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Effect of sertraline on 6-hydroxydopamine-induced catalepsy in hemi-parkinsonian rats

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ABSTRACT

Parkinson's disease is a neurodegenerative condition. In this disease nigro striatal dopaminergic pathway is demaged. In addition to dopaminergic neurons which predominantly are affected, some other neurotransmitter systems (i.e. serotonergic system) are also involved in pathophysiology of this disease. Hence, we studied the effect of sertraline, as a selective serotonin reuptake inhibitor, on catalepsy produced by unilateral infusion of 6-hydoxydopamine (6-OHDA) into the substantia nigra, compact part (SNc). Male wistar rats weighting 180-200g were used in the present study. In order to induce experimental parkinsonism, 6-OHDA (8 µg/rat) was infused unilaterally into the SNc of rats. 6-OHDA induced catalepsy ($p<0.001$) was evaluated by the aid of a bar test 5, 60, 120 and 180 minutes after intraperitoneal (i.p.) injections of the drugs. Sertraline (1 and 2 mg/kg i.p.) markedly attenuated the cataleptic behavior ($P<0.001$). This effect of sertraline is reversed by NAN-190 (0.5 mg/kg, i.p.) ($p<0.001$). In conclusion sertraline possibly via activation of $5HT_{1A}$ receptors is able to improve motor disorder in this model of Parkinson's disease.

Key words: Parkinson's disease, 6-OHDA, sertraline, catalepsy, rat

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INTRODUCTION

Parkinson's disease is an age related neurodegenerative and a debilitating disorder. Approximately, 6 million people in the world affected by this disease [7]. Motor deficits such as bradykinesia, Akinesia, rigidity and tremor are the major symptoms of this disease [9].

Precise mechanism underlying of Parkinson's disease poorly has been understood. Accordingly, degeneration of dopaminergic neurons, projecting from Subestentia nigra compact pars (SNc) to the striatum, is responsible for this disease. This destruction leads to a reduction in dopamine synthesis and striatal dopamine levels [13]. Dopamine replacement therapy with L-Dopa is the gold strategy for symptomatic treatment of Parkinson's disease [6, 14]. Since long-term use of this regimen fails to effect and patients experience motor disorders such as dyskinesia and wearing off [9], it seems that new therapeutic strategies must be utilized to effectively overcome of Parkinson's disease associated motor disorders. In addition to movement dysfunction, non-motor disorders such as depression and anxiety are experienced by Parkinson's disease patients [20].

Sertraline is a selective serotonin re-uptake inhibitor (SSRI) that is widely used to treatment of depressive conditions in patients with PD [16]. Studies show that the serotonergic system plays a pivotal role in the modulation of normal motor functions. This effect is mediated through 5-HT_{1A} receptors within the basal ganglia [9,3]. It seems that activation of 5-HT_{1A} receptor is able to exert anti-parkinsonism property [13]. Since sertraline increases serotonin levels in synaptic cleft [16], thus whether sertraline can act as an antiparkinsonian drug in 6-hydroxydopamine (6-OHDA) induced hemi-parkinsonian rats is of interest.

MATERIALS AND METHODS

Chemicals

All chemicals purchased from *Sigma Chemical Co*. (USA). Except for sertraline which received as a gift from *SOHA Pharmaceutical Co*. Solutions were made freshly prior to experimentation by dissolving in 0.9% normal saline. The drugs were injected intraperitoneally (i.p.) except for 6-OHDA which was injected into left subestentia nigra. Movement disorder was assessed by bar test on 5, 60, 120 and 180 min after drug administration.

Animals

Male wistar rats weighting 180-200g were used in the present study. Animals were allocated in standard polypropylene cages, four per cage, under 12:12 like/dark schedule and at the temperature 25 ± 2°C. All animals were provided food and water *ad libitium*. All Experiments were done according to ethical guideline of Tabriz University of Medical Sciences for the care and use of laboratory animals (National Institutes of Health Publication No 85-23, received 1985).

6-OHDA lesion surgery

6-OHDA lesion surgery was performed under general anesthesia. For this propose, rats were anaesthetized deeply with intraperitoneal (i.p.) injection of Ketamine (80mg/kg) and xylasine (5 mg/kg). Then their heads were mounted in a stereotactic apparatus frame at flat skull position. The scalp was shaved with standard shaving machine and scraped with iodine and a small central incision made to appear skull. A 23 gauge sterile stainless steel cannula as a guide cannula, firmly was implanted to injection site for subsequent insertion of the injection tube into the SNc. The coordinates for this position were designated according to the rat brain in stereotaxic coordinates [15]: 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 intranigral injection of 6-OHDA to limit degeneration of noradrenergic neurons [1]. 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/mine into the left subestentia nigra. At the end of injection, injection tube was kept for an additional 2 min and then slowly was retracted. All of these procedure were exploited for Sham-operated animals but they only were injected 2 µl vehicle of 6-OHDA (0.9% saline containing 0.2% (w/v) ascorbic acid).

Catalepsy evaluation

Catalepsy was measured by means of standard bar test. In this method, interior paws of rats were placed over a 9 cm high standard wooden bar and time course of retention of rats in this imposed posture was considered as a bar test elapsed time. The end point of catalepsy was considered to occur when both front paws were removed from the bar or if the animal moved its head in an exploratory paradigm. A cut-off time of 180 seconds was applied. All observations were carried out by an observer that was unaware from entity of treatment.

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

Effect of 6-OHDA on catalepsy behavior

Catalepsy elapsed time was measured in three groups of rats including of normal, sham operated and 6-OHDA (8µg/2µl/rat)-lesioned groups. As it has been shown in table 1, 6-OHDA (8µg/2µl/rat) was able to exert ($p<0.001$) marked immobilization in contrast with normal and sham operated groups.

Effect of Sertraline on the intact rats

Four groups of intact rats received normal saline as well as one of three different doses of sertraline (0.5, 1 and 2 mg/kg, i.p.), respectively. As shown in table 2, sertraline alone is not able to induce movement disorders in bar test.

Effect of NAN-190 on the intact rats

As shown in table 3, NAN190 alone (0.1, 0.5 and 1 mg/kg, i.p.) did not produced any significant effect ($P>0.05$) in bar test.

Effect of Sertraline on 6-OHDA- induced catalepsy

In order to assign the effective dose of sertraline on catalepsy behavior, parkinsonian rats were treated with different (0.5, 1 and 2 mg/kg) doses of Sertraline. Table 4 depicts the acute anti-cataleptic effect of sertraline at doses of 1 and 2 mg/kg. (P<0.001).

Effect of NAN-190 pretreatment with Sertraline on the 6-OHDA- induced catalepsy

To test the selectivity of the 5-HT_{1A} agonist-induced behavior, animals were pretreated with selective 5-HT_{1A} antagonist, NAN-190 (0.5 mg/kg, i.p.), 15 min before intra-peritoneal injection of 1 mg/kg sertraline. As seen in table 5, anti-cataleptic effect of sertraline was significantly blocked by pretreatment with NAN-190 (P<0.001).

Table 1. Elapsed time in bar test in control, sham-operated and 6-OHDA

Groups Time (min)	Elapsed Time in Bar Test (second)		
	Normal	Sham	6-OHDA
5	12.8±1.6	10.5±1.2	102.2±4.6***
60	10.5±1.5	11±1.4	100.5±3.5***
120	11±1.1	11±1.2	101.5±3.6***
180	10.9±1.2	12.5±1.3	100.5±3.5***

*(8µg/2µl/rat) lesioned rats (n= 8/ group). Values are expressed as mean ±SEM.; *******P< 0.001 when compared with normal and sham-operated group.*

Table 2. Elapsed time in bar test after administration of normal saline and different doses of sertraline in intact rats

Groups Time (min)	Elapsed Time in Bar Test (second)			
	Saline	Sertraline 0.5 (mg/kg)	Sertraline 1 (mg/kg)	Sertraline 2 (mg/kg)
5	12.8±1.6	12.2±1.7	11±1.7	11.2±1.1
60	10.5±1.5	11.2±1.3	12.2±1.1	11.6±1.6
120	11±1.1	11.6±1.6	12.6±1.4	11.6±1.3
180	10.9±1.2	11.2±1.5	12.8±1.1	11.6±0.9

(n= 8/ group). Values are expressed as mean ±SEM.

Table 3. Elapsed time in bar test after administration of normal saline and different doses of NAN190 in intact rats

Groups Time (min)	Elapsed Time in Bar Test (second)			
	Saline	NAN190 0.1 (mg/kg)	NAN190 0.5 (mg/kg)	NAN190 1 (mg/kg)
5	12.8±1.6	11.4±1.3	11±1.09	10.6±1.3
60	10.5±1.5	13.5±0.9	14±1.6	12.8±1.2
120	11±1.1	13.9±1.2	11±0.9	10.2±1.5
180	10.9±1.2	12.5±1.5	12.9±1.5	11.8±1

(n= 8/ group). Values are expressed as mean ±SEM.

Table 4. Elapsed time in bar test after administration of saline (S) and different doses of Sertraline in 6-hydroxydopamine-lesioned rats(n= 8/ group).

Groups Time (min)	Elapsed Time in Bar Test (second)			
	6-OHDA+S	6-OHDA+Ser 0.5 mg/kg	6-OHDA+Ser 1 mg/kg	6-OHDA+Ser 2 mg/kg
5	102.2±4.6	96.2±3.1	94.4±5.4	97.8±5.1
60	100.5±3.5	88.3±2.9	75.3±3.3***	73.6±3***
120	101.5±3.6	94.6±3.1	72±3.4***	68.1±2.9***
180	100.5±3.5	93.6±2.6	72.8±2.4***	66.5±3.9***

*Values are expressed as mean ±SEM. *** = P< 0.001 compared with 6-OHDA+N.S group.*

Table 5. Effect of NAN190 pretreatment with Sertraline (1mg/kg, i.p.) on catalepsy induced by 6-hydroxydopamine (6-OHDA)(n= 8/ group).

Groups	Elapsed Time in Bar Test (second)			
	6-OHDA+ S	NAN190 0.5 mg/kg	6-OHDA+Ser 1 mg/kg	6-OHDA+NAN190+Ser 1 mg/kg
Time (min)				
5	102.2±4.6	11±1.09	94.4±5.4	100.2±4.6
60	100.5±3.5	14±1.6	75.3±3.3***	97.8±3.4###
120	101.5±3.6	11±1	72±3.4***	102.1±5###
180	100.5±3.5	12.8±1.4	72.8±2.4***	94.6±3.7###

*Values are expressed as mean ±SEM. *** = P< 0.001 compared with 6-OHDA+ Saline (S) group and ### = P< 0.001 compared with 6-OHDA+Sertarline (1 mg/kg).*

DISCUSSION

The main results of this study indicate that sertraline exerts anti-parkinsonian effect in rat model of Parkinson's disease. In the preclinical investigation of Parkinson's disease, rat models have been frequently used in which 6-OHDA was infused stereotaxically to dopaminergic structures. Accordingly 6-OHDA is injected into the Substantia nigra compact pars (SNc), Medial forebrain boundle (MFB), striatum [2] and intraventral pallidum [17]. In addition to this, some other toxins such as MPTP, MPP^+, paraquat and rotenone are also widely used for modeling of Parkinson's disease in rodents [11]. In this study intra-SNc infusion of 6-OHDA resulted in marked catalepsy. Generally in rodents, catalepsy as a marker for akinesia [18] and immobility [9] can be induced by different molecules such as 6-OHDA [13] and haloperidol [12]. Evaluation of catalepsy is done by bar test which considered as a standard test in parkinsonian rodents [12,17].

Our results showed that acute administration of sertraline is able to attenuate 6-OHDA induced catalepsy. This is in accordance with other studies that indicate $5HT_{1A}$ receptors activation can exert anti-parkinsonian effect in parkinsonian rodents [13, 16].

Following dopaminergic neuron degeneration, hyperinnervation of serotonergic neurons occurs [8] and up-regulation of 5-HT receptors is done, which manipulates dopaminergic system-related defects [9,10]. Hence it seems that serotonergic system plays important role in Parkinson's disease and Levodopa induced motor impairments [9]. Modulation of normal motor activity by this system is mediated through the $5\text{-}HT_{1A}$ receptors. These receptors are found both within the basal ganglia circuitry [3] and dorsal raphe neurons [3,4].

Transmission of serotonine is blocked by sertraline that consequently leads to elevation of this neurotransmitter levels within the synaptic cleft and its interaction with variety of serotonine receptors such as $5HT_{1A}$ receptors [16]. Activation of these receptors leads to dopamine release [5] and prolongation of dopamine effect in parkinsonian animals [13].This effect is mediated by inhibition of adenyl cyclase and opening of potassium channels [10]. In this study, NAN-190 ($5\text{-}HT_{1A}$ receptor antagonist) vanished the anti-cataleptic effect of sertraline in parkinsonian rats. Thus, it seems this effect of sertraline may be mediated by activation of $5\text{-}HT_{1A}$ receptors.

Approximately 40 % of patients with Parkinson's disease suffer from depression as a clinical problem. [19]. SSRIs are widely used to treat depressive conditions in patients with PD [16].

In conclusion, regarding to the results of this study, sertraline is able to improve motor behavior in this model of Parkinson's disease. Thus, it seems to be used as an adjuvant therapy in PD.

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