted ($p < 0.05$ and 0.01) in the presence of NAN-190.

Discussion

According to the obtained results the acute administration of fluoxetine improved anti-parkinsonian effects of L-DOPA in 6-OHDA-lesioned rats. The 6-OHDA-lesioned rats are generally used in the study for PD and L-DOPA related adverse motor complications.⁶ In this study intra-SNc injection of 6-OHDA caused marked catalepsy and motor imbalance when assessed by bar test and rotarod test, respectively. In rodents catalepsy is considered as a test for akinisia²³ and can be reproduced by 6-OHDA and neuroleptic drugs.^{6,13,19} Bar test is a standard test which is used commonly to assess catalepsy in rodents.^{6,19} Furthermore, unilateral injection of 6-OHDA induces motor imbalance that can be measured by rotarod as a standard motor-balance test.^{6,20} Indeed unilateral lesion of substantia nigra forces a rat to change its weight abnormally for movement and equilibrium; hence this results in motor disorders.²⁴ Our results showed that 6-OHDA-lesioned rats fail to maintain their balances on rotarod and a significant reduction in retention time on rotarod was observed in these animals. We observed that L-DOPA abolished catalepsy in 6-OHDA-lesioned rats only on days 5, 10 and 15. The anti-cataleptic and motor imbalance improving effects of L-DOPA were

attenuated markedly on day 20. It seems that long-term administration of L-DOPA causes some plastic

alterations in the striatum,¹⁴ which these neuronal changes result in L-DOPA- induced motor disorders.²⁵

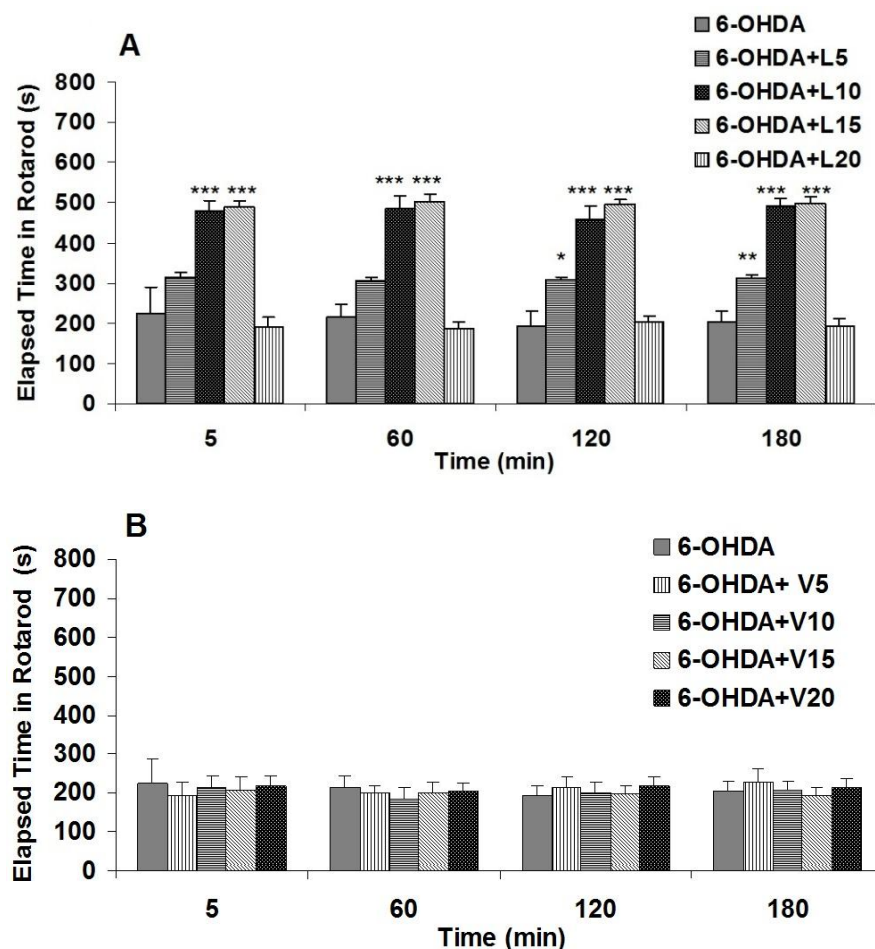


Figure 2. The results of rotarod test in 6-OHDA (8 μ g/2 μ l/rat)-lesioned rats injected with L-DOPA (15mg/kg) (Panel A) and L-DOPA's vehicle (Panel B) twice daily on the days 5, 10, 15 and 20. Each bar shows the mean \pm SEM of elapsed time (s), n = 8 rats for each group; *p<0.05, **p<0.01 and *** p<0.001 when compared with 6-OHDA lesioned rats. (L=L-DOPA on days 5, 10, 15, 20)- (V=Vehicle on days 5, 10, 15, 20).

According to the obtained results, co-administration of fluoxetine and L-DOPA enhanced anti-cataleptic effect of L-DOPA on day 21. This result confirms our study showing an anti-cataleptic effect for fluoxetine in 6-OHDA-lesioned²⁰ or haloperidol-treated animals.²⁶ Fluoxetine was not able to improve the effect of L-DOPA in rotarod on day 21. This may be due to sedative effect of fluoxetine.²⁷ Fluoxetine increases effect of GABA on GABA_A receptors resulting in induction of sedative state.^{27,28} This is in accordance to the results of other study showing that fluoxetine dose not increase rotarod elapsed time in parkinsonian rats.²⁹ Under normal conditions, dopaminergic neurons regulate dopamine levels through D2 autoreceptors and dopamine transporters.¹⁶ However serotonergic neurons have not these regulatory systems. Thus activation of these neurons impacts on L-DOPA derived dopamine and results in fluctuations in extracellular dopamine levels.^{14,16} This pulsatile release of dopamine may cause intermittent dopamine receptor stimulation that

eventually causes subsequent motor problems like wearing off and LID.²⁵ It has been suggested that in 6-OHDA-induced PD, serotonergic neurons are involved in LID.^{14,16}

All components of basal ganglia receive serotonergic projection from dorsal raphe nuclei⁶ which modulates nigrostriatal dopaminergic transmission.²⁶ It seems this system plays essential role in the modulation of motor behaviors. This effect is mediated via 5-HT_{1A} receptors within the basal ganglia circuits.¹⁸ 5-HT_{1A} receptors are also located on dorsal raphe neurons that alter their own activity.³⁰ Activation of 5-HT_{1A} receptors prolongs dopamine effect in parkinsonian animals.¹² Therefore it seems that 5-HT_{1A} activators might have promising anti-parkinsonian and antidyskinetic properties. Our previous studies have shown that activation of 5-HT_{1A} receptors exert anti-cataleptic effect in parkinsonian rats.^{10,19} Stimulation of this receptor could improve anti-cataleptic effect of 6-OHDA in rats.¹² It is supposed that specific serotonin reuptake inhibitors

(SSRIs) which increase serotonin levels in synaptic cleft²⁶ may have similar effect through affecting on 5-HT_{1A} receptors. In this study, NAN-190 (5-HT_{1A} receptor antagonist) reversed the catalepsy-improving

effect of fluoxetine in L-DOPA-treated rats. Thus, we can say that fluoxetine improves anti-cataleptic effect of L-DOPA by affecting on 5-HT_{1A} receptors.

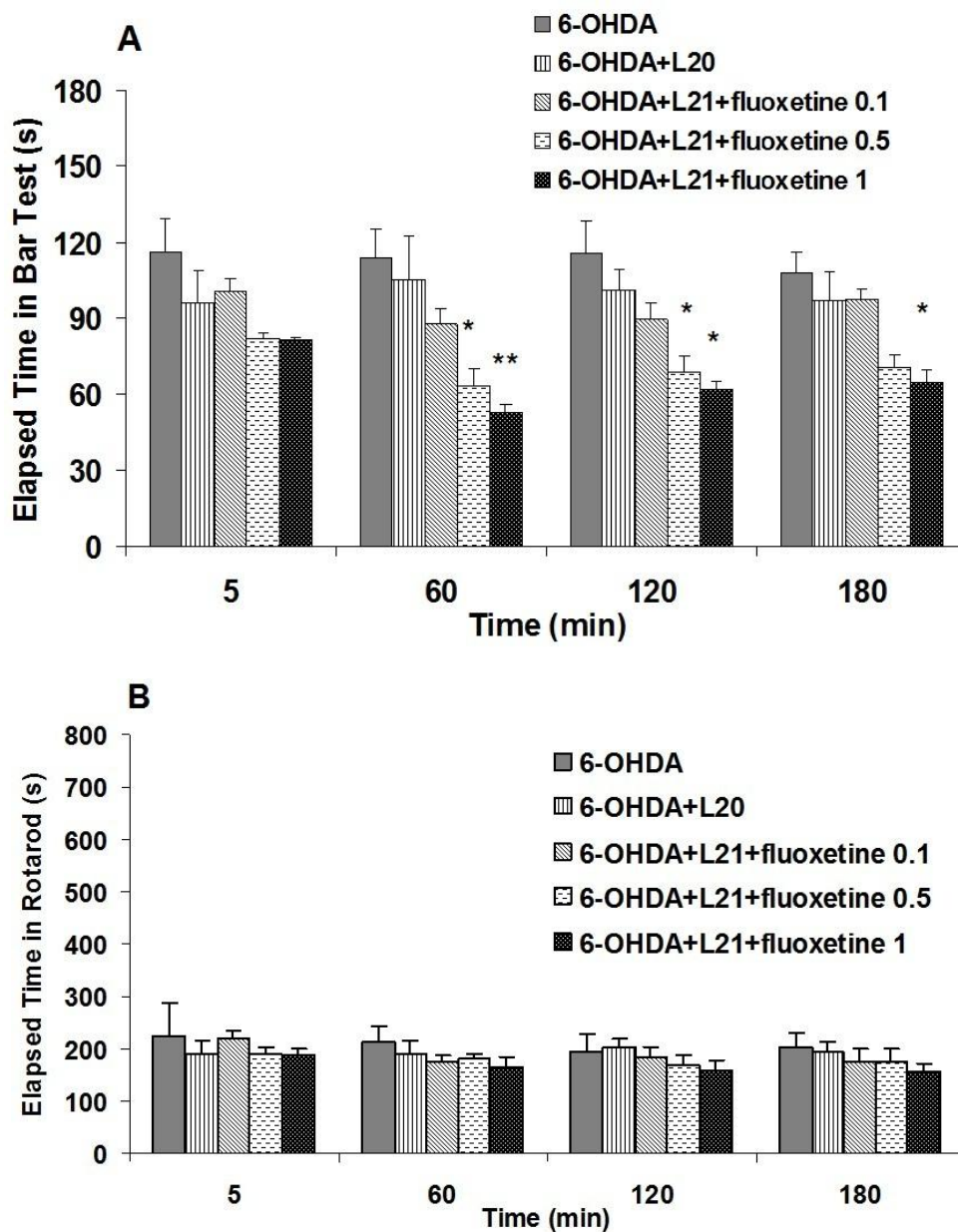


Figure 3. The bar test (panel A) and rotarod (panel B) from the co-administration of fluoxetine (0.1, 0.5 and 1 mg/kg) with L-DOPA (15 mg/kg) on day 21 in 6-OHDA-lesioned rats and 6-OHDA lesioned rats treated with L-DOPA (15 mg/kg) on day 20. Each bar represents the mean±SEM of elapsed time (s), n = 8 rats for each group; *p<0.05 and ** p<0.01 when compared with 6-OHDA lesioned rats. (L=L-DOPA on days 20 and 21).

Aside from motor impairments, depression is other comorbid clinical problem of PD that reduces quality of life. Approximately 40% of patients with PD experience depressive syndrome.³¹ SSRIs are widely used to treat depressive conditions in patients with PD.²⁶ Regarding to the results of this study, fluoxetine is able to improve anti-parkinsonian effect of L-DOPA. Then, it can be used as an adjuvant therapy in PD.

We conclude that fluoxetine improves anti-cataleptic effect of L-DOPA in 6-OHDA-lesioned rats. This effect is mediated by the stimulation of 5-HT_{1A} receptors. In addition, we suggest that investigation of a possible clinical application for fluoxetine should be carried out to test its usefulness in diminishing LID. Further investigations must be done for explaining exact mechanism of the interactions between serotonergic and dopaminergic neurons.

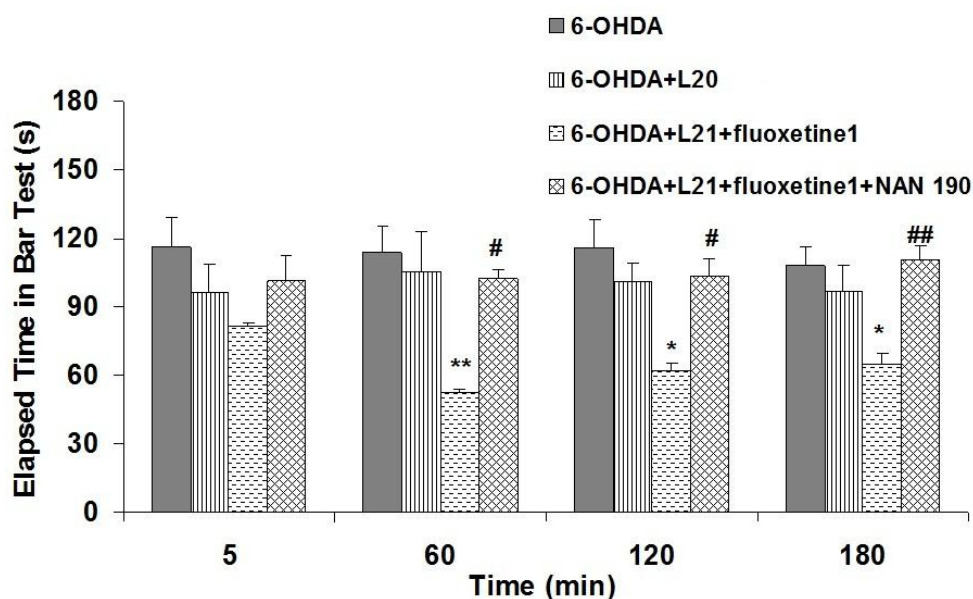


Figure 4. The bar test results from the co-administration of NAN-190 (0.5 mg/kg) with L-DOPA (15 mg/kg) and fluoxetine (0.5 mg/kg) on day 21 in 6-OHDA lesioned rats treated with L-DOPA (15 mg/kg) on day 21. Each bar represents the mean \pm SEM of elapsed time (s); $n = 8$ rats for each group; * $p < 0.05$ and ** $p < 0.01$ when compared with 6-OHDA-lesioned rats; # $p < 0.05$ and ## $p < 0.01$ when compared with 6-OHDA-lesioned rats co-treated with L-DOPA (15 mg/kg) and fluoxetine (0.5 mg/kg) on day 21. (L=L-DOPA on days 20 and 21).

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Conflict of Interest

There is no conflict of interest in this study.

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