Buspirone improves haloperidol-induced Parkinson disease in mice through 5-HT<sub>1A</sub> receptors

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Received 23 Sept 2009; Revised 30 Oct 2010; Accept 5 Nov 2010

ABSTRACT

Background and the purpose of the study: The available literatures show that 5-HT<sub>1A</sub> receptors are widely distributed throughout the basal ganglia, and their activation facilitate dopamine release. Neuroleptic drugs such as haloperidol induce Parkinson-like syndrome through blocking brain D<sub>2</sub> receptors. This study aimed to investigate effect of buspirone, a partial agonist of 5HT<sub>1A</sub> receptor, on motor dysfunctions induced by haloperidol and involvement of 5HT<sub>1A</sub> receptors in this regard.

Methods: Study was performed on the male mice weighing 25-30 g. Animals were divided randomly to groups of 10 animals. Motor dysfunction was induced by intraperitoneal (i.p.) injection of haloperidol (1 mg/kg). Catalepsy was assayed by bar-test method 5, 60, 120 and 180 minutes after drug administration and motor imbalance was studied by rotarod test.

Results and major conclusion: Results showed that buspirone (20 mg/kg, i.p.) decreased significantly haloperidol-induced catalepsy and balance disorder in a dose dependent manner. Furthermore, 8-OH-DPAT (10 mg/kg, i.p.), as an agonist of 5-HT<sub>1A</sub> receptor, decreased haloperidol-induced catalepsy and balance disorder. The effect of buspirone (20 mg/kg, i.p.) on haloperidol-induced motor disorder was abolished by NAN-190 (10 mg/kg, i.p.), as a 5-HT<sub>1A</sub> receptor antagonist. From the results it may be concluded that buspirone improves haloperidol-induced catalepsy and balance disorder through activation of 5-HT<sub>1A</sub> receptors.

Keywords: Buspirone, Motor dysfunction, Haloperidol, 5-HT<sub>1A</sub> receptors

INTRODUCTION

Parkinson’s Disease (PD) is a progressive neurodegenerative disease occurring in approximately 1% of the population of age over 50 years. It’s most prominent symptoms are tremor, muscle stiffness and bradykinesia. Some non-motor symptoms such as cognitive behavior disorder and depression are usually observed in patients. The disease is accompanied by preferential loss of dopaminergic neurons of the substantia nigra pars compacta (SNc) (1) and the influence of other neurotransmitter systems have not been studied extensively. The fact that serotonergic system are also involved in PD has been raised from previous studies (2) and postmortem research has shown reduced levels of basal ganglia serotonin (5-HT) as well as its metabolite 5-hydroxy-INDoleactic acid (5HIAA) (3). While there are some reports on the inhibitory effect of 5-HT on striatal dopamine (DA) release (4), other studies have shown that 5-HT facilitates DA outflow (5). This discrepancy results from differences in receptor types and subtypes (6). 5-HT<sub>1A</sub> receptors are widely distributed through the basal ganglia (7). They are located on dorsal raphe neurons with efferents to the striatum, and are also localized on cortical neurons sending glutamatergic projections to the basal ganglia (1). Studies have shown that 5-HT<sub>1A</sub> receptor stimulation Showed antiparkinsonian effects in 6-hydroxypredamine (6-OHDA)- lesioned rats (8). This effect is most likely caused by the increase in 5-HT<sub>1A</sub> receptor activation, resulting in inhibition of serotonin release (1). Although stimulation of 5-HT<sub>1A</sub> receptor is associated with an increase in dopamine turnover (9), dopaminergic cell firing (10) and dopamine release (11), suggesting that 5-HT<sub>1A</sub> agonists might have potential therapeutic value in the treatment of parkinson’s disease, Other studies have reported that administration of the 5-HT<sub>1A</sub> agonist did not affect basal DA release in the nucleus accumbens or the striatum (4,12).

In animal studies, neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydroxypyridine (MPTP) and 6-OHDA and neuroleptic drugs (e.g. haloperidol) are used commonly to create experimental model of PD by which certain aspects of the disease such as catalepsy, motor imbalance and slowing of movement can be modeled (1,13). The cataleptic
immobility induced in rodents by typical neuroleptics (e.g., haloperidol, chlorpromazine, fluphenazine) is a behavioral method to study nigrostriatal function and its modulation by other neurotransmitters (14). Drugs which attenuate haloperidol-induced motor disorders might reduce the extrapyramidal signs of PD (15). Thus investigation of the effects of buspirone on extrapyramidal side effects of haloperidol appeared of interest. The present study was designed to determine effect of buspirone on catalepsy and motor imbalance induced by haloperidol as well as possible involvement of 5-HT_{1A} receptors by using 8-OH-DPAT and NAN-190 as agonist and antagonist of 5-HT_{1A} receptors respectively.

**MATERIAL AND METHODS**

**Chemicals**

All chemicals were obtained from Sigma Chemical Company (USA) except for buspirone and haloperidol that were purchased from Heumann Company (Germany) and Daru-Pakhsh Company (Iran) respectively. Solutions were prepared fresh on the days of experimentation by dissolving drugs in physiological saline (0.9% NaCl). The drugs were injected intraperitoneally (i.p.) and movement disorders were assessed by bar test and rotarod of 5, 60, 120 and 180 min after drugs administration.

**Animals**

The experiments were carried out on male Swiss albino mice weighing 25-30 g. Animals were housed in standard polypropylene cages, ten per cage, under a 12:12 h light/dark schedule at an ambient temperature of 23±2 °C and had access to food and water freely. All experiments were carried out under the ethical guidelines of the Tabriz University of Medical Sciences, for the care and use of laboratory animals (National Institutes of Health Publication No 85-23, revised 1985).

**Motor impairment study**

Motor impairment was induced with haloperidol (1 mg/kg, i.p.) and measured by bar test and rotarod methods at 5, 60, 120 and 180 min after drug administration. In each tests animals were used only once. The dose of the haloperidol was chosen to produce a moderate degree of catalepsy and motor imbalance, so that either attenuation or potentiation of the both phenomenon could be detected (15). The drugs (and saline for the controls) were injected ip with a 29-G needle, 15 min before haloperidol. All observations were made between 9:00 AM and 16:00 PM in a quiet room by an observer who was blind to treatments.

Catalepsy was measured by means of a standard bar test, as the time that mouse maintained an imposed position with both front limbs extended and resting on a 3-cm high wood bar (0.9 cm in diameter). The end point of catalepsy was considered the time that both front paws were removed from the bar or if the animal moved its head in an exploratory manner. A cut-off time of 720 seconds was applied (15).

The rotarod test was used to assess the ability of the animal to maintain balance on a 1-inch diameter rod revolving at a constant rate of 6 revolutions per minute (16). This test requires a high degree of sensorimotor coordination and is therefore used to test more subtle neurological deficits. The ability of all animals to pass the rotarod test was checked regularly prior and after drug administration.

**Expression of data and statistics**

Descriptive statistics and comparisons of differences between each data set were calculated by use of InStat software. The data were expressed as mean ± SEM, and were analyzed by one-way ANOVA in each experiment. Statistical significance was accepted at the level of p<0.05. In the case of significant variation (p<0.05), the values were compared by Tukey test.

**RESULTS**

**Effect of buspirone on haloperidol-induced motor impairment**

Six groups of mice were treated with saline, haloperidol (1 mg/kg, i.p.) alone and haloperidol (1 mg/kg, i.p.) with four different doses of buspirone (5, 7.5, 10 and 20 mg/kg, i.p.). As it has been shown in figure 1A and 1B, haloperidol was able to induce significant (p<0.001) catalepsy and motor imbalance (p<0.001) when compared with saline-treated mice. Buspirone, as a partial agonist of 5-HT_{1A} receptors, reduced haloperidol-induced catalepsy (p<0.001, 0.01, 0.05) almost in a dose dependent manner (Fig. 1A). Results showed that buspirone (20 mg/kg, i.p.) improves markedly (p<0.001) haloperidol induced motor imbalance (Fig. 1B).

**Effect of 8-OH-DPAT on haloperidol-induced motor impairment**

The effect of 8-OH-DPAT (10 mg/kg, i.p.) on haloperidol-induced catalepsy and motor 2 imbalance was determined. Results showed that 8-OH-DPAT attenuated haloperidol-induced catalepsy (p<0.001) and motor imbalance (p<0.001) in comparison with haloperidol alone. In group of animals treated with 8-OH-DPAT alone, there was not any remarkable alteration in bar test and rotarod elapsed time (Fig. 2A, 2B).

**Effect of buspirone and NAN-190 co-injection on haloperidol-induced motor impairment**

As it has been shown in figure 3A, NAN-190 (10 mg/kg, i.p.) as a 5-HT_{1A} receptor antagonist, abolished (p<0.001, 0.05) anticaatalytic effect of buspirone (20 mg/kg, i.p.). This drug also decreased (p<0.001, 0.01)....
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Bar test, p<0.001, c: p<0.05 and d: p<0.01 vs haloperidol+B20 group. B= buspirone

Elapsed Time in Bar Test (s), n=10 mice for each group. a : p<0.001 vs saline group , b :

Figure 1. Effects of buspirone (5, 7.5, 10 and 20 mg/kg, i.p.) on haloperidol-induced motor impairment (A: Bar test, B: Rotarod). Each bar represents the mean±SEM of elapsed time (s), n=10 mice for each group. a : p<0.001 vs saline group, b: p<0.001, c: p<0.01 and d: p<0.05 vs haloperidol treated group. B= buspirone

Figure 2. Effect of 8-OH-DPAT (10 mg/kg, i.p.) on haloperidol-induced motor impairment (A: Bar test, B: Rotarod). Each bar represents the mean±SEM of elapsed time (s), n=10 mice for each group. a: p<0.001 vs saline group, b: p<0.001 vs haloperidol treated group.

Figure 3. Effect of buspirone (20 mg/kg, i.p.) and NAN-190 (10 mg/kg, i.p.) co-injection on haloperidol-induced motor impairment (A: Bar test, B: Rotarod). Each bar represents the mean±SEM of elapsed time (s), n=10 mice for each group. a: p<0.001 vs saline group; b: p<0.001, c: p<0.01 and d: p<0.05 vs haloperidol+B20 group. B= buspirone

the effect of buspirone (20 mg/kg, i.p.) on haloperidol-induced motor imbalance (Fig. 3B).

DISCUSSION

Parkinson's disease is caused by degeneration of dopaminergic neurons of substantia nigra, pars compacta. The most important characteristic of this disease is reduction of dopamine release from the end of striatal dopaminergic nerves. This disease is accompanied with movement disorders e.g. tremor, muscle rigidity and slow movement (1). Some neurotoxins such as MPTP, 6-OHDA, or neuroleptic drugs (e.g. haloperidol) are used frequently to create experimental models of this disease (1, 13). In this study effect of buspirone and possible involvement of 5-HT₁ receptors on haloperidol-induced catalepsy and motor imbalance was investigated. Bar test (15) and rotarod (17) are standard tests that are usually used to evaluate catalepsy and motor imbalance disorders, respectively. Results of this study showed that acute administration of haloperidol induced catalepsy and imbalance in the rotating rod (rotarod) which is in accordance with results of other studies (13) where haloperidol (D2 antagonist) was used to create an empirical model of Parkinson disease.
Buspirone, as a partial agonist of 5-HT \textsubscript{1A} receptors, improved prominently haloperidol-induced catalepsy and motor imbalance. This finding substantiates studies reporting that 5-HT \textsubscript{1A} receptor agonists attenuate movement disorders induced by dopamine neurotoxins which was assessed by other experimental methods (18). Haloperidol is a potent typical neuroleptic drug which is used for treatment of some neuropsychiatric diseases. Parkinson-like syndromes and extrapyramidal symptoms are the major problems resulting from the use of this drug in psychotic patients (19). Therefore, special attention are paid to adjuvant therapy to reduce the severity of motor complications induced by haloperidol or any other neuroleptic drugs. Apart from affecting 5-HT \textsubscript{1A} receptors, buspirone has also D\textsubscript{2} and \(\alpha\)-adrenoceptor blocking effects (20, 21). Therefore, it is possible that its effects on improvement of haloperidol induced motor deficiency may be due to its effects on these receptors. In this study it was shown that 8-OH-DPAT could reduce haloperidol-induced movement disorders considerably and NAN-190 (5-HT\textsubscript{1A} antagonist) abolished improving effect of buspirone on motor disorders induced by haloperidol. It might be due to effects of buspirone on and as a result involvement of \(\alpha\) or D\textsubscript{2} receptors may be neglected.

It has been shown that the 5-HT\textsubscript{1A} receptor is present on dorsal raphe neurons with efferents to the striatum, and on cortical neurons sending glutamatergic projections to the basal ganglia (1). Stimulation of 5-HT\textsubscript{1A} receptors in these regions leads to decrease and increase of serotonin and dopamine release respectively (9) by the inhibition of adenylyl cyclase and opening of potassium channels (22). Therefore, it may be suggested that the effect of buspirone on haloperidol-induced motor disorders is due to decrease of inhibitory effects of serotonin on the release of dopamine.

Anxiety is a co-morbid problem that is observed commonly in patients suffering from psychosis (23). Therefore, adjuvant therapy with buspirone in addition of reducing symptoms of anxiety, might be decrease in movement complications induced by haloperidol or other neuroleptic drugs. On the basis of results of this study further investigation on a possible usefulness of buspirone in decreasing motor side effects of neuroleptic drugs is suggested.

ACKNOWLEDGEMENTS
We wish to thank the Director of Drug Applied Research Center, Tabriz University of Medical Sciences for the grant No. 5-79-4968 in supporting this study.

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