REVERSAL OF HALOPERIDOL-INDUCED MOTOR DEFICITS BY MIANSERIN AND MESULERGINE IN RATS

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ABSTRACT

Although haloperidol is widely prescribed for the treatment of schizophrenia, its beneficial effects are accompanied by extrapyramidal side effects (EPS). Role of 5-HT-2A/2C receptors in the attenuation of acute Parkinsonian-like effects of typical antipsychotics is investigated by prior administration of mianserin and mesulergine to rats injected with haloperidol. In the first part of study effects of various doses of haloperidol (0.5, 1.0, 2.5 and 5.0 mg/kg) were determined on motor activity and a selected dose (1 mg/kg) was used to monitor attenuation of parkinsonian effects by two different doses of 5-HT-2A/2C receptor antagonists mianserin (2.5 & 5.0 mg/kg) and mesulergine (1.0 & 3.0 mg/kg). Rats treated with haloperidol at doses of 0.5-5.0 mg/kg exhibited impaired motor coordination and a decrease in exploratory activity in an open field. The dose response curve showed that at a dose of 1 mg/kg significant and submaximal effects are produced on motor coordination and exploratory activity. Coadministration of mianserin and mesulergine attenuated and reversed haloperidol-induced motor deficits in a dose dependent manner. The mechanism involved in the attenuation / reversal of haloperidol-induced parkinsonian like symptoms by mianserin and mesulergine is discussed. Prior administration of mianserin or mesulergine may be of use in the alleviation of EPS induced by conventional antipsychotic drugs. The findings have potential implication in the treatment of schizophrenia and motor disorders.

Keywords: Mianserin, Mesulergine, Haloperidol, Exploratory activity, Extrapyramidal symptoms, Motor coordination.

INTRODUCTION

Although the first generation of antipsychotic drugs such as chlorpromazine and haloperidol are widely prescribed for the treatment of schizophrenia, their beneficial effects are accompanied by extrapyramidal side effects (EPS). The short-term effects include Parkinsonism (Haleem *et al.*, 2002, 2003, 2004) and the later appearing tardive dyskinesia (Drew *et al.*, 1990; Haleem *et al.*, 2007a, b). A goal of current research is, therefore, to alleviate the adverse effects of neuroleptics on motor behavior. Multiple receptors for serotonin (5-HT) exist in the central nervous system. 5-HT-2A and 5-HT-2C receptors are located on the cell body and dendrites of dopaminergic neurons (Clemette *et al.*, 2000; Esposito, 2006) in the caudate nucleus, nucleus accumbens, olfactory tubericle and pyriform cortex (Pazos and Palacios, 1985; Jacob and Azmitia, 1992). A potential role of 5-HT-2A/2C receptors in the control of motor activity was also suggested because drugs with agonist activity towards 5-HT-2A/2C receptors elicited hypolocomotion and akinesia in experimental animals (Kennett and Curzon, 1989; Haleem, 1993, Ikram *et al.*, 2007). A hypothesis therefore emerged that release of dopamine (DA) from the inhibitory influence of 5-HT following the blockade of 5-HT-2A/2C receptor could alleviate acute parkinsonian like effects of typical neuroleptics.

Studies in animal model show that acute administration of haloperidol elicits parkinsonian like symptoms which are quantified in rats by a suppression of exploratory activity and impaired motor coordination leading to a state of catalepsy (Haleem *et al.*, 2002, 2003, 2004; Karl *et al.*, 2006). Several studies have shown that catalepsy induced by DA D-2 receptor blockade cannot be reversed by pretreatment with 5-HT-2A receptor antagonists (Arnt *et al.*, 1986; Elliot *et al.*, 1990; Wadenberg, 1992; Wadenbergetal, 1996). However, some investigators have reported an attenuation of neuroleptics induced catalepsy following pretreatment with some 5-HT-2 receptor antagonist (Neal-Beliveau *et al.*, 1993; Bligh-Glover *et al.*, 1995; Bonhomme *et al.*, 1997; Reavill *et al.*, 1999; Wadenberg *et al.*, 2001). Psychiatric patients are often treated with several psychotropic drugs in combination. In this respect, antidepressant agents may be co-administered with antipsychotics in schizophrenic patients with concomitant depressive and negative symptoms (Plasky, 1991; Evins and Goff, 1996; Zoccali *et al.*, 2003). Mianserin and mesulergine are clinically effective antidepressant drugs acting as an antagonist at 5-HT-2A and 5-HT-2C (Pinder, 1991; Walting *et al.*, 1995; Thomas *et al.*, 1998). Clinical studies have shown that mianserin enhances the effect of typical antipsychotic

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drugs, particularly on negative symptoms such as withdrawal retardation, as well as akathisia and some aspects of cognitive dysfunction (Mizuki *et al.,* 1990, 1992; Poyorovsky *et al.,* 1999; Grinshpoon *et al.,* 2000; Shiloh *et al.,* 2002; Poyorovsky *et al.,* 2003).

In a previous study we have shown that stimulation of somatodendritic 5-HT-1A receptor by a selective agonist such as 8-hydroxy-2-di-n-propylaminotetralin (8-OH-DPAT) and buspirone decreased the availability of 5-HT possibly at 5-HT-2C receptors in the striatum and so attenuate neuroleptics induced catalepsy (Haleem *et al.,* 2004; see review Haleem, 2006). The present study was therefore designed to test the hypothesis that coadministration of 5-HT-2A/2C receptor antagonists such as mianserin and mesulergine could reverse the elicitation of parkinsonian like symptoms induced by haloperidol in a rat model. In the first part of study effects of various doses of haloperidol (0.5, 1.0, 2.5 and 5.0 mg/kg) were determined on motor activity and a selected dose (1 mg/kg) was used to monitor attenuation of parkinsonian effects by two different doses of 5-HT-2A/2C receptor antagonists mianserin (2.5 & 5.0 mg/kg) and mesulergine (1.0 & 3.0 mg/kg).

MATERIALS AND METHODS

Animals and treatments

Locally bred male albino wistar rats weighing 200-220g were housed individually with free access to standard rodent diet and water.

Experimental Protocol

A. Effects of haloperidol on motor activity

Effects of different doses of haloperidol on exploratory activity in an open field and motor coordination were monitored in a separate experiment. The experiment was conducted for selecting a dose of haloperidol that cannot produce maximal (100%) cataleptogenic effect. Animals divided into five equal groups were injected with saline (1 ml/kg) or haloperidol at doses of 0.5, 1.0, 2.5 and 5.0 mg/kg activity in an open filed was monitored for 5 min starting 30 min post injection. Effects on motor coordination were monitored 45 min post injection.

B. Effects of low mianserin on haloperidol-induced parkinonian like symptoms

Animals randomly divided to six equal groups: (i) Saline plus saline (ii) Mianserin (2.5 mg/kg) plus saline (iii) Mianserin (5.0 mg/kg) plus saline (iv) Saline plus haloperidol (1 mg/kg) (v) Mianserin (2.5 mg/kg) plus haloperidol (1 mg/kg) and (vi) Mianserin (5.0 mg/kg) plus haloperidol (1 mg/kg) were injected (first injection) with saline (1 ml/kg) or mianserin at doses of 2.5 and 5.0 mg/kg). The second injection of saline or haloperidol (1 mg/kg) was made 20 minutes later. The animals were injected according to balanced design between 10:00 and 12:00 h. Behavioral assessments of motor activity in an open field and motor coordination respectively were carried out after 30 minutes and 45 minutes of 2nd injection (saline or haloperidol).

C. Effects of mesulergine on haloperidol-induced parkinonian like symptoms

Animals randomly divided to six equal groups: (i) Saline plus saline (ii) Mesulergine (1.0 mg/kg) plus saline (iii) Mesulergine (3.0 mg/kg) plus saline (iv) Saline plus haloperidol (1 mg/kg) (v) Mesulergine (1.0 mg/kg) plus haloperidol (1 mg/kg) and (vi) Mesulergine (3.0 mg/kg) plus haloperidol (1 mg/kg) were injected (first injection) with saline (1 ml/kg) or mesulergine at doses of 1.0 and 3.0 mg/kg. The second injection of saline or haloperidol (1 mg/kg) was made 20 minutes later. The animals were injected according to balanced design between 10:00 and 12:00 h. Behavioral assessments of motor activity in an open field and motor coordination respectively were carried out after 30 minutes and 45 minutes of 2nd injection (saline or haloperidol).

Monitoring activity in an open field activity

The open field apparatus used in this investigation consisted of a big square area 76x76 with walls 42 cm high. The floor was divided into 25 equal squares. To determine activity, an animal was placed in the center square of the open field and immediately after the placement the number of squares crossed was scored for 5 minutes only.

Motor Coordination

Motor coordination was assessed on a Rotor-rod (UGOBASILE, Biological research apparatus, COMERIO, Varese, Italy). The motor rod with a drum of 7.0 cm diameter was adjusted to a speed of 2-20 revolution/min during the training session and a fixed speed of 20 revolution/min during the test session. A day before the treatment rats were trained in a single session until they attained 150 s on the Rotor-Rod. The latency to fall in a test session of 150 s was taken as a measure of motor coordination.

Statistical analysis

Dose related effects of haloperidol on exploratory activity in an open field and motor coordination were analyzed by one way ANOVA. Effects of mianserin or mesulergine on haloperidol-induced deficits of exploratory activity in an open field and motor coordination were analyzed by two way analysis of variance (ANOVA). Post hoc comparisons were carried out by Newman-Keuls test. *P* values <0.05 were taken as significant.

RESULTS

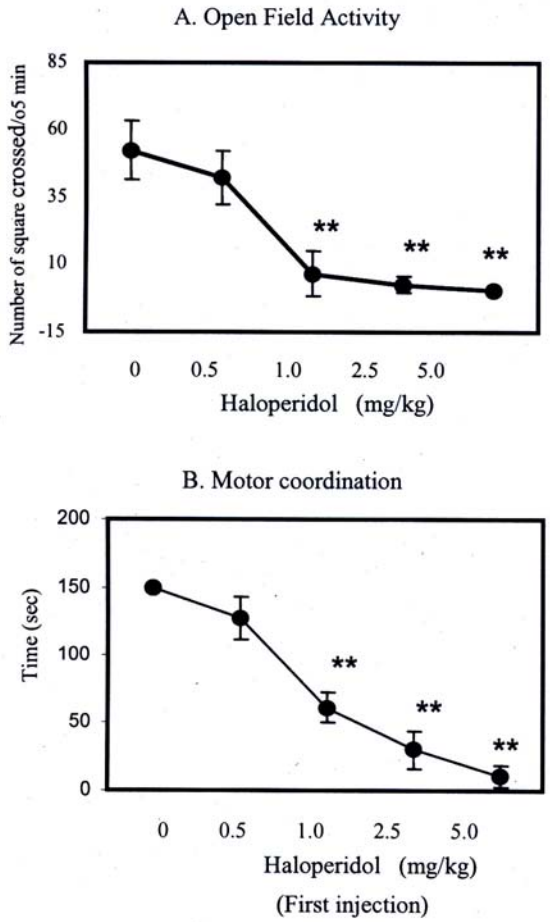

Fig. 1: Shows the motor and cataleptic effects of various doses of haloperidol. ANOVA (df 4, 18) showed significant effects of haloperidol (0.5, 1.0, 2.5 and 5.0 mg/kg) on motor activity ($F = 32$ $p<0.01$) and motor coordination ($F = 61$ $p<0.01$). Post hoc analysis showed significant decrease exploratory activity and impairment of motor coordination was produced at a dose of 1mg/kg. The effects were dose dependent while complete akinesia and 100% catalepsy occurred at a dose of 5.0 mg/kg of haloperidol. A dose of haloperidol that did not produce maximum effects was therefore used in further study to investigate the effects of mianserin on the attenuation of haloperidol-induced motor deficits

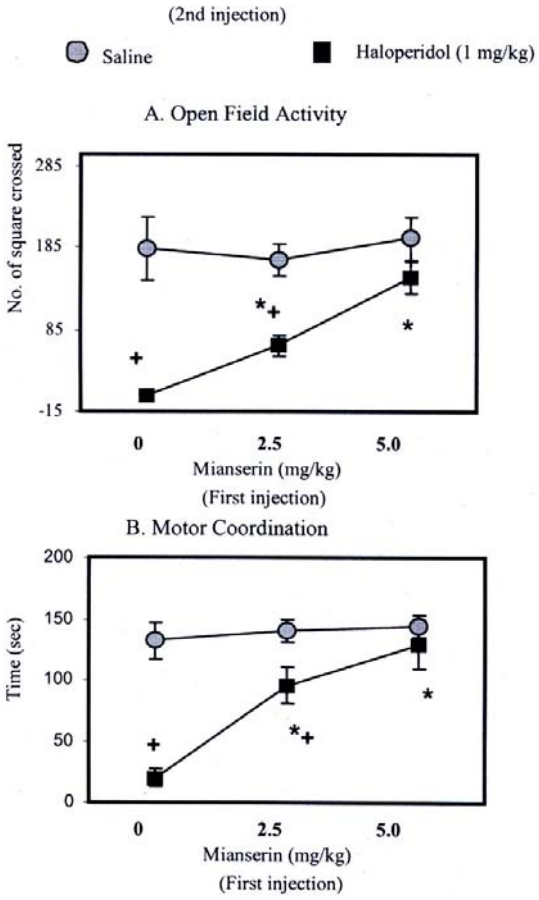

Fig. 2: Shows the effects of haloperidol on the activity in an open field (2A) and motor coordination (2B) in rats cotreated with saline or mianserin. Two way ANOVA (2, 18) showed significant effects of haloperidol on open field activity ($F=84$, $p<0.01$) and motor coordination ($F=52$, $p<0.01$). Effects of mianserin were also significant for activity in an open field ($F=7.0$ $p<0.01$) and motor coordination ($F=36$, $p<0.01$). Interaction between haloperidol and mianserin was significant for activity in an open field ($F = 29$, $p<0.01$) and motor coordination ($F = 30$, $p<0.01$). Post hoc test showed that administration of mianserin at doses of 2.5 and 5.0 mg/kg did not significantly decrease exploratory activity in the open field but coadministration of mianserin with haloperidol dose dependently attenuated haloperidol-induced deficits of motor coordination and deficits of exploratory activity

DISCUSSION

The present study was conducted to test the hypothesis that administration of mianserin and mesulergine could attenuate haloperidol-induced deficits of motor behavior. We report that administration of haloperidol produces dose dependent decrease in exploratory activity in an open field (fig. 1A). Motor coordination was also impaired in a dose dependent manner (fig. 1B). The dose response curve showed that at a dose of 1 mg/kg significant and submaximal effects are produced on motor coordination and exploratory activity. We also report that coadministration of mianserin (2.5 & 5.0 mg/kg) and mesulergine (1.0 & 3.0 mg/kg) attenuated and reversed haloperidol-induced motor deficits in a dose dependent manner (figs. 2 & 3).

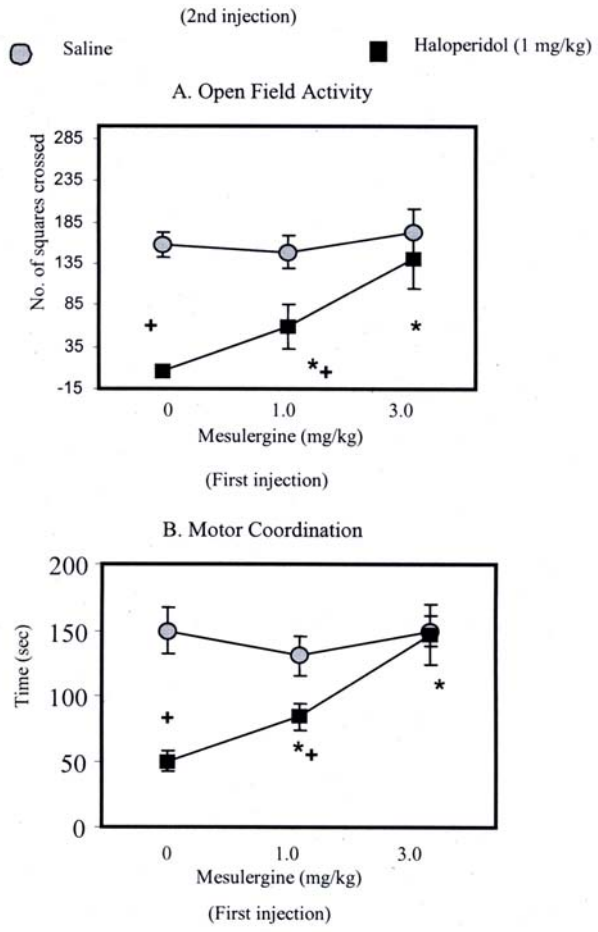

Fig. 3: Shows the effects of haloperidol on the activity in an open field (3A) and motor coordination (3B) in rats cotreated with saline or mesulergine. Two way ANOVA (1, 18) showed significant effects of haloperidol on open field ($F=150$, $p<0.01$) and motor coordination ($F=21$, $p<0.01$). Effects of mesulergine were also significant for activity in an open field ($F=4.0$ $p<0.05$) and motor coordination ($F=16$, $p<0.01$). Interaction between haloperidol and mesulergine was significant for activity in an open field ($F = 92$, $p<0.01$) and motor coordination ($F=7.0$, $p<0.05$). Post hoc test showed that administration of mesulergine at doses of 1.0 and 3.0 mg/kg did not significantly decrease exploratory activity in the open field but coadministration of mesulergine with haloperidol dose dependently attenuated haloperidol-induced deficits of motor coordination and deficits of exploratory activity

The DA system has traditionally been regarded crucial to the control of motor activity (Petry *et al.,* 1993; Clausing *et al.,* 1995; See Haleem, 2006). With respect to the anatomical site of action a view has developed that striatum is involved in the control of motor behavior. The typical effect of administering a DA receptor antagonist is a suppression of spontaneous exploratory locomotor behavior and elicitation of a state known as catalepsy. Selective antagonists of DA D-2 receptors such as haloperidol can elicit catalepsy (Wanibuchi and Usuda, 1990; Haleem *et al.,* 2002, 2004). Haloperidol-induced deficits of motor coordination in animals represent a valuable model to study EPS (Haleem *et al.,* 2007). In agreement with previous studies (Hicks, 1990; Haleem *et al.,* 2002), administration of haloperidol produced a dose dependent decrease in open field activity (fig. 1A). Performance on Rota-rod was also impaired in a dose dependent manner (0.5 to 5.0 mg/kg) (fig. 1B).

The serotonergic system is known to play a role in the modulation of activity of dopaminergic neuron. We and other authors have previously reported that administration of 5-HT-1A agonists such as 8-OH-DPAT and buspirone attenuated haloperidol-induced parkinsonian effects (Hicks, 1990; Andersson and Kilpatrick, 1996; Wadenberg, 1996; Haleem *et al.,* 2004, 2007). We demonstrated that a decrease in the availability of 5-HT in the striatum by the stimulation of somatodendritic 5-HT-1A receptors is involved in the attenuation of haloperidol-induced catalepsy (Haleem *et al.,* 2004, 2007). Inhibitory influence of 5-HT on the activity of dopaminergic neurons via the stimulation of 5-HT-2C receptors located on the cell body and terminal region of dopaminergic neurons (Clemette *et al.,* 2000; Esposito, 2006). It was suggested that administration of 5-HT-1A agonists decrease the availability of 5-HT at 5-HT-2C receptors in the striatum to release dopaminergic neurotransmission from the inhibitory influence of 5-HT (Haleem *et al.,* 2004; see review Haleem, 2006). Other authors have reported that local administration of 5-HT-2A/2C receptor antagonist into the ventral tegmental area or the nucleus accumbens did not alter basal locomotor activity (McMohan *et al.,* 2001; Fillip and Cunningham, 2002). Haloperidol-induced parkinsonian like effects (1 mg/kg) in rats could be antagonized by the administration of 5-HT-2A/2C receptor antagonists such as ritanserin (Lucas *et al.,* 1997) and SB-228357 (1-5[-fluoro-3(3-pyridyl) phenyl-carbamoyl]-5-methoxy-6-trifluor methyl indoline) (Hicks, 1990; Neal-Beliveau *et al.,* 1993; Reavill *et al.,* 1999). Clinical studies showed that neuroleptic-induced akathisia was decreased by the administration of mianserin (Poyorovsky *et al.,* 1999; Stryjer *et al.,* 2004; Midowink *et al.,* 2006; Ranjan *et al.,* 2006), a mixed 5-HT-2A/2C receptor antagonist (Pinder, 1990). We find that the systemic administration of mianserin and mesulergine did not alter basal locomotor activity in open field (figs. 2A & 3A). Motor coordination was also not impaired (figs. 2B & 3B) in these groups but coadministration of mianserin (2.5 & 5.0 mg/kg) and mesulergine (1.0 & 3.0 mg/kg) with a selected dose of haloperidol attenuated and completely reversed parkinsonian like effects induced by haloperidol in a dose dependent manner (figs. 2 & 3). The ability of mianserin as well as mesulergine to attenuate haloperidol-induced motor deficits in a dose dependent manner as observed in the present study is consistent with the notion that

antagonist activity of a drug towards 5-HT-2A/2C receptors (Saller *et al.,* 1990) could release DA neurotransmission from the inhibitory influence of 5-HT to ameliorates parkinsonian like effects of the neuroleptics drug (See review Kapur and Ramington, 1996).

In conclusion, the present study shows that mianserin and mesulergine, clinically effective antidepressant drugs, attenuated and completely reversed haloperidol-induced motor deficits in a dose dependent manner. It is therefore suggested that prior administration of mianserin and mesulergine may be of use in the alleviation of EPS induced by conventional antipsychotic drugs. It may be interesting to investigate the chronic effects of mianserin and/ or mesulergine in the attenuation of haloperidol-induced vacuous chewing movements as the effect of chronic treatment would be expected to have greater clinical relevancy.

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