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BEHAVIORAL EFFECTS OF 8-OH-DPAT IN SINGLE AND REPEATED HALOPERIDOL INJECTED RATS

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ABSTRACT

Haloperidol is an antipsychotic drug and shown to be antagonist at D_2 receptors and found to cause severe impairment of locomotor performance. The serotonin (5HT1A) receptor agonist 8-OH-DPAT has been reported to attenuate extrapyramidal side effects of haloperidol. The present study was designed to examine the modulatory effect of serotonergic activities on haloperidol induced up-regulation of dopamine D2 receptors. In the acute phase of study, 8-OH-DPAT (0.5mg/kg/ml) elicited behavioral syndrome was monitored in rats preinjected with haloperidol(5mg/kg/ml). Results of single haloperidol administration revealed that 8-OH-DPAT induced forepaw treading ($p<0.05$) and hyperlocomotion($p<0.01$) were smaller in haloperidol than saline preinjected rats. In repeated phase of study, 8-OH-DPAT (0.5mg/kg/ml) induced behavioral syndrome was monitored in rats injected with haloperidol for 10 days (x2). The result of repeated haloperidol administration showed that 8-OH-DPAT elicited flat body posture ($p<0.01$) was greater in repeated haloperidol injected rats than repeatedly saline injected rats.

Relationship between 5HT1A receptors and D_2 receptors has been discussed. It is suggested that combining neuroleptics with 5HT1A ligands is thought to improve the preclinical profile of neuroleptics and may be of interest in the development of new compounds that have greater therapeutic potential and/or better tolerated.

INTRODUCTION

The discovery of drugs that are effective in the treatment of psychotic illnesses, have been perhaps the most important psychopharmacological event of the second half of the 20th century. Antipsychotic, mood-stabilizing and antidepressant agents used to treat the most severe mental illnesses have had remarkable impact in psychiatric practice and theory.

Although antipsychotic drugs have been widely prescribed for the treatment of schizophrenia since the 1950's (Baldessarini, R.J., 1985), their beneficial effects are accompanied by involuntary movement disorders. Janssen in 1974 discovered the antipsychotic properties of haloperidol a butyrophenone, a non-specific D-2 antagonist (Christensen et al 1984; Tam and Cook, 1984), is a potent neuroleptic associated with a high incidence of acute extrapyramidal side effects (Rona *et al.,* 1999) and tardive dyskinesia (Kelly *et al.,* 1990) Haloperidol is regarded as the dopamine receptor blocking agent acting chiefly on the CNS (Aden *et al.,* 1970). The antischizophrenic actions of haloperidol was similar to but more potent than phenothiazines and correspondingly

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more potent in elevating the concentration of methoxylated metabolites of dopamine in brain (Carlsson and Lindqvist, 1963). The increase in dopamine activity may be related to the decreased activity of one or more neurotransmitters such as 5-HT, acetylcholine (Synder *et al.,* 1974).

Subchonic treatment of rats with haloperidol result in behavioral and biochemical supersensitivity of DA receptor (Ungerstedt and Ljungberg, 1977; Seeman, 1980). Chronic administration of D_2 receptor antagonists increases the density of D_2 receptor (Burt *et al.,* 1997; McGonigle *et al.,* 1989).

5-HTIA receptor agonist 8-OH-DPAT reduce the effects of the classical neuroleptic haloperidol (Ellenbroek *et al.,* 1994). Serotenergic agonists are true partial agonists for D_2 receptor. The 5-HTIA receptor is one of several types of receptors for 5-HT that exist in brain (Pedigo *et al.,* 1981). Autoradiographic studies of rat brain using l^3HI- 8-OH-DPAT reveal a high density of 5HTIA binding sites in both the mid brain, raphe nuclei & in certain fore brain regions. 5-HTIA receptors located both presynaptically on 5-HT cell bodies in the raphe nuclei where its activation inhibits the firing of raphe neuron (Sprouse and Aghajanian, 1987) and post synaptically being particularly high in hippocampal and Cortical areas (Jacobs and Azmitia, 1992).

Administration of 5-HTIA receptor agonist (8-OH-DPAT) produces a characteristic behavior syndrome comprising forepaw treading, head weaving, hind limb abduction & hyperlocomotion which is sensitive to antagonism by 5-HTIA receptor antagonist such as propanolol (Hjorth *et al.,* 1982; Goodwin *et al.,* 1987a).

The present study was designed to examine the effects of single and repeated prior administration of haloperidol on behavioral responses to 8-OH-DPAT.

MATERIALS AND METHOD

Experimental animals:

Animals used in this experiment were male Wistar rats purchased from HEJ Research Institute of Chemistry, Pakistan. The animals weighed 200-250 gm. The rats were housed individually in cages with saw-dust covered floor where they had free access to dry food pellets and fresh tap water at room temperature with regular 12 hours light 7:00 am to 7:00 pm dark scheduled. Behavioral experiments were conducted between 9:00 am to 11:00 am in a separate testing room.

All animals were handled 2-3 days before starting experiments.

Drugs and Injections:

Drugs used for the treatment were:

1- Haloperidol (searl) available in 5 mg/ml ampoules was injected.

2- 8-hydroxy-2-(di- n- propylamino) tetralin (8-OH-DPAT) (purchase from RBI Research Biochemical, USA). The drug was prepared in Saline (0.9% W/V NaCl) and injected I.P. at a dose of 0.5 mg/kg body weight.

Experimental Protocol:

The animals were randomly assigned as test and control group. In case of single administration, test animals were injected with 5 mg/kg/ml haloperidol while control animals were

injected with saline (0.9% NaCl). Animals were injected with 8-OH-DPAT at a dose of 0.5mg/kg after 30 minutes post injection. Behavioral syndrome was monitored for 20 minutes.

In case of repeated administration animals were randomly divided in to test (haloperidol treated) and control (saline treated) groups. Test animals were injected with haloperidol at a dose of 5mg/kg/ml twice daily. Control animals were injected with saline (1 mg/kg NaCl) two times daily (8.00-9.00 a.m. and 2.00-3.00 p.m) for 5 days. On the 6^{th} day, both the groups were again divided in to saline and 8-OH-DPAT injected rats. 8-OH-DPAT was injected at a dose of 0.5 mg/kg/ml. Behavioral syndrome was monitored for 20 minutes after 8-OH-DPAT administration Test and control animals were again injected with haloperidol (5mg/kg/ml x 2) and saline (1mg/kg) two times on 7^{th}, 8^{th} and 9^{th} day. On the 10^{th} day of treatment animals were injected with saline or 8-OH-DPAT (0.5mg/kg/ml) and behavioral syndrome was monitored for 20 minutes..

Behavioral Syndrome:

Animals were transferred to Perspex observation cages (26 x 26 x 26 cm) with sawdust covered floor. Behavioral scoring started after 8-OH-DPAT (0.5 mg/kg/ml) injection. Each animal was continuously observed for 20 minutes. Forepaw treading and hyperlocomotion were counted. Flat body posture was scored on 0-4 scale of absent to maximum intensity.

Statistical analysis:

The results are presented as the means ± S.D. 5-HT behavioral syndrome data was analyzed by Mann – Whitney U-test. Values $P< 0.05$, $P< 0.01$ were considered statistically significant.

RESULTS

Fig 1 shows the effect of 8-OH-DPAT (0.5mg/kg/ml) elicited 5-HT syndrome (forepaw treading, hyperlocomotion and flat body posture) in single saline and haloperidol (5 mg/kg/ml) injected rats.

Data analyzed by Mann-Whitney U-test revealed that 8-OH-DPAT induced forepaw treading ($P<0.05$) and hyperlocomotion ($P<0.01$) were smaller in haloperidol than saline pre-injected rats. 8-OH-DPAT elicited flat body posture ($P>0.05$) was not significant.

Fig .2 shows the effect of 8-OH-DPAT (0.5mg/kg/ml) elicited 5-HT syndrome i.e. forepaw treading, hyperlocomotion and flat body posture in repeated saline and repeated haloperidol injected rats.

U-test showed that 8-OH-DPAT elicited flat body posture ($p<0.01$) was greater in repeated haloperidol injected rats than their respective controls. Intensity of forepaw treading ($p>0.05$) and hyperlocomotion ($P>0.05$) were not significantly different in repeatedly haloperidol and repeatedly saline treated rats.

DISCUSSION

Two responses that have been used to study 5HTIA receptor activation in intact rats are hypothermia and the "5-HT syndrome" (Paul *et al.,* 1994). Stereotypic increase in locomotor activity is a well-characterized component of 5-HT syndrome (Ortman, 1985). The 5-HT syndrome is a collection of behaviors that include flat body posture, reciprocal forepaw treading, side to side body movement, resting tremor, hind limb abduction and straub tail (Grahame-Smith, 1971 a, b, Jacobs, 1976, Tricklebank, 1985). It can be induced in rats by treatment that increase

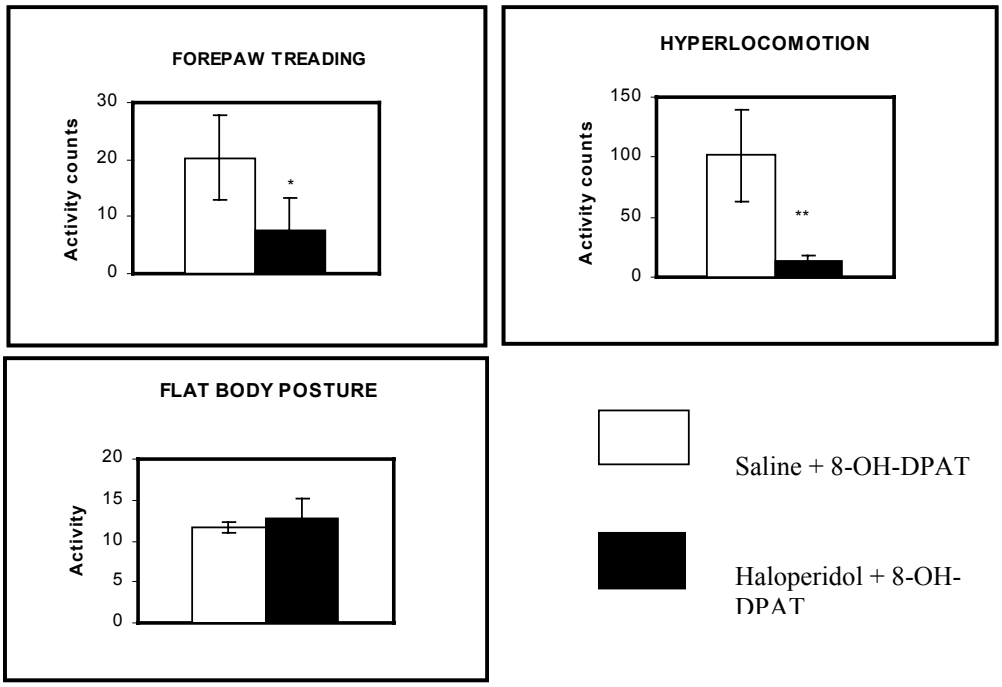

Fig. 1: 8-OH-DPAT(0.5 mg/kg/ml) induced forepaw treading, hyperlocomotion and flat body posture in saline (0.9% NaCl) and haloperidol (5 mg/kg/ml) injected rats. Values are means ± S.D. (n=3). Significant differences by Mann-Whitney U-test. *$p<0.05$, ** $p<0.01$ from saline + 8-OH-DPAT injected rats.

synaptic levels of 5-HT (Grahame-smith, 1971a; Trulson and Jacobs, 1976, Kennett 1987) or by some drugs that directly stimulate 5-HT1A receptor (Grahame-smith 1971b, Hiorth *et al*., 1982). The syndrome is produced by the administration of a number of 5-HT agonists such as 5 – methoxy – N, N-dimethyl tryptamine (5-Me ODMT) and 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) (Glennon et al 1986, Hillegaart et al 1989). Selective 5-HT1A receptor agonist such as 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino) tetralin), flesinoxan, 5-methylurapidil and others, increased locomotor behavior in rats following s.c. injection (Kalkman and Soar 1990). Fig 1 shows that intensity of forepaw treading & hyperlocomotion were smaller in haloperidol than saline pre injected rats. Acute administration of neuroleptics increases dopaminergic neuronal firing and augmented synaptic release of DA (Seeman, 1985).

Chronic administration of D_2 receptors antagonist increases the density of D_2 receptors (Burt *et al.,* 1977, McGonigle *et al*, 1989). We examined the modulatory effect of 8-OH-DPAT on rats pretreated with haloperidol. Fig 2 shows that 8-OH-DPAT elicited flat body posture was greater in repeated haloperidol injected rats. Repeated administration of haloperidol may induce DA receptor sensitivity when given in clinically relevant dose (Rupanik *et al.*, 1984).

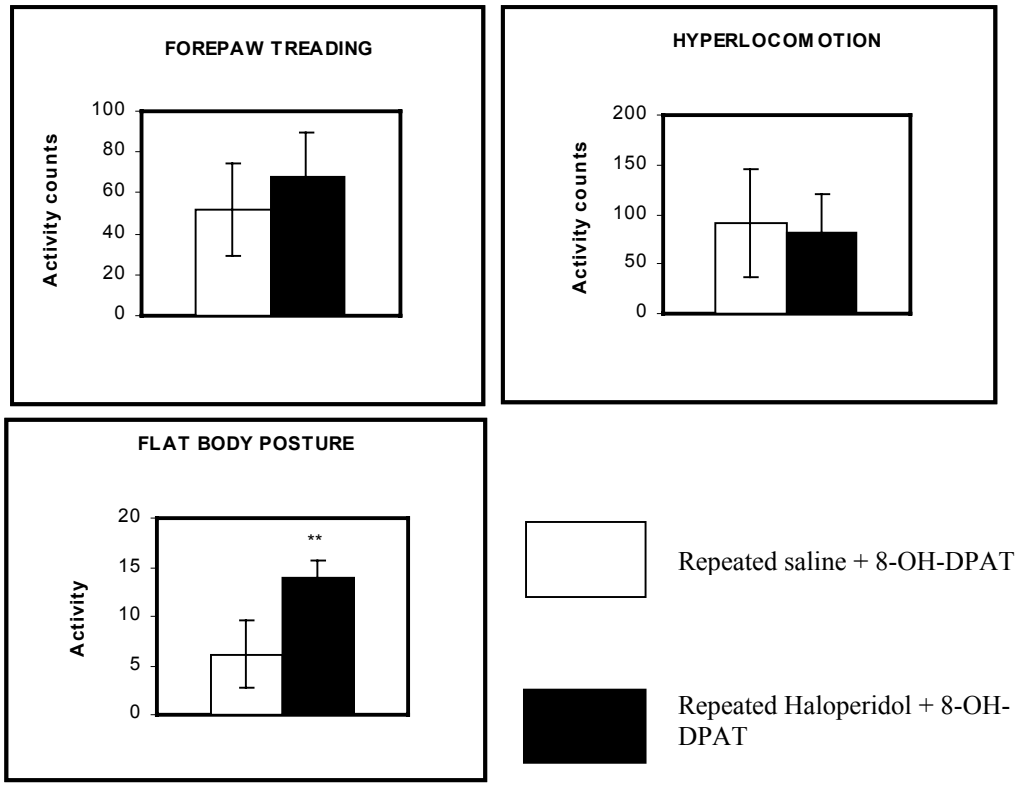

Fig. 2: 8-OH-DPAT (0.5mg/kg/ml) induced forepaw treading, hyperlocomotion and flatbody posture in repeated saline and repeated haloperidol (5 mg/kg/ml for 10 days x 2) injected rats. Values are means ± S.D. (n=6). Significant differences by Mann-Whitney U-test. **p<0.01 from repeated saline + 8-OH-DPAT injected rats.

Administration of high doses of haloperidol was found to cause a long lasting effect on both DAergic and serotenergic neurons that paralleled severe impairment of locomotor performance (Susan et al 1992). The postsynaptic D_2 receptors activate locomotor activity (Levesque, 1990; Levant, 1997) 5-HTIA receptor agonist 8-OH-DPAT reduce the effects of the classical neuroleptic haloperidol (Ellenbroek *et al*, 1994) and also increased locomotor behavior (Kalkman and Soar, 1990).

The result of repeated study showed that behavioral effects of 5-HTIA agonist may be mediated, in part by DA release in various brain regions (Ichikawa and Meltzer, 1999).

The fact that activation of 5-HTIA receptors after systemic administration of DPAT at low doses can increase DA cell firing in the VTA and substantia nigra (Sinton and Fallen, 1988; Kelland *et al.,* 1990; Arborelius *et al.*, 1993; Prisco *et al.*, 1994) and increase extracellular DA levels in NAc (Boulenguez *et al.,* 1996) and VTA (Chen and Reith 1995) suggests that actions of DPAT at the level of the mesoaccumbens circuit may contribute to the observed behavioral effects.

5-HT syndrome is mediated by post synaptic 5-HT1A receptors. Two components of 5-HT syndrome is due to the action at post synaptic sites (i.e. flat body posture and forepaw treading) (Connell and Curzon, 1996). 5-HT1A postsynaptic receptors are supersensitized after chronic administration of haloperidol. The result of repeated administration indicates that serotonergic agonists behave as typical partial agonist for D_2 receptor (Rinken *et al.,* 1999) and when 8-OH-DPAT administered acutely attenuate cataleptic side effect of antipsychotics (Assie *et al.,* 1997).

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CONCLUSION

The present study shows that 8-OH-DPAT elicit some components of 5-HT syndrome in rats following repeated haloperidol administration. The components of syndrome induced by 8-OH – DPAT in rats following single haloperidol injection were smaller. Repeated haloperidol administration upregulates D_2 receptors (Burt *et al,* 1977; McGongile *et al.,* 1989). The present study shows an interaction of 5HT1A receptors+ D2 receptors in manifestation of atleast some of the components of syndrome. The present study also suggests that an upregulation of 5HT1A receptors may be involve in upregulation of 5HT1A receptors may be involve in the extrapyramidal symptoms observed in patients receiving longterm haloperidol administration.

REFERENCES

Aden, N.E., Butcher, S., Corrodi, H., Fure, K. and Ungerstedt, U. (1970). Receptor activity and turnover of dopamine and Nor-adrenaline after neuroleptics. *Eur. J. Pharmacol*. **11**: 303-314

Arborelius, L., Chergui, K., Murase, S., Nomikos, G.G., Hook, B.B., Chouret, G., Kacksell, U. and Svensson, T.H. (1993). The 5HTIA receptor selective ligands, (R) -8-OH-DPAT and (S) – UH-301, differentially affect the activity of midbrain dopamine neurons. *Naunyn-Schmiedeberg's Archi Pharmaco.l* **347**: 353-362.

Assie, M.B., Cosi , C., Koek, W. (1997). 5-HT1A receptor against properties of the antipsychotic, nemonpride: Comparison with bromerguride and clozapine. *Eur J Pharmacol*. **334**(2-3): 141-147.

Baldessarini, R.J. Drugs and the treatment of psychiatric disorders. In: Gilman AG, Goodman LS, Rall TW, Murad F., Eds. (1985). The Pharmacological Basic of Therapeutics, New York MacMillan Publishing Co. pp.391-447.

Boulenguez, P., Rawlins, J.N., Chauveau, J., Joseph, M.H., Mitchell, S.N. and Gray, J.A. (1996). Modulation of dopamine release in nucleus accumbens by 5-HT1B agonists: Involvement of the hippocampo-accumbens pathway. *Neuropharmacology.* **35**: 1521-1529.

Burt, D.R., Creese, I. and Snyder, S.H. (1977). Antischizophrenic drugs: chronic treatment elevates dopamine receptor binding in brain *science (Wash DC)* **196**: 326-328.

Carlsson, A. and Lindqvist, M. (1963). Effect of chloropromazine and haloperidol on formation of 3-methoxytyramine and nonmetanephrine in mouse brain. *Acta pharmacol. Toxicol.* **20***:* 140-144.

Chen, N.H. and Reith, M.E.A. (1995) Monoamine interactions measured by microdialysis in the ventral tegmental area of rats treated systemically with 8-hydrory – 2 (di-n-propylamino) – tetralin. *J Neurochem.* **64**: 1585-1597.

Christensen A.V.,.Arnt, J., Hyttel, J,. Larsen, J.J. and Sevendsen, O. (1984). Pharmacological effects of a specific dopamine D-1 antagonist SCH 23390 in comparison with neuroleptics. *Life science*. **34**: 1529-1540.

Ellenbroek, B.A., Prinssen, E.P., Cools, A.R. (1994). A role of serotonin receptor subtypes in behavioral effects of neuroleptic drugs. A paw test study in rats. *Eur J Neurosci.* **6**(1): 1-8.

Garza, R.D.L. and. Cunnigham, K.A. (2000). The effect of the 5-hydroxytryptamine-1A agonist 8-hydroxy-2-(di-n-propylamino) tetralin on spontaneous activity, cocaine-induced hyperactivity and behavioral sensitization. A microanalysis of locomotor activity. *The J Pharmacol Exp Ther.* **292**(2): 610-617.

Glennon, A., Slusher, R.M., Lyon, R.A., Titeler, M., Mckenny, J.D. (1986) 5-HT-1 And, 5-HT-2 binding characteristics of some quipazine analogues. *J Med chem*. **29**: 2375-80.

Grahame-Smith, D.G. (1971b). Studies in vivo on the relationship between brain tryptophan, brain 5-HT synthesis and hyperactivity in rats treated with a monoamine oxidase inhibitor. *J. Neurochem*. **18**: 1053-1066.

Grahame-Smith, D.G. (1971a). Inhibitory effect of chloropromazine on the syndrome of hyperactivety produced by L-tryptophan or 5-methoxy – N,N,-demethyltryptamine in rats treated with a monoamine oxidase inhibitor.) *Br. J Pharmacol.* **43**: 856-864.

Goodwin, G.M., De Souza, R.S., Green, A.R. and Heal, D.J. (1987). The pharmacology of the behavioral and hypothermic responses of rats to 8 – hydroxyl-2-(di-n-propylamino) tetralin (8-OH-DPAT). *Psychopharmacology (Berlin)* **91**: 506-511.

Hillegaart, V., Wedenberg, M.L., Alheniles, S. (1989). Effect of 8-OH-DPAT on motor activity in the rat. *Pharma Biochem Behav.* **32**: 797-800.

Hjorth, S., Carlsson, A. Lindberg, P. Sanchez D., Wikstrom, H., Alridsson, L.E. Hacksell, U. and Nilsson,J (1982)..LG. 8-hydroxy-2 (di-n-propylamino) tetralin, 8-OH-DPAT, a potent and selective simplified ergot congener with central 5-HT-receptor stimulating activity. *J. Neural Transon.* **55**: 169-188.

Ichikawa, J. and Meltzer, H.Y. (1999). R (+)-8-OH-DPAT, a serotonin 1A receptor agonist, potentiated S(-)- sulpride- induced dopamine release in rat medial prefrontal cortex and nucleus accumbens but not striatum. . *The J Pharmacol Exp Ther.* **291**(3): 1227-1232.

Jacobs, B.L. (1976.) An animal behavior model for studying central serotenergic synapses. *Life Sci*. **19**: 777-786.

Jacob, B.L. and Azmitia, E.C (1992). Structure and function of the brain serotonin system. *Physiol Rev* **72**: 165-229.

Janssen, P.A. (1974) Butyrophenones and diphenyl butyl piperidines. In: *Psychopharmacological Agents*, Vol. 3. (Gorden, M., ed). Academic Press Inc., New York. pp.128-158.

Kalkman, H.D., Soar, J. (1990). Determination of the 5HT receptor subtype involved in 8-OH-DPAT induced hyperlocomotion potential difficulties arising from inadequate pharmacological tools. *Eur J Pharmacol* **191**(3): 383-90.

Kennett, G.A., Marcoll, M., Dourish, C.T., Curzon, G. (1987). Single administration of 5-HT-IA agonists decreases 5-HT-IA presynaptic, but not post synaptic receptor – mediated response relationship to antidepressant like action. *Eur. J. Pharma* **138**: 53-60.

Kelland, M.D., Freeman, A.S. and Chiodo, L.A. (1990). Serotonergic afferent regulation of the basic physiology and pharmacological responsiveness of nigrostriatal dopamine neurons. *J Pharmacol Exp Ther.* **253**: 803-811.

Kelly, L.D., William T., O' Connor, Kehr, J. and Ungerstedt, U. (1990). Regional specific effects of clozapine and haloperidol on GABA and dopamine release in rat basal ganglia. *Eur Journal of pharmacology*, **187**: 385-397.

Levant, B. (1997). The D_3 dopamine receptor: Neurobiology and potential clinical relevance. *Pharmocol Rev*. **49**: 231-252.

Levesque, D. (1996) Aminotetralin drugs and D_3 receptor functions. *Biochem Pharmacol.* **52**: 511-518.

McGonigle, P., Boyson, S.J., Reuter, S., and Molenoff, P.B. (1989). Effects of chronic treatment with selective and non selective antagonist on the subtypes of dopamine receptors. *Synapse* **3**: 74-82.

O'Connell, M.T., Curzon, G. (1996) A comparison of the effects of 8-OH-DPAT. *EurJ Pharmacol.* **312**(2): 137-43.

Ortman, R. (1985). The 5-HT Syndrome and the drug discrimination paradigm in rats. Application in behavioral studies on the central 5-HT system. *Pharmaco psychiatry.* **18**: 198-201.

Paul, A.S., Chou, J.M., Tang, H. and Frazer, A. (1994). Differential induction of 5-HTIA-mediated responses in vivo by three chemically dissimilar 5-HTIA agonists. *J Pharma Exp Ther*. **270**: 198-208.

Pedigo, N.W., Yamamura, H.I and Nelson, D.L (1981) Discrimination of multiple [3H]5-hydroxytryptamine binding sites by the neuroleptic spiperone in rat brain. *J. Neurochem*. **36**: 220-226.

Prisco, S., Pagannone, S. and Esposito, E (1994). Serotonin dopamine interaction in the rat ventral tegmental area: An electrophysiological study in vivo. *J Pharmacol Exp Ther* **271**: 83-90.

Rinken, A., Ferre, S., Terasmaa, A., Owman, C. and Fuxe, K. (1999). Serotonergic agonists behave as partial agonists at the dopamine D_2 receptor. *Neuro Report* **10**, 493-495.

Rona, J., Anil, K.M. and Pickar, D. (1999): Predicting to clozapine; status of current research. *CNS Drugs*. **11**: 317-326.

Rupniak, N.M., Kilpatrick, G., Hall, M.D., Jenner, P., Marsden, C.D. (1984). Differential alterations in striatal dopamine receptor sensitivity induced by repeated administrations of clinically equivalent doses of haloperidol, sulpiride or clozapine in rats. *Psychopharmacology (Berl)*, **84(4)**: 512-519.

Schroder, U., Schroder, H., Augustin, W. and Sabel, B.A. (1994). Haloperidol–induced behavioral super sensitivity is increased by monosialoganglioside treatment in rats without affecting spiroperidol – binding. *J Pharma Exp Ther.* **271**: 1193-1196.

Seeman, P: (1980) Brain dopamine receptors. *Pharmacol* Rev. **32**: 229-313.

Seeman, P. (1985). Neurolepties (Antipsychotics). In: Principles of Medical Pharmacology. (Kalant, H., Roschlaui, W.H.E and Sellers, E.M., eds) 4th ed., Oxford University Press, pp.321-336.

Shireen, E., Qurat-ul-ain., Batool, F., Saify., Z.S. and Haleem, D.J.(2001). Neurochemical effects of 8-OH-DPAT in rats injected with haloperidol. *Pak.J of Pharmaceutical Sciences* (in press).

Sinton, C.M. and Fallen, S.L. (1988). Electrophysiological evidence for a functional differentiation between subtypes of 5-HTIA receptor. *Eur J Pharamacol* **157**: 173-181.

Sprouse, J.S. and Aghajanian, G. K. (1987). Electrophysiological responses of serotonergic dorsal raphe neurons to 5HTIA and 5HTIB agonists. *Synapse.* **1**: 3-9.

Stanwood, G.D., Lucki, I., and McGoingle, P. (2000).Differential regulation of Dopamine D_2 and D_3 Receptors by chronic drug treatments. *J Pharma Exp Ther*. **295**: 1232-1240.

Susan, K.J., Wagner, G.C. and Fischer, H. (1992) Neurochemical and motor effects of high dose haloperidol treatment: Exacerbation by tryptophan supplementation. *P.S.E.B.M.***200**:.571-575.

Synder, S.H., Banerjee, S.P., Yamamura, H.I. and Greenberg, D. (1974). Drugs, neurotransmitters and schizophrenia. *Science* **184**: 1243-1252.

Takween, S., Zuberi, M.S.A., Ahmed, P.S., Haider, S. and Haleem, D.J. (2000). Neurochemical estimation of brain biogenic amines in normal and hyperglycemic rats after haloperidol administration. *Pak. J. Pharmacology.* **17**(1&2): pp 23-28.

Tam, S.W. and Cook, L. (1984). Sigma opiates and certain antipsychotic drugs mutually inhibit (+) – [3-H] SKF 10, 047 and [3-H] haloperidol binding in guinea pig brain membranes. *Proc. Natl. Acad. Sci*. **81**: 5618-5621.

Tricklebank, M.D. (1985). The behavioral response to 5-HT receptor agonists and subtypes of the central 5-HT receptor. *Trends Pharmacol Sci* **6**: 403-407.

Trulson, M.E. and Jacobs, B.L. (1976). Behavioral evidence for the rapid release of CNS serotonin by PCA and fenfluramine. *Eur. J. Pharmacol*. **36**: 149-154.

Ungerstedt, U.T. and Ljungberg, T. (1977). Behavioral patterns related to dopamine neuro-transmission: Effect of acute and chronic antipsychotic drugs. *Adv. Biochem. Psychopharmacol*. **16**: 193-209.