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NEUROCHEMICAL EFFECTS OF 8-HYDROXY-2-di-n-PROPYLAMINO TETRALIN IN RATS TREATED WITH HALOPERIDOL

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ABSTRACT

In view of a possible role of presynaptic serotonin (5-hydroxytryptamine, 5-HT) receptors in the precipitation of extrapyramidal side effects (EPS), the present study was designed to investigate the neurochemical effects of a selective 5-HT1A ligand, 8-hydroxy-2- (di-n-propylamino) tetralin (8-OH-DPAT) in rats following single (5mg/kg) and repeated (two-times a day for 9 days at dosage of 5mg/kg) haloperidol administration. Haloperidol plus 8-OH-DPAT injected animals exhibited a decrease in dopamine (DA) and an increase in DA metabolite homovanillic acid (HVA) levels in the striatum and rest of the brain. The two groups of animals exhibited comparable levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the striatum and rest of the brain. Animals injected with haloperidol and killed 24hrs after the last injection of haloperidol exhibited higher DA and HVA levels in the striatum but not in the rest of the brain. Conversely, dihydroxyphenylacetic acid (DOPAC), the other metabolite of DA, decreased in the rest of the brain. 5-HIAA concentrations increased in the striatum but not in the rest of the brain. Administration of 8-OH-DPAT significantly decreased 5-HT and 5-HIAA levels in the rest of brain and did not alter 5-HIAA in the striatum of repeated saline injected rats. Conversely, same dose of 8-OH-DPAT injected to repeatedly haloperidol injected animals did not decrease 5-HT and 5-HIAA concentrations in the rest of the brain but decreased 5-HIAA levels in the striatum. No effect of 8-OH-DPAT injections occurred on striatal or rest of the brain DA metabolism in repeatedly saline injected animals except that DOPAC decreased in the striatum of both groups. The results are discussed in the context of a role of somatodendritic 5-HT1A receptors in the regulation of DA metabolism following single and repeated administration of haloperidol. It is suggested that an increase in the responsiveness of these receptors may be involved in the precipitation of EPS observed in patients on haloperidol therapy.

INTRODUCTION

Psychotic symptoms in different neuropsychiatric disorders are treated by neuroleptic drugs (Reuss and Unsicker, 2001; Robert, Force and Kung, 2002). These drugs cause profound sedation and abnormal posturing as if the animal had been seized (Pearson, 2000). Evidence that neuroleptic drugs have common ability to block the dopamine (DA) receptor is based either on their ability of inhibiting DA stimulated adenylate cyclase activity (Miller, 1974) or in displacing the high affinity binding of ligand to the DA receptor (Seeman, 1975). A typical neuroleptic, haloperidol is a DA receptor antagonist for the treatment of positive symptoms of schizophrenia (Perry, 1995). This drug has a high affinity (80%) for blockade of DA D-2 receptor and an appreciable affinity for blockade of DA D-1 receptor (Hyttel, 1985; Hurley, 1996; Manglapus,

1999). It has been reported that haloperidol increases dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) content of the caudate-putamen, nucleus accumbens and medial prefrontal cortex (Andersen and Kilptrick, 1996) due to an increase in DA turnover and firing rate (Hand, 1987).

Haloperidol therapy is associated with a high incidence of acute extrapyramidal symptoms (EPS) including Parkinsonism, acute akathisia, acute dystonia (Barnes and Philips, 1998) and tardive dyskinesia (Kelly etal, 1990). Previous studies revealed that blockade of DA transmission accounts for the initial Parkinsonism and that sustained blockade of transmission results in DA receptor supersensitivity. Therefore, tardive dyskinesia may represent the DA overactivity in the striatum leading to the increased output of abnormal behavior (Iversen, 1981; Jenner and Marsden, 1988; Jann, 1990). Experimental evidence suggests that central dopaminergic transmission is under serotonergic modulation. For instance, neuroleptic-induced catalepsy in rodent, a behavior mainly due to the blockade of DA receptor in the striatum, can be affected by serotonergic modulation. In this regard, serotonergic mechanisms are of particular importance both in view of their modulation of dopaminergic transmission and their key role in the control of mood, cognition and motor behavior (Millan, 2000). Recent data suggest that atypical neuroleptics show fewer extrapyramidal symptoms due to the greater modulation of serotonergic system (Ninan and Kulkarni, 1999).

It is well documented that serotonin (5-HT) mediates a wide range of physiological function by interacting with multiple receptors and these receptors have been implicated as playing important roles in certain pathological and psychophysiological conditions. 5-HT1A receptors are implicated in the etiology of schizophrenia (Newman-Tancredi etal, 1998). These receptors are present postsynaptically as well as presynaptically on the cell body dendrites in the raphe nuclei (Sprouse and Aghajanian, 1987). Administration of 8-OH-DPAT decrease brain 5-HT metabolism due to the stimulation of presynaptic 5-HT1A receptors (Kreiss and Lucki, 1992). It is suggested that 8-OH-DPAT partly attenuated haloperidol-induced dyskinesia due to its weak DA agonist properties (Liebaman, 1989). Later studies showed that systemic administration of 8-OH-DPAT increased extracellular DA levels in the ventral tagmental area and nucleus accumbens (Boulenguez, 1996). This effect of 8-OH-DPAT is produced at much higher doses of the drug (Piercey, Smith and Lum, 1988). Evidence suggests that 5-HT1A agonist increase cortical DA release which may underlie efficacy against negative symptoms and reduced extrapyramidal symptoms. Therefore, atypical neuroleptics (like clozapine) with substantial 5-HT1A receptor agonist property exhibits fewer extrapyramidal symptoms (Assie, 1997).

To understand a role of 5-HT1A receptors in the precipitation of EPS, the present study was designed to investigate whether single or repeated administration of haloperidol could modulate the sensitivity of feedback control over 5-HT synthesis. This effect has been tested by comparing the effects of 8-OH-DPAT at a dose of 0.5mg/kg on 5-HT metabolism and also on DA metabolism in rats following single or repeated (two-times a day for 9 days) administration of haloperidol at a dose of 5mg/kg.

MATERIALS AND METHOD

***Experimental Animals**:*

Locally bred Albino-Wistar rats purchased from Hussain Ebrahim Jamal (HEJ) Research Institute of Chemistry, University of Karachi, weighing about 200g were used. The rats were caged individually with sawdust-covered floor. The animals had free access to the standard rodent diet and tap water. All animals were handled 2 days before starting the experiment.

Drugs and their Administration:

Haloperidol (Serenace) available in 5mg/ml/kg ampoules was injected intraperitoneally (i.p.). 8-OH-DPAT purchased from RBI Chemicals dissolved in saline (0.9% NaCl) at a dose of 0.5 mg/ml/kg used in the treatment and the route of administration was also i.p.

Experimental Protocol:

A. Neurochemical effects of 8-OH-DPAT in rats following single injection of haloperidol:

The animals were injected with saline (0.9% NaCl) or haloperidol at a dose of 5mg/kg in a balanced design. After 30 minutes all animals were injected with 8-OH-DPAT at a dose of 0.5 mg/kg of 8-OH-DPAT injections and decapitated 1 hr after 8-OH-DPAT injections. Brains removed quickly from the skull were dissected into striatum and rest of the brain. The samples were stored at -70 ^{0}C for neurochemical analysis by high performance liquid chromatography with electrochemical detection (Haleem and Parveen, 1994; Batool et al, 2001; HPLC-EC).

B. Neurochemical effects of 8-OH-DPAT in rats following repeated injection of haloperidol:

Animals were assigned to test and control groups. Animals of test group were injected with haloperidol at a dose of 5mg/kg two-times daily for 9 days between 8:00-8:30 am. (1st injection) and 3:00-3:30 pm. (2nd injection). Control animals were injected with saline 1 ml/kg two-times a day at times when test animals were injected with haloperidol. On the 10th day, 24hrs after the last injection of saline or haloperidol, a group of repeated saline and another group of repeated haloperidol injected animals were injected with 8-OH-DPAT at a dosage of 0.5 mg/kg. Control animals of both the groups were injected with saline. The animals were decapitated 1 hr after the saline or 8-OH-DPAT injections. Brains removed immediately were dissected into striatum and rest of the brain. Samples were stored at -70 ^{0}C for neurochemical analysis by HPLC-EC as described elsewhere (Haleem and Parveen, 1994; Batool *et al*, 2001).

Neurochemical assays of monoamines and their metabolites:

Monoamines and their metabolites were extracted as described elsewhere (Haleem et al, 1998). A 5µm Shim Pak ODS; 4.6 mm i.d ×15 cm separation column was used. HPLC separation system was methanol (14%), octyl sodium sulphate (OSS, 0.23%) and EDTA (0.05%) in 0.1M phosphate buffer of pH 2.9. Electrochemical detection of brain indoleamines was done at an operating potential of 0.8 V (glassy carbon electrode Vs Ag/Agcl reference electrode).

Statistical Analysis:

The results are presented as means $\pm$ S.D. Data analyzed by Two-way analysis of variance (ANOVA). Posthoc comparisons were done by Newman-Keuls test. Values of $P<0.05$ and $P<0.01$ were considered statistically significant.

RESULTS

Fig. 1 shows the levels of 5-HIAA (1A) and 5-HT (1B) in the rest of the brain and striatal 5-HIAA (1C) of saline + 8-OH-DPAT and haloperidol + 8-OH-DPAT injected rats. Statistical analysis by two-tailed t-test revealed that values of 5-HIAA in the striatum of the two groups were comparable. Mean values of 5-HT and 5-HIAA in the rest of the brain were smaller in haloperidol + 8-OH-DPAT than saline + 8-OH-DPAT injected rats. Differences by t-test were not significant.

Fig. 2 shows the effects of 8-OH-DPAT on 5-HIAA (2A) and 5-HT (2B) levels in the rest of the brain and striatal 5-HIAA (2C) of repeatedly saline and repeatedly haloperidol injected rats. Two-way ANOVA (df 1, 8) showed significant effects of 8-OH-DPAT on 5-HIAA in the striatum

(F=8.355, P<0.05) and in the rest of the brain (F=12.13, P<0.05). Effects of 8-OH-DPAT for 5-HT levels were not significant in the rest of the brain (F=4.90, P<0.05). Effects of haloperidol on 5-HIAA levels were significant in the striatum (F=138.57, P<0.01) but not in the rest of the brain (F=0.03, P>0.05). Interaction between haloperidol and 8-OH-DPAT was not significant for 5-HIAA (F=2.95, P>0.05) in the striatum 5HT (F=1.38, P>0.05) and 5-HIAA (F=0.43, P>0.05) in the rest of the brain.

Posthoc analysis by Newman-Keuls test showed that 8-OH-DPAT significantly decreased 5-HIAA levels in both, the striatum and rest of the brain of repeatedly saline but not in repeatedly haloperidol-injected rats. The levels of 5-HIAA in the striatum were higher in animals repeatedly injected with haloperidol and killed after saline or 8-OH-DPAT injection than in animals injected with saline and killed after saline or 8-OH-DPAT injection. These differences of 5-HIAA and 5-HT in the rest of the brain were not significant.

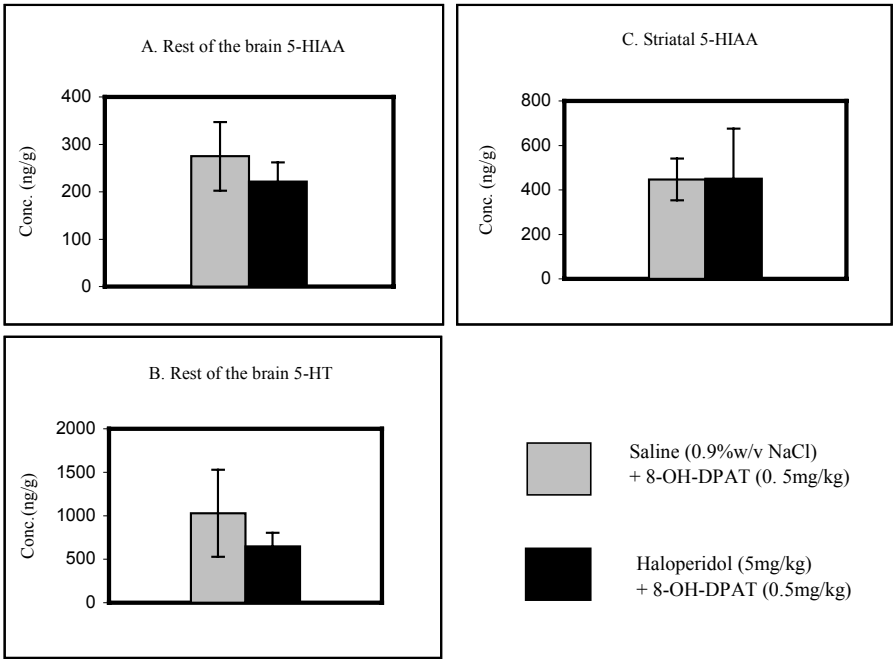

Fig. 1: Effects of 8-OH-DPAT (0.5mg/kg) on 5-HIAA (1A) and 5-HT (1B) levels in the rest of the brain and striatal 5-HIAA (1C) in saline and haloperidol (5mg/kg) injected rats. Values are mean ± S.D. (n=3). Differences by two-tailed t-test were not significant.

Fig. 3 shows catecholeamine metabolism in the striatum and in the rest of the brain of saline + 8-OH-DPAT and haloperidol + 8-OH-DPAT injected rats. Data analyzed by t-test revealed a significant increase in the concentration of striatal and rest of the brain HVA in haloperidol + 8-OH-DPAT than saline + 8-OH-DPAT injected rats. DA levels were smaller in the striatum but not in the rest of the brain of haloperidol + 8-OH-DPAT than saline + 8-OH-DPAT injected rats. Differences of DOPAC levels in the striatum or rest of the brain were not significant.

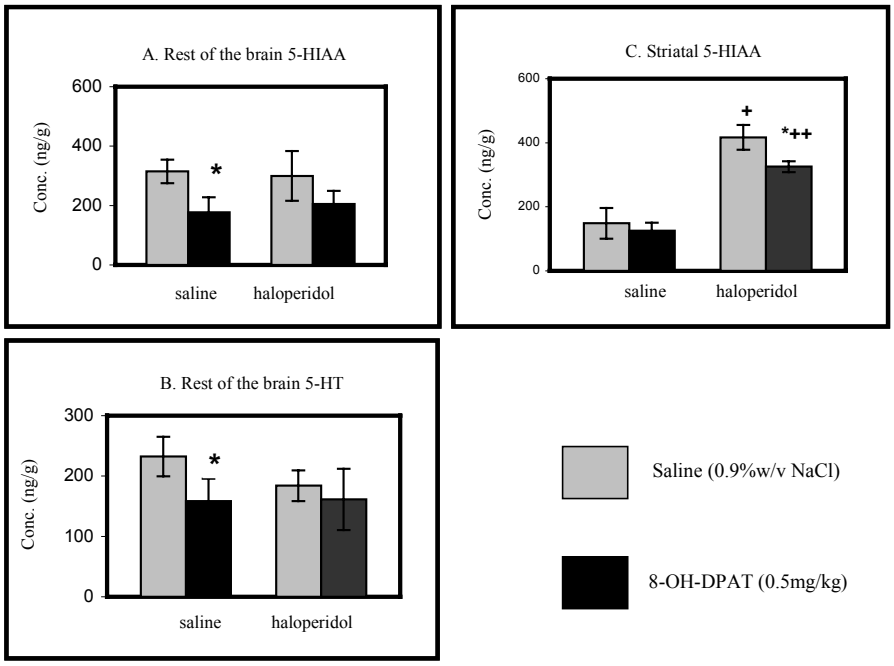

Fig. 2: Effects of 8-OH-DPAT (0.5mg/kg) on 5-HIAA (2A) and 5-HT (2B) levels in the rest of the brain and striatal 5-HIAA (2C) in repeated saline and repeated haloperidol (5mg/kg for 9 days) injected rats. Values are mean $\pm$ S.D. (n=3). Significant differences by Newman-Keuls test. *P<0.05 in 8-OH-DPAT injected rats from respective saline injected rats, +P<0.05, ++P<0.01 in repeated haloperidol injected rats from respective repeated saline injected rats following Two-Way ANOVA.

Fig. 4 shows catecholamine metabolism in the striatum and in the rest of the brain of repeated saline + 8-OH-DPAT and repeated haloperidol + 8-OH-DPAT injected rats. Two-way ANOVA (df 1, 8) revealed significant effects of 8-OH-DPAT (0.5 mg/kg) on striatal ($F=26.889$, $P<0.01$) and rest of the brain ($F=7.974$, $P<0.05$) DOPAC and non-significant effect on striatal ($F=0.19$, $P>0.05$) and rest of the brain ($F=4.484$, $P>0.05$) DA. Effects of 8-OH-DPAT were not significant for striatal ($F= 1.714$, $P>0.05$) and rest of the brain ($F=1.196$, $P>0.05$) HVA. Effects of haloperidol were significant for striatal DA ($F=60.75$, $P<0.01$), striatal HVA ($F=7.705$, $P<0.05$) and rest of the brain DOPAC ($F=20.97$, $P<0.01$). Effects were non-significant for striatal DOPAC ($F=1.737$, $P>0.05$), rest of the brain DA ($F=2.63$, $P>0.05$) and rest of the brain HVA ($F=4.94$, $P>0.05$). Interaction between 8-OH-DPAT and haloperidol were not significant for striatal ($F=0.007$, $P>0.05$) and rest of the brain ($F=2.78$, $P>0.05$) DA, striatal ($F=0.025$, $P>0.05$) and rest of the brain ($F=0.156$, $P>0.05$) DOPAC and striatal ($F=0.789$, $P>0.05$) and rest of the brain ($F=2.52$, $P>0.05$) HVA.

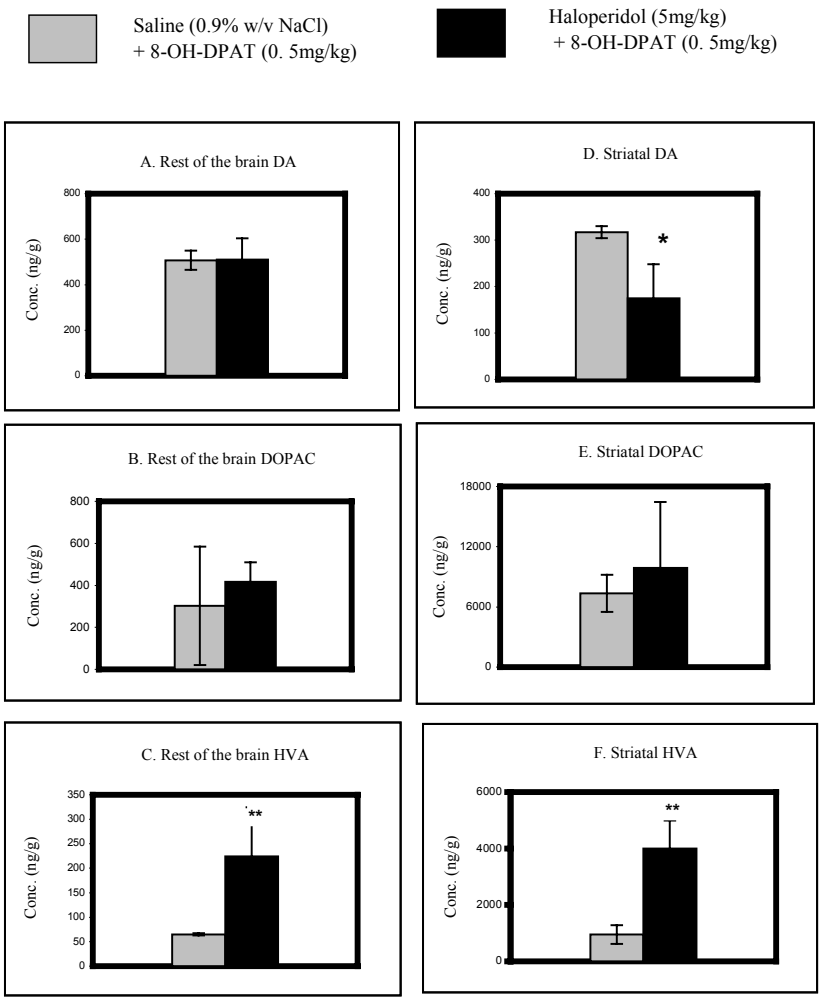

Fig.3: Effects of 8-OH-DPAT (0.5mg/kg) on catecholeamine metabolism in the striatum and in the rest of the brain of saline and haloperidol (5mg/kg) injected rats. Values are $\pm$ S.D. (n=3). Significant differences by two-tailed t-test. *P<0.01, **P<0.01 from respective saline + 8-OH-DPAT injected rats.

Posthoc analysis by Newman-Keuls test showed that 8-OH-DPAT significantly decreased levels of striatal DOPAC in repeatedly saline and repeatedly haloperidol injected rats. 8-OH-DPAT did not alter levels of striatal DA, striatal HVA, rest of the brain DA, rest of the brain DOPAC and rest of the brain HVA in repeatedly saline or in repeatedly haloperidol injected rats. Animals repeatedly injected with haloperidol and killed after saline or 8-OH-DPAT injection exhibited levels of striatal DA and striatal HVA higher and levels of rest of the brain DOPAC lower than respective repeatedly saline injected rats.

DISCUSSION

Neuroleptic medication reduces the psychotic symptoms of schizophrenia through DA receptor blockade in the limbic and cortical areas (Meltzer, 1993; Xiberas *et al,* 2001). It is

therefore suggested that frontal cortex DA neurons may be a common site for antipsychotic action while blockade of DA receptors in the striatum may be associated with the development of EPS (Borison and Diamond, 1983; Mefford *et al*, 1988). It is generally assumed that 5-HT agonists are true partial agonists for D2 receptors (Pedigo *et al.,* 1981). Thus, activation of 5-HT1A receptors after systemic administration of 8-OH-DPAT increases DA cell firing in the ventral tegmental area, nucleus accumbens and substantia nigra (Kelland *et al.,* 1990; Arborelieus *et al.,* 1993; Prisco *et al,* 1994; Boulenguez *et al.,* 1996). It is well documented that DOPAC and HVA are

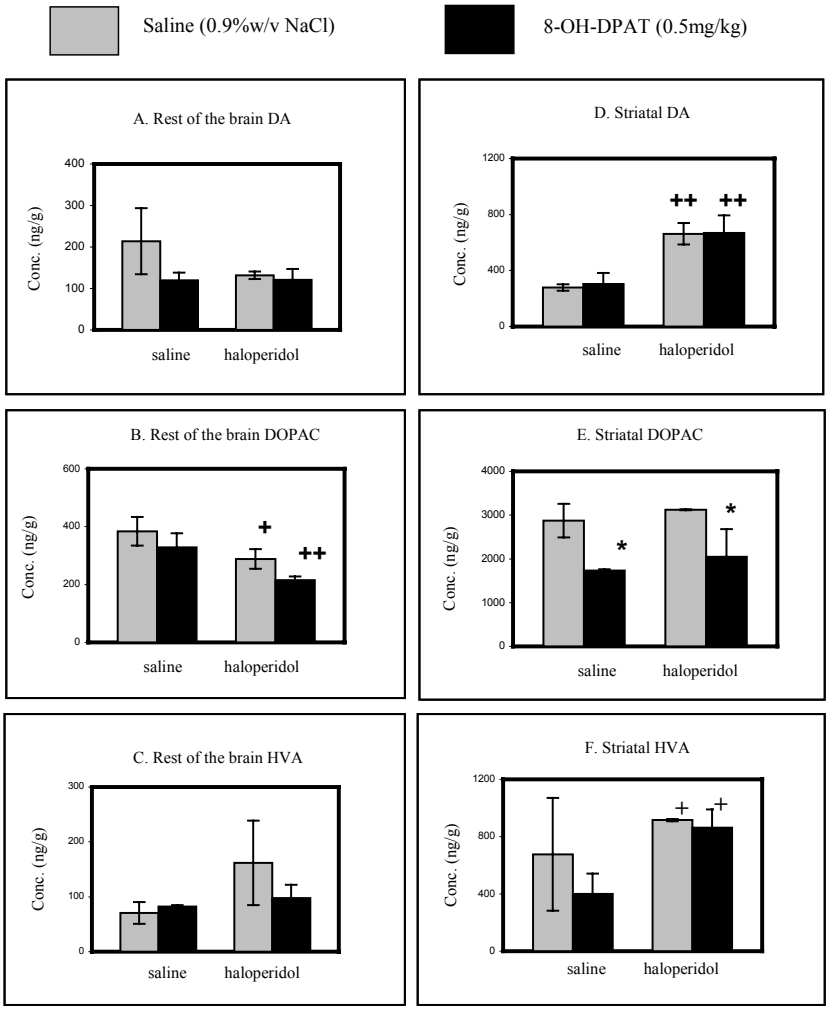

Fig. 4: Effects of 8-OH-DPAT (0.5mg/kg) on catecholeamine metabolism in the striatum and in the rest of the brain of repeatedly saline and repeatedly haloperidol (5mg/kg for 9 days) injected rats. Values are $\pm$ S.D. (n=3). Significant differences by Newman-Keuls test. *P<0.01 in 8-OH-DPAT injected rats from respective saline injected rats, +P<0.05, ++P<0.01 in repeated haloperidol injected rats from respective repeated saline injected rats following Two-Way ANOVA.

quantitively the most significant metabolites of DA. Of these, DOPAC is often considered to be an index of intraneuronal DA catabolism (Westerink, 1985).

In the present study, effects of single haloperidol administration on striatal and rest of the brain monoamine concentrations were not monitored. Similar studies from our laboratory reported that single haloperidol injection at a dose of 5mg/kg increased DA turnover in the rest of the brain and striatum (Haleem *et al,* 2002). However, we find that 5-days of repeated (2times a day) injections of high (5mg/kg) dose of haloperidol decreases DA and DOPAC concentration in the rest of the brain suggesting a decrease in the synthesis in atleast some brain regions other than striatum. It is also noted that both DA and HVA levels increased in the striatum suggesting an increase in DA release in atleast this brain region. The present results show a decrease in DA concentration in the striatum of single haloperidol + 8-OH-DPAT than saline + 8-OH-DPAT injected animals. This could occur because of increased release and metabolism of DA to HVA following haloperidol administration. Conversely, an increase in DA levels were found in the striatum but not in the rest of the brain of repeated saline + 8-OH-DPAT and in repeated haloperidol + 8-OH-DPAT injected rats.

Many studies have shown that acute administration of haloperidol produces a dose dependent increase in DOPAC (Karoum and Egan, 1992) and HVA (Teismann and Ferger, 2000) levels which are of greater magnitude and longer duration in the striatum (Fregnan and Porta, 1981). The results of present study show that HVA but not DOPAC levels in the striatum and in the rest of the brain were higher in single haloperidol + 8-OH-DPAT than saline + 8-OH-DPAT injected animals. Administration of 8-OH-DPAT did not modify basal DOPAC outflow in the striatum as well as the stimulatory effects haloperidol (Lucas etal, 1997). On the other hand, a larger decrease in DOPAC levels in the striatum but not in the rest of the brain of repeated saline + 8-OH-DPAT and repeated haloperidol + 8-OH-DPAT injected rats could occur because of repeated administration of haloperidol. The present study is therefore consistent that 8-OH-DPAT at a dose of 0.5mg/kg was not sufficient to alter striatal and rest of the brain DA and HVA levels in repeated saline and single or repeated haloperidol injected rats.

Serotonergic system may play a role in modulating the activity of dopaminergic neurons (Johnson *et al,* 1992). Several types of receptor for 5-HT exist in the brain (Pedigo *et al,* 1981). 5-HT1A receptors are located postsynaptically as well as presynaptically on cell bodies in the raphe, where its activation inhibits the firing rate of serotonerigic neurons. 5-HT turnover and release is decreased in many brain areas where these serotonergic neurons project (Chaput, deMontigny and Blier, 1986; Sprouse and Aghajanian *et al,* 1987; Hammon *et al,* 1988; Huston *et al*, 1989; Sharp *et al,* 1989; Haleem *et al,* 1990). In the present study, administrations of 8-OH-DPAT decrease 5-HT and 5-HIAA in the rest of the brain of saline injected animals. The decreases were not significant in the striatum. Previous studies show that administration of 8-OH-DPAT decreases 5-HT turnover in this brain region (Haleem, 1999) but the decreases are not always significant (Haleem *et al,* 1990). The single administration of haloperidol at a dose of 5mg/kg increases 5-HIAA in the striatum has been also shown previously (Haleem *et al,* 2002).

The present study shows that repeated administration of haloperidol also increase 5-HIAA concentrations in the striatum. The increases were not observed in the rest of the brain. Similarly, Burki *et al* (1975) and Westerink *et al* (2001) were reported that haloperidol was more effective in stimulating the release and turnover of DA in the striatum. Antoniou *et al* (2000) showed that chronic haloperidol administration did not affect the serotonergic activity in the hippocampus. This could be because striatum is a projection area of dorsal raphe neurons (DRN) and enrich of dopaminergic neurons (He *et al,* 2001). DA induced membrane depolarization in the DRN is

mediated by the activation of D2 like DA receptor (Haj-Dahmane, 2001). This effect is antagonized by haloperidol (Millan, 1998). It is also reported that repeated haloperidol injections increased the number of dopaminergic D2 receptors (Ishikane, 1998) and affinity of dopaminergic receptors towards agonist binding in the brain (Viyoch *et al,* 2001). Thus, increases of 5-HIAA in the striatum are explicable in terms of an increase in dopamine D2 receptor density in the dorsal raphe (DR).

It is interesting to note that administration of 8-OH-DPAT significantly decreased 5-HIAA levels in the striatum of repeated haloperidol injected but not in the repeated saline injected rats. On the other hand, 8-OH-DPAT- induced decreases of 5-HT turnover observed in the rest of the brain of repeated saline injected animals were not observed in the rest of the brain of repeated haloperidol injected rats. These results are explicable in terms of supersensitivity of presynaptic 5-HT1A receptors population that controls 5-HT synthesis and release in the striatum. Conversely, the effectiveness of somatodendritic 5-HT1A receptors that provide a feedback on 5-HT release in other brain regions is decreased.

CONCLUSION

In conclusion, the present study shows that the effectiveness of the somatodendritic 5-HT1A receptors that control the release of 5-HT in the striatum is increased following repeated administration of haloperidol. On the other hand, the effectiveness of somatodendtritic 5-HT 1A receptors controlling 5-HT release in other regions is decreased in rats repeatedly injected with haloperidol. A role of 5-HT in the control of motor activity has been shown in many studies. The present results suggest that 5-HT1A receptor dependent changes of 5-HT release particularly in the striatum and upregulation of D2 receptor density are both involved in the greater incidence of EPS following long term administration of haloperidol.

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