BEHAVIORAL EFFECTS OF 1-(m-CHLOROPHENYL)PIPERAZINE (m-CPP) IN A RAT MODEL OF TARDIVE DYSKINESIA

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ABSTRACT

The present study was designed to monitor the responsiveness of 5-hydroxy tryptamine (5-HT)-2C receptor in rats treated with haloperidol exhibiting tardive dyskinesia (TD). Results show that haloperidol injected at a dose of 1 mg/kg twice a day for two weeks elicited vacuous chewing movements (VCMs). Which increased in a time dependent manner following the drug administration for 3-5 weeks. The behavioral effects of 1-(m-chlorophenyl)piperazine (m-CPP) a 5-HT-2C and 5-HT-1B agonist were monitored 2 days after 5 weeks of saline or haloperidol administration. The results show that hypophagic as well as anxiogenic-like effects of m-CPP are greater in repeated haloperidol than repeated saline injected animals, while hypolocomotive effects of m-CPP are not different in repeated saline and haloperidol injected animals. Results are discussed in the context of role of 5-HT-2C receptors in the regulation of the activity of dopaminergic neuron and its possible impact on elicitation of TD.

Keywords: Haloperidol; Tardive dyskinesia; VCMs; m-CPP; 5-HT-2C receptor.

INTRODUCTION

Schizophrenia is a chronic relapsing psychotic disorder affecting mainly thought and behavior. Neuroleptic drugs are widely prescribed for the treatment of schizophrenia but unfortunately, their use is often associated with a high incidence of extrapyramidal symptoms that include acute Parkinsonism (Synder *et al*., 1974; Ayd, 1983) and delayed tardive dyskinesia (TD; Kalwans, 1985).

TD is manifested by involuntary movements particularly in the oral lingual masticatory area (Kalwans, 1985) of rats chronically treated with typical neuroleptics such as haloperidol (Robovits, 1972; Tarsy and Baldessarini, 1974; 1977). Vacuous chewing movements (VCMs) in rat are widely accepted as a rat model of TD. It has been shown that rats repeatedly treated with haloperidol develop VCMs (Ellison and See, 1989). It is generally assumed that TD persists after haloperidol withdrawal indicating that haloperidol produced long term changes in brain function (Meshul *et al*., 1992; 1994).

An increase in the responsiveness of postsynaptic as well as presynaptic 5-hydroxy tryptamine (5-HT)-1A receptors (Haleem and Khan, 2003) and dopamine D2 receptors binding (Uranova *et al*., 1991) in rat brain has been also observed following prolonged neuroleptic treatment.

Dopamine is crucial for the control of motor activity. Serotonin can inhibit the activity of dopaminergic neurons (Bailey *et al*., 1993). This action of serotonin is due to the stimulation of 5-HT 2C receptors located on the somatodendritic as well as nerve terminal region of dopaminergic neurons (Pessia *et al*., 1994; Millan *et al*., 1998).

The most common 5-HT 2C receptor agonist 1-(m-chlorophenyl)piperazine (m-CPP; Murrphy *et al*., 1993; Kennett *et al*., 1993) increases 5-HT release (Hikiji *et al*., 2001) via the stimulation of 5-HT 2C receptors (Gibson *et al*., 1996) and decreases DA release in the striatum (Alex *et al*., 2005) and other regions (Prisco *et al*., 1994) of rat brain. The drug produces hypolocomtion (Lucki *et al*., 1989; Gleason and Shannon, 1998), hypophagia (Samanin *et al*., 1979; Schuhler *et al*., 2005) and anxiogenesis (Kennett, 1992; Fone *et al*., 1996) in rats.

It may be hypothesized that the responsiveness of 5-HT 2C receptors is also altered by long term administration of haloperidol and is involved in the elicitation of TD. The present study was designed to monitor the responsiveness of 5-HT 2C receptor following long term administration of haloperidol in rats exhibiting TD.

MATERIALS AND METHODS

Animals

Locally bred female albino Wistar rats weighing 180-220 g purchased from HEJ Research Institute, University of Karachi, Pakistan, were housed individually with free access to cubes of standard rodent diet and tap water 3 days before starting the experiment.

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Drugs
Haloperidol (Serenace, Searle, USA) purchased as injectable ampoules of 5 mg/ml, was injected intraperitoneally at a dose of 1 mg/kg body weight twice daily. m-CPP purchased from Sigma was dissolved at a dose of 3 mg/kg body weight. Control animals were injected with saline in volume of 1 ml/kg body weight.

Experimental protocol
Twenty four animals were divided into two groups (i) saline injected (ii) haloperidol injected (twice a day). The animals received respective treatment for 5 weeks. VCMs were scored weekly and after a wash out period of two days. Behavioral effects of m-CPP were monitored after a wash out period of 2 days. The animals deprived of food 24-h prior administration of m-CPP.

For monitoring the effects of m-CPP repeated saline and repeated haloperidol injected animals were further divided into saline and m-CPP injected groups. Motor coordination, activity in an open field and time spent in the lit compartment of a light-dark box respectively were monitored 15 min, 30 min and 45 min of post-injection. Hypophagic effects of m-CPP were monitored as 2-h and 4-h food intake starting 1-h after m-CPP or saline injection.

BEHAVIORAL STUDIES

Vacuous Chewing Movements (VCMs) quantification
Animals were placed individually in an activity box (26x26x26 cm) with sawdust-covered floor and were allowed to adapt the observation cage for a period of 15 minutes. VCMs were monitored during 10 minutes observation period. For calculation purposes, each burst of purposeless chewing was counted as one, if its duration was at least 3 seconds.

Rota-rod activity
Motor coordination was assessed for all rats on a rota-rod. The rota-rod had a 7 cm radius and a speed of 16 revolution/minute. Prior to any treatment rats were trained in a single session until they attained 150 seconds on rota-rod. Performance was monitored 15-min after the injection of m-CPP.

Open field activity
To monitor activity in a novel environment, open field apparatus was used. The open field apparatus used in the present investigation consisted of a square area 76x76 with walls 42 cm high. The floor was divided by lines into 25 equal squares. To determine activity a rat was placed in the center square of the open field. The numbers of squares crossed with all four paws were scored for 5 minutes as described earlier (Haleem, 1996).

Light-dark activity
The test was conducted in a locally-made compartment box. The compartment of equal size (26x26x26 cm), with an access (12x12 cm) between the compartments, differed in their sensory properties. Walls of one compartment were light (transparent) and other dark (black). A rat placed in this box is expected to pass more time in the dark compartment. To determine the activity a rat was introduced via the dark compartment of the box. Time spent in the light compartment was monitored for a cut off time of 5 minutes.

STATISTICAL ANALYSIS

Data on effect of haloperidol withdrawal on VCMs analyzed by Student's t-test. Data on effect of haloperidol on intensity of VCMs analyzed by two-way ANOVA. Effects of m-CPP on behavioral data in saline and haloperidol treated animals were also analyzed by two-way ANOVA. Post-hoc comparison was done by Newman-Keuls test: $p<0.05$ taken as significant.

RESULTS

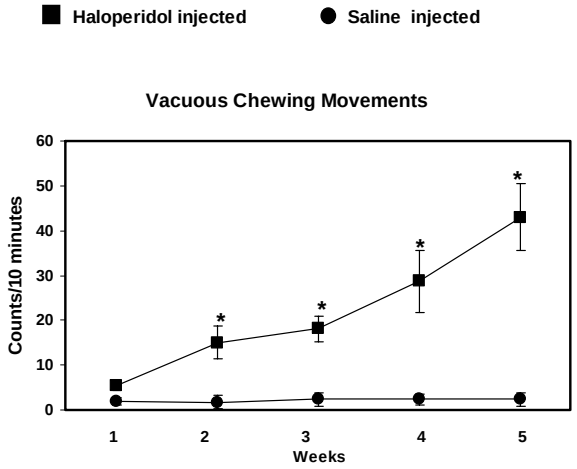

Fig. 1: The intensity of haloperidol-induced VCMs. Values are means ± S.D. (n=12). 1-h after the administration of haloperidol and saline. Significant differences by Newman-Keuls test: *$p<0.01$ from respective saline treated animals following two-way ANOVA.

Fig. 1 shows the intensity of haloperidol-induced VCMs. Data analyzed by two-way ANOVA showed significant effect of haloperidol ($F=879.72$ df=1,110 $p<0.01$), weeks ($F=39.10$ df=4,110 $p<0.01$) and a significant interaction between haloperidol*weeks ($F=144.03$ df=4,110 $p<0.01$). Post-hoc analysis showed that administration of haloperidol elicited VCMs after 2 weeks of administration. The intensity of VCMs increased in a time dependent manner during 3-5 weeks of drug administration.

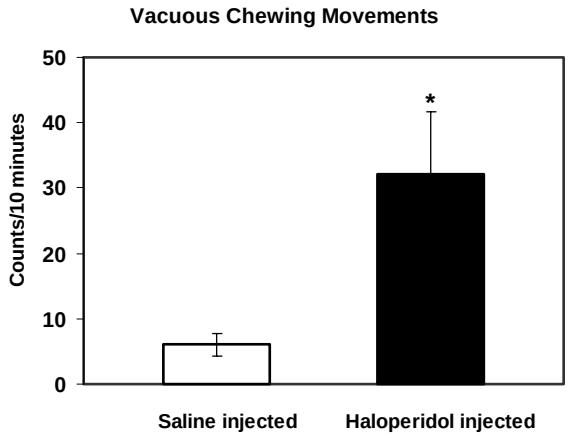

Fig. 2: The intensity of haloperidol-induced VCMs. Values are means ± S.D. (n=12). 48-h after 5 weeks administration of saline or haloperidol. Significant differences *p<0.01 by t-test.

Fig. 2 shows the haloperidol-induced VCMs after a wash out period of 2 days. Data analyzed by Student's t-test showed haloperidol-induced VCMs persisted after 2 days of drug withdrawal.

Fig. 3 shows the effect of m-CPP on motor coordination and the activity in an open field (squares crossed) in repeated saline and repeated haloperidol injected animals. Data on motor coordination analyzed by two-way ANOVA (df=1,20) showed significant effects of haloperidol (F=280.20 p<0.01), m-CPP (F=292.54 p<0.01) and a significant interaction between haloperidol*m-CPP (F=34.21 p<0.01). Post-hoc analysis showed that administration of m-CPP impaired motor coordination in saline as well as haloperidol treated animals. Motor coordination was also impaired in repeated haloperidol plus saline treated animals.

Data on the activity in an open field (squares crossed) analyzed by two-way ANOVA (df=1,20) showed significant effects of haloperidol (F=80.20 p<0.01), m-CPP (F=292.61 p<0.01) and a significant interaction between haloperidol*m-CPP (F=34.21 p<0.01). Post-hoc analysis showed that administration of m-CPP decreased open field activity of repeated saline and repeated haloperidol treated animals. The activity was also decreased in repeated haloperidol plus saline than repeated saline plus saline injected animals. These were also smaller in repeated haloperidol plus m-CPP than repeated saline plus m-CPP treated animals.

Fig. 4 shows the effect of m-CPP on time spent in light box (light-dark activity) in repeated saline and repeated haloperidol injected animals. Two-way ANOVA (df=1,20) showed significant effect of haloperidol (F=86.08 p<0.01), m-CPP (F=101.55 p<0.01) and a significant interaction between haloperidol and m-CPP (F=18.51 p<0.01). Post-hoc analysis showed that administration of m-CPP decreased time spent in light compartment of saline as well as haloperidol treated animals. Haloperidol plus saline and haloperidol plus m-CPP treated animals spent lesser time in light compartment than saline plus saline and saline plus m-CPP treated animals respectively.

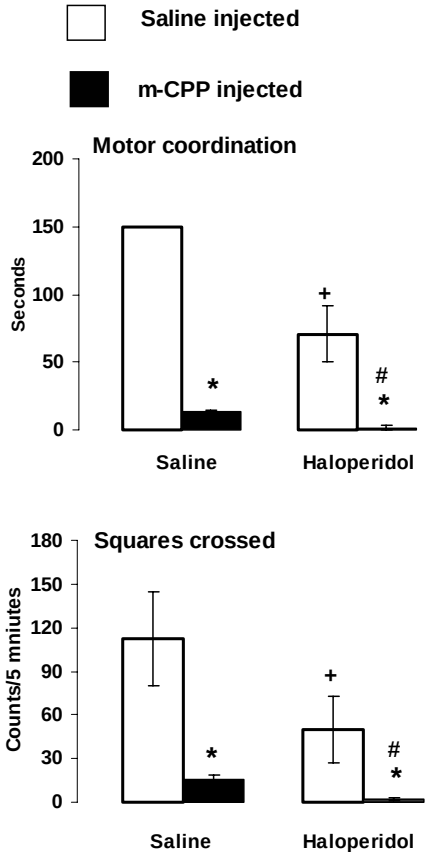

Fig. 3: Effects of m-CPP on motor coordination and the activity in an open field (squares crossed) in repeated saline or repeated haloperidol treated animals. Values are means ± S.D. (n=6). Significant differences by Newman-Keuls test: *p<0.01 from respective saline injected animals, #p<0.01 from saline plus m-CPP injected animals, +p<0.01 from saline plus saline injected animals following two-way ANOVA.

Fig. 5 shows the effect of m-CPP on 2-h and 4-h food intake (post-injection) in repeated saline and haloperidol treated animals. Data on 2-h food intake analyzed by two-way ANOVA (df=1,20) showed significant effect of haloperidol (F=5.0 p<0.01), m-CPP (F=22.33 p<0.01) and a significant interaction between haloperidol and m-CPP (F=5.5 p<0.01). Post-hoc analysis showed that administration of m-CPP decreased food intake in repeated saline and repeated haloperidol treated animals. 2-h food intakes were greater in repeated haloperidol plus saline than repeated saline plus saline treated animals.

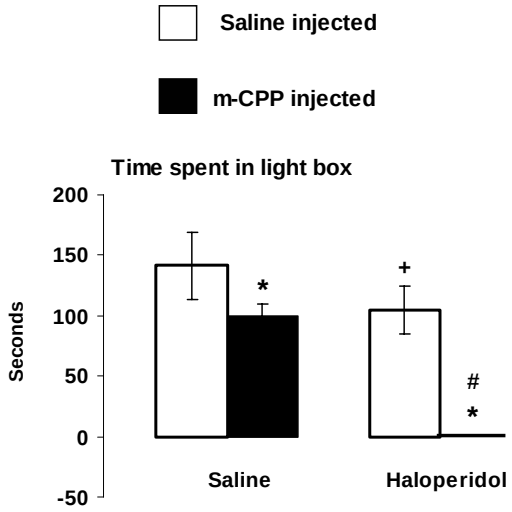

Fig. 4: Effects of m-CPP on time spent in light compartment of a light-dark activity box in repeated saline or repeated haloperidol treated animals. Values are means ± S.D. (n=6). Significant differences by Newman-Keuls test: *p<0.01 from respective saline injected animals, #p<0.01from saline plus m-CPP injected animals, +p<0.01 from saline plus saline injected animals following two-way ANOVA.

Data on 4-h food intake (Post-injection) analyzed by two-way ANOVA (df=1,20) showed significant effect of haloperidol (F=12.20 p<0.01) and m-CPP (F=245.48 p<0.01). Interaction between haloperidol and m-CPP (F=0.13 p>0.05) was not significant. Post-hoc analysis showed that administration of m-CPP decreased food intake of saline and haloperidol treated animals. 4-h food intakes were comparable in saline plus saline and haloperidol plus saline injected animals, but smaller in haloperidol plus m-CPP than saline plus m-CPP treated animals. The results suggest an increase in the sensitivity of hypophagic 5-HT-2C receptors following administration of haloperidol.

DISCUSSION

Our data confirm reports that long term administration of haloperidol-induced VCMs (Naidu *et al*., 2002). It was observed that long term administration of haloperidol for two weeks elicited VCMs which were potentiated from 3-5 weeks (fig. 1). Withdrawal from repeated administration of haloperidol attenuated the intensity of VCMs (fig. 2). The aim of the present study was to determine the responsiveness of 5-HT-2C receptors in rats exhibiting TD. Previously, it has been reported that m-CPP (a 5-HT-2C receptor agonist) produced hypolocomotion, anxiogenesis and hypophagia (Freo *et al*., 1992; Fone *et al*., 1998). In the present study, these behavioral effects of m-CPP were greater in haloperidol treated than saline treated animals (figs. 4 and 5).

A typical effect of administering dopamine receptor antagonist (such as haloperidol) is a suppression of spontaneous exploratory and locomotor behavior and elicitation of state known as catalepsy (Wannibuchi and

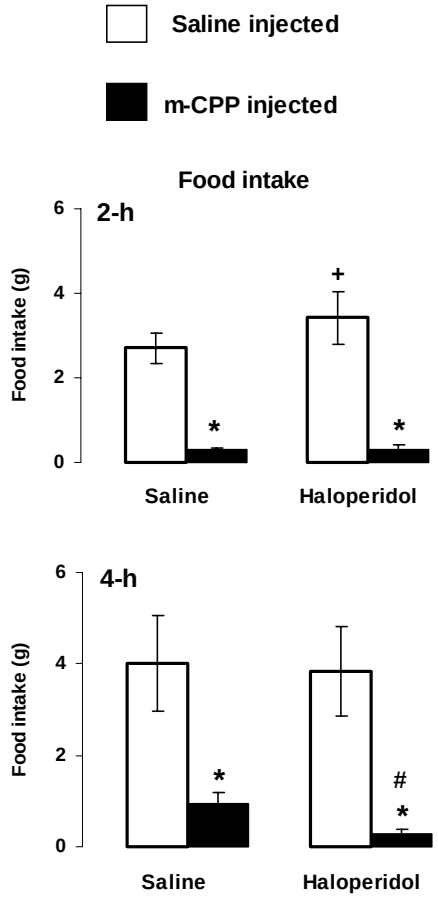

Fig. 5: Effects of m-CPP on 2-h and 4-h food intake (post-injection) in repeated saline or repeated haloperidol treated animals. Values are means ± S.D. (n=6). Significant differences by Newman-Keuls test: *p<0.01 from respective saline injected animals respectively, #p<0.01 from saline plus m-CPP injected animals, +p<0.01 from saline plus saline injected animals following two-way ANOVA.

Usuda, 1996; Haleem *et al*, 2002) and repeated administration develops TD (Ellison and See, 1989; Taminga *et al*., 1990). Enhanced oral activity has been reported after sub-chronic (3-4 weeks) exposure to haloperidol (early onset VCMs) (Egan *et al*., 1996) or only after chronic (6-12 months) haloperidol administration (tardive VCMs) (Widdington, 1990; Egan *et al*., 1996). Several hypotheses have been formulated to explain the development of VCMs, including the existence of dopaminergic receptor supersensitivity (Klawans and Rubovits, 1972; 1977) a dopamine D1/D2 receptor imbalance (Casey, 1995; Waddington, 1997) and a GABA deficiency (Gale, 1980; Fibger and Llolyd,

1984). The present study shows that an increase in the effectiveness of 5-HT-2C receptors may also have a role in haloperidol-induced VCMs in rats.

It is often suggested that dopamine receptor supersensitivity arising from upregulation of dopamine D2 receptor following neuroleptic therapy accounts for the development of TD (Kalwans, 1973, Chiu *et al*., 1981). Previous studies have shown that administration of haloperidol increased 5-HT (Johnson *et al*., 1992) and 5-HIAA concentration in many brain regions including the striatum (Haleem *et al*., 2002). The increase also occurred following withdrawal from repeated administration (Haleem and Khan, 2003). Pre-clinical and clinical studies suggest that an increase in serotonin transmission may be important contributing factor in the onset of dyskinesia (Meltzer and Nash, 1991; Melamed *et al*., 1996). The present study shows an increase in the effectiveness of 5-HT-2C receptor dependent responses in rats exhibiting VCMs.

The serotonergic system is known to play a role in the modulation of the activity of dopaminergic neurons. The nature of the modulation seems to be inhibitory. The inhibitory effect of serotonin towards dopamine is due to the activation of 5-HT-2C receptor which inhibits dopaminergic transmission (Pessia *et al*., 1994) and release (Millan *et al*., 1998) in the frontal cortex.

The arylpiperazie compound m-CPP is currently the agonist of choice to examine 5-HT-2C receptor function (Murphy *et al*., 1991; Kennett, 1993; Baxter *et al*., 1995). The drug increased release of 5-HT (Hikiji *et al*., 2004) and decreased dopamine in different brain regions (Prisco *et al*., 1994) via the stimulation of post-synaptic 5-HT-2C receptor (Gibson *et al*., 1996). Studies have shown that acute administration of m-CPP induced hypolocomtion, anxiogensis and hypophagia (Samanin *et al*., 1979; Kennett *et al*., 1987; Kennett and Curzon, 1988; Kennett *et al*., 1997; Sills *et al*., 1985; Freo *et al*., 1993; Kennett *et al*., 1995; Fone *et al*., 1996**),** which were consistent with our present results (figs. 3-5). In addition, important finding of the present study is that m-CPP-induced hypophagia as well as anxiogenic-like behavior were greater in haloperidol than saline treated animals. On the other hand hypolocomotive effects of m-CPP were not different in haloperidol and saline treated animals. On the other hand, hypolocomotive effects of m-CPP if also greater repeated haloperidol injected animals cannot demonstrated in the present experimental paradigm because repeated haloperidol administration decreased motor activity and haloperidol plus m-CPP injected animals exhibited akinesia.

Acute administration of m-CPP reduces locomotor activity in rats (Kennett and Curzon, 1988; Kennett *et al*., 1997). It is thought that ability of m-CPP to suppress spontaneous locomotor behavior in rats involves the 5-HT-2C receptor (Kennett and Curzon, 1988). A selective 5-HT-2C receptor antagonist 6-Chloro-5-methyl-l-[2(2-methylpyridyl-3-oxy)-pyrid-5-yl-carbomyl] indoline (SB-242084) has also been shown to suppress potently m-CPP-induced hypolocomotion (Kennett *et al*., 1997). Furthermore, lesions of 5-HT neurons with 5,7 dihydroxy tryptamine potentiated the hypolocomotive effect of m-CPP, possibly by development of post-synaptic supersensitivity (Lucki *et al*., 1989). Previously we have shown that long term administration of haloperidol induces a supersensitivity at somatodendritic 5-HT-1A receptors (Haleem and Khan, 2003) that is expected to decrease the availability of 5-HT at postsynaptic 5-HT-2C receptors (Haleem *et al*., 2006). It is suggested that a decrease in the availability of 5-HT at postsynaptic site may be involved in the supersensitive 5-HT-2C receptor dependent responses observed in the present study (figs. 3-5).

In conclusion, the present study shows that some of the responses of m-CPP such as anxiogenic like effects and hypophagic effects were clearly greater in haloperidol than saline injected animals. Other effects of m-CPP such as impaired motor coordination and decreased exploration activity if also greater in haloperidol than saline injected animals was not detectable because of the floor effect. Motor coordination was impaired and exploratory activity decreased in repeated haloperidol injected animals. An increase in the effectiveness of 5-HT-2C receptors would be expected to enhance inhibitory serotonergic influence on the activity of dopaminergic neurons. It is therefore suggested that drug decreasing serotonergic influence on the activity of dopaminergic neurons may prove useful for the treatment of TD.

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