Co-treatment with imipramine averted haloperidol-instigated tardive dyskinesia: Association with serotonin in brain regions

Noreen Samad[1], Farzana Yasmin[2] and Darakhshan Jabeen Haleem[3]
[1]Department of Biochemistry, Bahauddin Zakariya University, Multan, Pakistan
[2]Department of Food and Biomedical Engineering, NED University of Engineering, Karachi, Pakistan
[3]Neuroscience Research Laboratory, Dr. Panjwani Center for Molecular Medicine & Drug Research, University of Karachi, Pakistan

Abstract: Outcome of imipramine (IMI) treatment was scrutinized on progression of haloperidol instigated tardive dyskinesia (TD). 0.2 mg/kg/rat dosage of haloperidol provided orally to rats for 2 weeks enhanced vacuous chewing movements that escalated when the process proceeded for 5 weeks. Following 2 weeks co-injection 5 mg/kg dosage of IMI was diminished haloperidol-instigated VCMs and fully averted following five weeks. The potency of 8-OH-DPAT-instigated locomotor activity exhibited higher in saline+haloperidol treated rats while not observed in IMI+ haloperidol treated rats. 8-OH-DPAT-instigated low 5-hydroxytryptamine (5-HT; serotonin) metabolism was higher in saline+ haloperidol treated rats when compare to IMI+ haloperidol treated rats in both regions of brain (striatum and midbrain). It is recommended that IMI possibly competent in averting TD, in cases receiving treatment to antipsychotics.

Keywords: Tardive dyskinesia, Imipramine, Haloperidol, Serotonin-1A receptor.

INTRODUCTION

Continuing administration of antipsychotic drugs instigated a neurological disorder Tardive dyskinesia (TD) (Haleem *et al.,* 2007a; Shireen, 2016), which is designated by many adverse effects (Casey, 1985; 2004).

Prolong treatment of haloperidol causes a syndrome designated as vacuous chewing movements (VCMs) which is supposed parallel to TD in human beings (Turrone *et al.,* 2002; Lister *et al*., 2017). Acute treatment of haloperidol reduced locomotor activity and alters motor coordination resulting of catalepsy (Haleem *et al.,* 2004; Karl *et al.,* 2006). In nigrostriatal pathway haloperidol blocks dopamine D2 receptors which may cause motor adverse effects (Farde *et al.,* 1992).

Implication of serotonin (5-HT) TD related symptoms is evidenced. 5-hydroxytryptamine (5-HT; serotonin) gives invigoration into the basal ganglia with regulation of dopamine neurotransmission (Alex and Pehek, 2007). It is reported from our laboratory that repeated administration of buspirone and 8-OH-DPAT, 5-HT-1A agonist (partial or full), diminished the haloperidol-instigated TD with subsequent decline in the effectiveness of 5-HT-1A receptor positioned on soma and dendrites (Samad & Co-workers 2016).

Imipramine (IMI; a 5-HT and nor-epinephrine reuptake inhibitor) has antidepressant effect (Rogoz *et al.,* 2007; Birkenhäger & Pluijms, 2016) and behavioral stimulation (Scheggi *et al*., 2011) with subsequent prolong treatment. Hence, the current research was intended to examine the possible contribution of the 5-HT system to the motor effects of chronic treatment of IMI on haloperidol-instigated model of TD.

METHODOLOGY

Animals

Rats (male albino Wistar) bought from ICCBS (Karachi, Pakistan), housed individually in a controlled standard environment. Institutional ethical and committee of animal care have approved all experimental work.

Drugs

Haloperidol purchased as drops (2.0mg/ml) were provided in water used for drinking. IMI mixed in saline and inserted intraperitoneally (*i.p).* + 8-OH-DPAT mixed in saline and inserted as *i.p.*

Experimental Protocol

In the beginning, effects of doses of IMI i.e. 5, 10 and 15 mg/kg on locomotion determined in a novel environment (open field) to ascertain a dosage that does not lessen locomotion and be able to used to examine likely properties on impede of VCMs instigated by haloperidol and sensitization of serotonergic receptors present on soma and dendrites in an animal model of TD. The drug or vehicle was administered subcutaneously. The behavior in a novel environment was monitored for 5 min.

After the selection of dose, 48 rats were randomly divided into 4 equal sets. (i) saline+ water (ii) saline+haloperidol (iii) IMI+ water (iv) IMI+haloperidol. Haloperidol (0.2 mg/kg/day) was administered orally in water which is use for drinking. IMI (5 mg/ml/kg body weight) was vanished in vehicle (saline) and administered subcutaneously. The

**Corresponding author:* e-mail: noreen.samad@bzu.edu.pk

drugs were administered everyday for 5 weeks. Behavioral appraisal of VCMs was conceded out weekly 1-h preceding to treatment of drugs. Effects of 8-OH-DPAT (0.25 mg/ml/kg b.w) ascertained after a drug malfunction phase of two days into similar divisions. So the presence of earlier administered drugs may not hinder with the possessions of 8-OH-DPAT.

Rats of every of the above 4 sets alienated into saline (1 mg/kg) or 8-OH-DPAT (0.25mg/kg) treated sub-groups (Haleem & Khan, 2003). Forepaw treading and hyperlocomotion instigated by the 8-OH-DPAT were counted for twenty-five minutes preliminary 5 min after drug administration. Rats were guillotined one-hour after the 8-OH-DPAT administration to save the striatum and midbrain (Samad and Co-workers, 2007) and refrigerated at a temperature of -70°C for the investigation of 5-HT metabolism.

Behavioral analysis

Open field

Open field test was observed for 5 min as reported earlier (Samad, 2015)

VCMs quantification

VCMs were observed for10 minutes. For estimation intent, every blow out of irregular chewing was scored as one, if its time period was minimum 3 seconds by (Samad *et al*., 2016).

5-HT syndrome induced by 8-OH-DPAT

Cage crossing and forepaw treading were scored as depicted (Samad *et al*., 2016)

Anatomization of brain and estimation of neurotransmitters

Anatomization technique of Brain

Brain samples were collected immediately following decapitation of animals. Regions of brain were obtained as depicted (Samad *et al*., 2016).

Estimations of 5-HT metabolism by HPLC-EC:

Levels of 5-HT and its metabolite were estimated by HPLC-EC as evidenced (Samad *et al*., 2016).

STATISTICAL ANALYSIS

Data was analyzed by ANOVA following Tukey's test. Analysis of data was performed by SPSS. <0.05 P values were appropriated as significant.

RESULTS

Fig. 1 presents the effects of IMI doses (5, 10 and 15 mg/kg) on a test conducted on open field. Significant effect of IMI [F(3,20)= 42.6 p<0.05] was obtained by ANOVA (One way). Tukey's test showed that exploratory activity was significantly decreased by 10 and 15 mg/kg doses of IMI, while non significant at 5 mg/kg dosage.

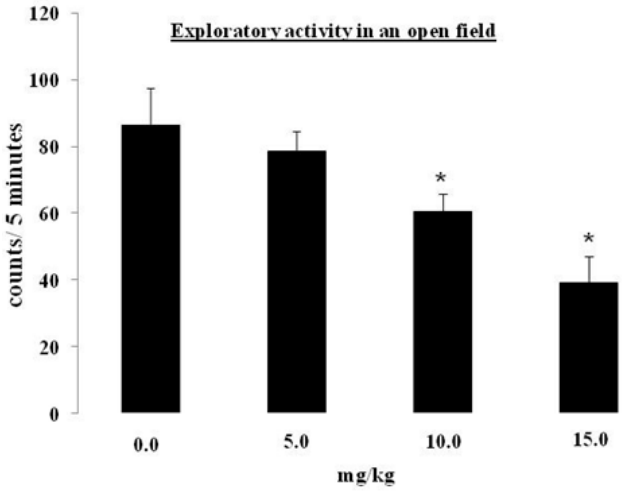

Fig. 1: Effects of various doses of IMI on exploratory activity in an open field. Values are means ± SD (n=6) 60 min post injection. Significant differences by Tukey's test *p<0.05 from saline treated animals following ANOVA (One way).

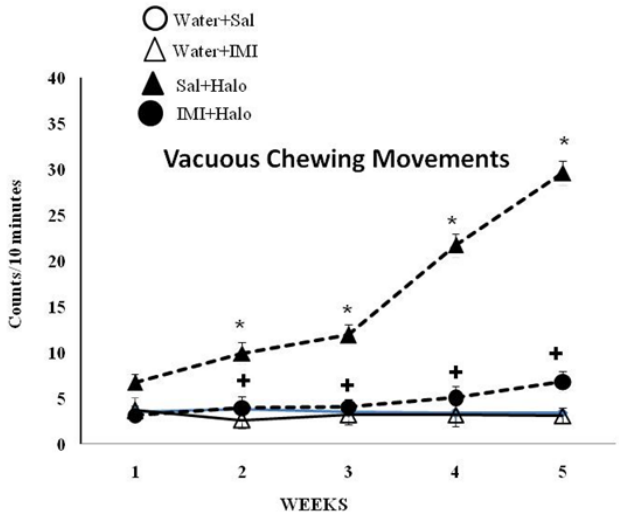

Fig. 2: Intensity of haloperidol-induced VCMs in animals treated with saline and IMI. Values are mean ±SD (n=12) 60 min post-injection. Significant differences by Tukey's test:*P<0.05 from water+saline treated animals, +P<0.05 from saline+haloperidol treated rats following ANOVA (Three way).

Fig. 2 presents the progressive increase of VCMs instigated by haloperidol in rats deal with IMI and saline. Significant effects of haloperidol [F(1,220)=1239.4 *P*<0.05], IMI [F(1,220)=878.9 *P*<0.05] and weeks [F(4,220)=147.6 *P*<0.05] were obtained by Three way ANOVA. Significant effects on interaction between haloperidol x weeks [F(4,220)=154.6 *P*<0.05], haloperidol x IMI [F(1,220)=767.6 *P*<0.05], IMI x weeks

[F(4,220)=82.8 *P*<0.05] and haloperidol x weeks x IMI [F(4,220)=84.0 *P*<0.05]. Tukey's test showed that VCMs were progressively increased following 5 weeks treatment of haloperidol. On the contrary, induction of haloperidol-elicited VCMs were setback by IMI.

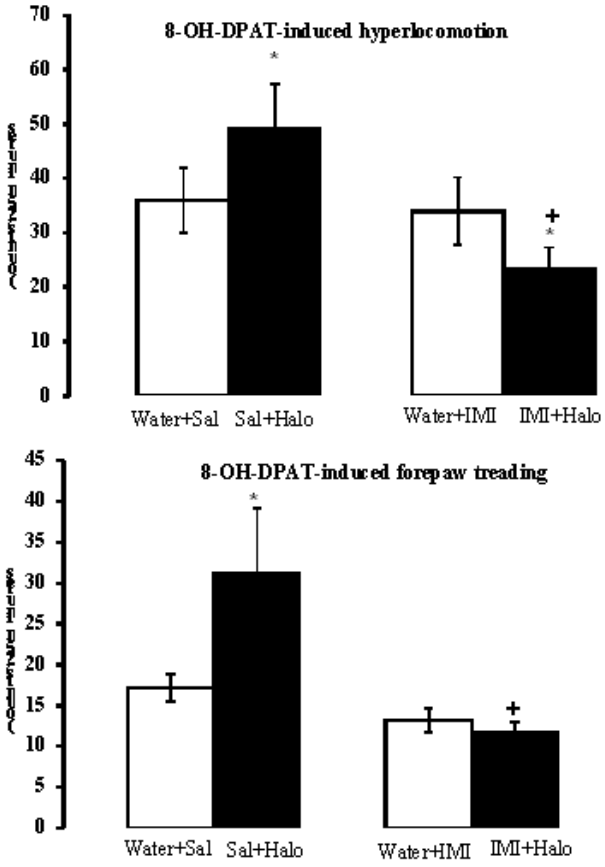

Fig. 3: 8-OH-DPAT-induced hyperactivity and forepaw treading in water+saline, saline+haloperidol, water+IMI and IMI +haloperidol treated animals. Values are means ± S.D. (n=6) from 5-30 min post 8-OH-DPAT injection and 48 h after haloperidol or IMI administration. . Significant differences by Tukey's test:*P<0.05 from water+saline and water+IMI treated animals, +P<0.05 from saline +haloperidol treated rats following ANOVA (Two-way).

Fig. 3 presents induction of intensity of serotonin syndrome by 8-OH-DPAT administration in all 4 groups. Non-significant effects of haloperidol on cage crossing [F(1,20)=0.3 *P*>0.05], while significant effects of IMI [F(1,20)=31.4 *P*<0.05] and interaction between two [F(1,20)=23.4 *P*<0.05] were obtained by ANOVA (Two way). Significant possessions of haloperidol [F(1,20)=15.0 *P*<0.05), IMI [F(1,20)=50.3 *P*<0.05] and interaction between two [F(1,20)=22.5 *P*<0.05] on forepaw treading were also obtained by ANOVA (Two way). Tukey's test showed that hyperlocomotion and forepaw treading instigated by 8-OH-DPAT were higher in saline+haloperidol when compare to water+saline treated rats. Conversely, IMI+haloperidol treated animals showed smaller hyperlocomotion than water+IMI. Rats co treated with IMI showed smaller 5-HT syndrome than saline +haloperidol treated rats.

Fig. 4 presents the metabolism of 5-HT in parts of brain subsequent administration of 8-OH-DPAT in rats pre-treated with water+saline, saliner+haloperidol, water+IMI and IMI+haloperidol treated rats. ANOVA (Three way) on data of 5-HT showed that haloperidol [F(1,40)=10.0 *P*<0.05], IMI [F(1,40)=91.2 p<0.05] and 8-OH-DPAT [F(1,40)=261.3 *P*<0.05] exhibited significant effects in the striatum. Non significant interaction amid IMI x 8-OH-DPAT [F(1,40)=0.03 *P*>0.05] whereas significant interaction was obtained amid haloperidol x 8-OH-DPAT [F(1,40)=6.1 *P*<0.05], IMI x haloperidol [F(1,40)=90.0 *P*<0.05] and 8-OH-DPAT x IMI x haloperidol [(F(1,40)=18.2 *P*<0.05]. Non significant effect of haloperidol [F(1,40)=1.0 *P*>0.05] whereas significant effects of IMI [F(1,40)=31.0 *P*<0.05] and 8-OH-DPAT [F(1,40)=503.1 *P*<0.05] were obtained in the midbrain. Non-significant interaction amid IMI x 8-OH-DPAT [F(1,40)=1.9 *P*>0.05] and haloperidol x 8-OH-DPAT [F(1,40)=2.6 *P*>0.05], whereas significant interaction amid IMI x haloperidol [F(1,40)=29.336 *P*<0.05] and haloperidol x IMI x 8-OH-DPAT [F(1,40)=76.2 *P*<0.05]. Tukey's test showed in the striatum and midbrain quantity of 5-HT was reduced following treatment of 8-OH-DPAT in water+saline in addition to saline+haloperidol pre-holded animals whereas these decreases were marked in the striatum in saline+haloperidol than water+saline treated animals. Water+IMI pre-treated rats exhibited smaller concentration of 5-HT following 8-OH-DPAT administration in brain regions (striatum and midbrain). On the other hand, IMI+haloperidol pre-treated animals showed low levels of 5-HT in the midbrain than striatum. In the striatum the levels of 5-HT were lesser in IMI+haloperidol than water+IMI treated rats.

ANOVA (Three way) on 5-HIAA obtained data showed significant effects of haloperidol [F(1,40)=29.3 *P*<0.05], IMI [F(1,40)=115.0 *P*<0.05] and 8-OH-DPAT [F(1,40)=138.0 *P*<0.05] in the striatum. Significant interaction amid IMI* haloperidol [F(1,40)=16.1 *P*<0.05], haloperidol *8-OH-DPAT [F(1,40)=5.1 *P*<0.05], IMI x 8-OH-DPAT [F(1,40)=36.2 *P*<0.05] and haloperidol x IMI x 8-OH-DPAT [F(1,40)=19.9 *P*>0.05]. Significant effects of haloperidol [F(1,40)=12.9 *P*<0.05] and 8-OH-DPAT [F(1,40)=133.0 *P*<0.05] in the midbrain, whereas non-significant effect of IMI [F(1,40)=0.0039 *P*>0.05]. Significant interaction amid IMI x haloperidol [F(1,40)=22.99 *P*<0.05], haloperidol x 8-OH-DPAT [F(1,40)=5.6 *P*<0.05], IMI x 8-OH-DPAT [F(1,40)=33.99 *P*<0.05] and haloperidol x IMI x 8-OH-DPAT [F(1,40)=34.99 *P*>0.05]. Tukey's test showed that in the brain regions (midbrain and striatum) concentration of 5-HIAA was decreased in both water+saline and saline+haloperidol pre-treated animals following 8-OH-DPAT administration. The level of 5-HIAA was increased

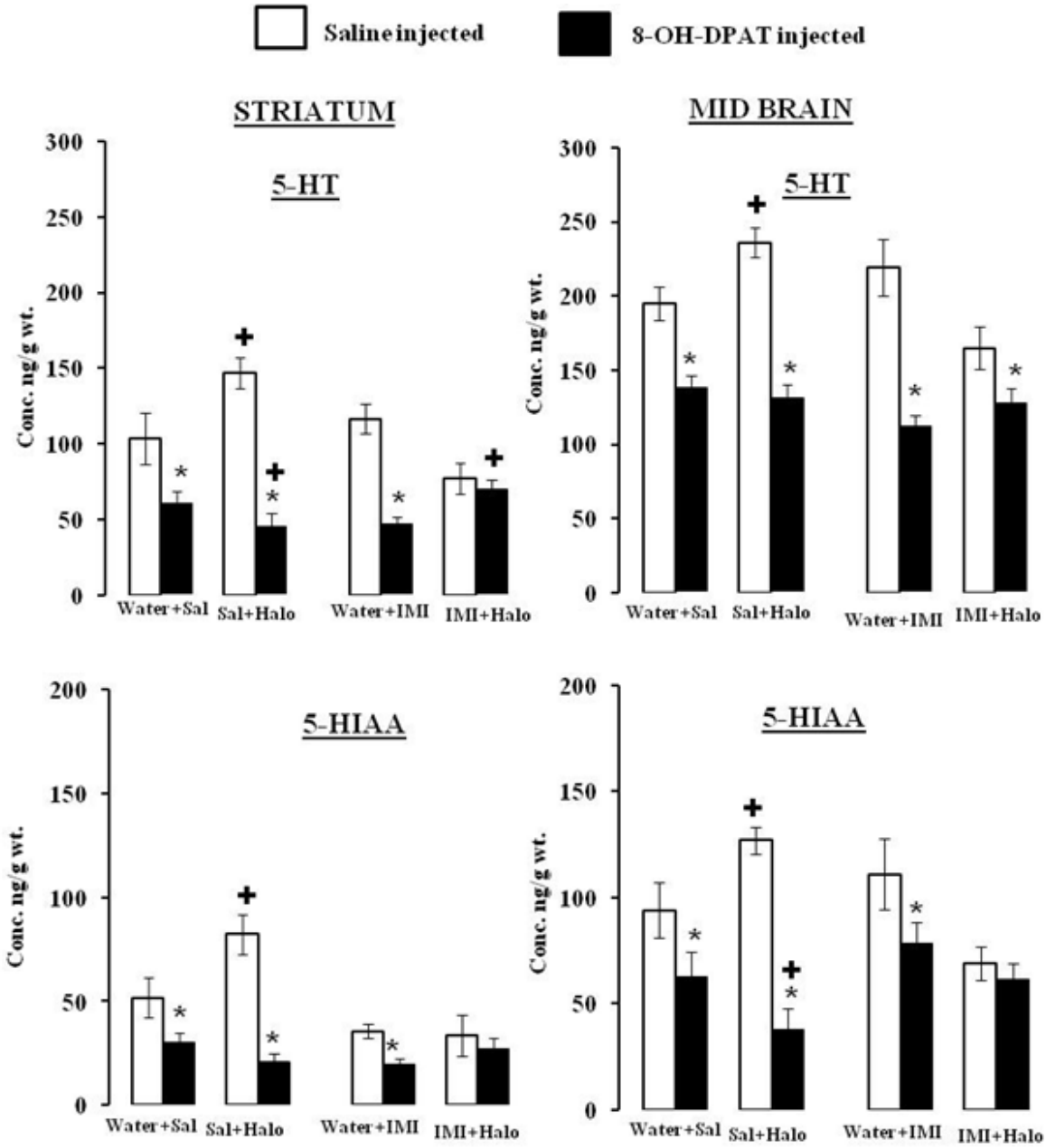

Fig. 4: 8-OH-DPAT-induced decreases of 5-HT and 5-HIAA levels in the striatum and midbrain of water+saline, saline +haloperidol, water +IMI and IMI+haloperidol treated animals. Values are means ± S.D. (n=6) 1 h post 8-OH-DPAT injection and 48 h after haloperidol or IMI administration. Significant differences by Tukey's test:*P<0.05 from respective saline treated animals, +P<0.05 from water+saline treated rats following ANOVA (Two-way).

in saline+haloperidol when compared to water+saline pre-injected animals in the midbrain.In the two brain regions following administration of 8-OH-DPAT levels of 5-HIAA become decreased in water+IMI pre-treated animals.

DISCUSSION

In preclinical studies many effects of antidepressant and TD on 5-HT functions have been reported. Here our findings show that long term treatment of IMI is ample to setback haloperidol-elicited VCMs and supersensitization of 5-HT-1A receptors located on cell soma and dendrites. Conversely, 8-OH-DPAT-elicited 5-HT syndrome observed more in haloperidol+saline treated rats than IMI+haloperidol treated rats. In the same way, there is a larger reduction in metabolism of 5-HT occurred in haloperidol+saline treated while not observed in IMI+haloperidol treated rats in both brain regions (striatum and midbrain).

Haloperidol inhibit increased locomotor activity elicits by amphetamine and reduces expedition (Karl and co-workers, 2006) and results catalepsy (Haleem *et al*., 2004). Chronic and sub-chronic treatments of haloperidol-elicit VCMs (Samad and Haleem, 2014; Samad *et al*., 2016). Our findings reveal that treatment with haloperidol-induced VCMs steps forward as the treatment persistent for 5 weeks (fig. 2).

Following administration of neuroleptics dopamine D2 receptors become up-regulated resulted in TD development (Klawans and Rubovits, 1972). In the caudate, nucleus accumbens and putamen proliferation of dopamine D2 receptors was observed subsequent continuing treatment of neuroleptics (Lau *et al*., 2003). In substentia nigra and ventral tegmental area the serotonergic contribution is may involved in control of movement (Barnes *et al.,* 1992). Previous studies have shown that haloperidol administration increased 5-HT metabolism in many regions of the brain in which striatum and midbrain are included (Samad *et al*., 2007; Samad, 2015). Preclinical and clinical studies recommend that in the commencement of TD, increased serotonergic transmission has a vital role (Samad *et al.,* 2016). Fig. 4 is in agreement with Samad *et al.* (2016) and supports that that, continual administration of haloperidol increased 5-HT metabolism suggesting, supersensitization of serotonergic 5-HT-1A receptors

Repeated therapy with haloperidol linked with induction of VCMs with supersensitivity of somatodendritic receptors (fig. 1). In many experiments interaction between serotonergic and dopaminergic systems have described supportive (Wedenberg, 1996; Arroyo *et al*., 2016) and opposed connections (Kapur, 1996; Neal-Beliveau *et al.,* 1993). The dorsal raphe project serotonergic neurotransmission openly to the substantia nigra and negatively amends dopamine neurons in the substantia nigra (Jacob and Azmitia, 1992; Kelland *et al*., 1990). Studies have shown that 5-HT-2A/2C receptors present on the cell soma and dendrites of neuron of dopamine are involved in inhibitory action (Ugedo *et al.,* 1989). Selective 5-HT-2C receptor antagonists improve atypical antipsychotics-induced extrapyramidal symptoms (EPS) possibly by increasing neuronal firing of dopamine from the inhibitory pressure of serotonin (Shireen and Haleem, 2011; Shireen, 2016).

Buspirone that preferably stimulate somatodendritic 5-HT-1A receptor as partial agonist at 5-HT-1A receptors, attenuate haloperidol-induced dyskinesia less than 8-OH-DPAT which is an agonist at 5-HT-1A receptors with selectivity (Samad and co-workers, 2007; Woźniak *et al*., 2016). It is connected with a greater reduction in 5-HT and 5-HIAA concentrations in the striatum of buspirone treated than 8-OH-DPAT-injcected animals. It was recommended that release of dopamine from the inhibitory pressure of serotonin is influenced by both buspirone and 8-OH-DPAT to alienate haloperidol-induced dyskinesia (Haleem, 2014). fig. 2 depicts that super sensitization of somatodendritic 5-HT-1A receptors observed subsequent five weeks administration of haloperidol possibly will impaired the serotonergic influence on dopaminergic system. So it is recommended that decrease influence of serotonergic neurotransmission on dopaminergic neurotransmission is concerned in the potentiating of VCMs, whereas normalization of pressure of serotonergic system when co-treated with IMI may possibly prevented the elicitation of haloperidol-induced VCMs.

IMI is an illustrious TCA (Wasik *et al.,* 2013). In the force swimming test, IMI (at doses 5mg/kg/day to 30 mg/kg/day), when administered acutely in rodents showed dose reliant reduction in locomotion (Wasik *et al.,* 2013) and exploration of open field (Cardoso *et al.,* 2009). fig. 1 is in accord to past research work.

5-HT-1A receptors has a vital role in dementia (Buhot *et al.,* 2000; Prommer, 2015), depression (Savitz *et al.,* 2009) and kinesia (Haleem *et al.,* 2007b). Serotonin interacts with most of the neurotransmitters such as (acetyl choline, glutamate, dopamine and GABA) and produce beneficial effects (Lucki *et al.,* 1994). In the frontal cortex the density of 5-HT-1A receptor and 5-HT-levels become increased when IMI administered acutely. Conversely, when IMI administered repeatedly the mass of 5-HT-1A receptor becomes reduced. It is reported that repeated treatment with IMI desensitized autoreceptors while sensitized postsynaptic receptors (Bijak, 1996; Albert, 2012). In the present study in both brain regions (striatum and midbrain) 5-HT metabolism become decreased following injections of IMI (fig. 4) without significant reduction in locomotion (fig. 1). fig. 4 recommended that repeated administration of IMI will possibly prevented the haloperidol-induced supersensitization of somatodendritic 5-HT-1A receptors by desensitization of these receptors (Albert, 2012; Nascimento *et al*., 2014).

Two (Haleem & Khan, 2003) and five (Samad and co-workers, 2007; fig. 2) weeks pre-treatment with haloperidol elicit 5-HT syndrome following 8-OH-DPAT administration. Additionally, co-treatment with IMI for 5 weeks reversed the 8-OH-DPAT-induced 5-HT syndrome (fig. 3).

Stimulation of somatodendritic 5-HT-1A receptors consequentially reduce the inhibitory control of serotonergic function on dopamine neurotransmission, that is reported mechanism of 8-OH-DPAT elicited-syndrome (Haleem and coworkers, 2004). Reserpine and haloperidol elicited reduction in the strength of 8-OH-DAPAT-induced 5-HT syndrome suggest the contribution

of dopamine D2 receptor in the whole mechanism (Haleem & Khan, 2003). The supersensitization of dopamine D2 receptor following repeated administration of haloperidol (Halperin *et al.* 1989). Fig. 4 showed that long term treatment with haloperidol also supersensitized somatodendritic 5-HT-1A receptors which results in additional inhibitory pressure of serotonergic system on locomotor activity might give marked hyperactivity as observed in animals. Conversely desensitization of somatodendritic 5-HT-1A receptor overturned the 8-OH-DPAT elicited hyperactivity (fig. 3) following co-treatment of IMI. While, fig 4 shows that co-treatment of IMI reversed the somatodendritic 5-HT-1A receptor reliant feedback.

CONCLUSION

Our study adds up the data concerning the method core the protective outcome of IMI on an animal model of TD. It is proven that alleviation of orofacial dyskinesia and augment in the sensitivity of somatodendritic 5-HT-1A receptor following prolong insertion of haloperidol is reversed by co-injection of IMI. It is obvious that influence of sensitized somatodendritic serotonergic on dopamine functions could be involved on the beginning of TD. Furthermore, it is suggested that IMI is not only useful as antidepressant drug in human, also helpful for the treatment of dyskinesias by stimulating somatodendritic 5-HT-1A receptors.

ACKNOWLEDGEMENT

The authors are thankful to Higher Education Commission (HEC) Pakistan to provide funding.

REFERENCES

Albert PR (2012). Transcriptional regulation of the 5-HT1A receptor: Implications for mental illness. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, **367**: 2402-2415.

Alex KD and Pehek EA (2007). Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. *Pharmacol. Ther.*, **113**: 296-320.

Arroyo L, Carreras R, Valent D, Peña R, Mainau E, Velarde A, Sabrià J and Bassols A (2016). Effect of handling on neurotransmitter profile in pig brain according to fear related behaviour. *Physiol. Behav.*, **167**: 374-381.

Barnes JM, Barnes NM and Couper SJ (1992). Behavioral pharmacology of 5-HT-3 receptor ligand. *Neurosci. Biobehav. Rev.*, **16**: 107.

Bijak M, Tokarski K, Czyrak A, Maćkowiak M and Wedzony K (1996). Imipramine increases the 5-HT1A receptor-mediated inhibition of hippocampal neurons without changing the 5-HT1A receptor binding. *Eur. J. Pharmacol.*, **305**: 79-85.

Birkenhäger TK and Pluijms EM (2016). Possible Synergy Between Electroconvulsive Therapy and Imipramine: A Case Report. *J. Psychiatr. Pract.*, **22**: 478-480.

Buhot MC, Martin S and Segu L (2000). Role of serotonin in memory impairment. *Ann. Med.*, **32**: 210-221.

Cardoso CC, Lobato KR, Binfaré RW, Ferreira PK and Rosa AO (2009). Santos AR, Rodrigues AL. Evidence for the involvement of the monoaminergic system in the antidepressant-like effect of magnesium. *Prog Neuropsychopharmacol. Biol. Psychiatry*, **33**: 235-242.

Casey DE (2004). Pathophysiology of antipsychotic drug-induced movement disorders. *J. Clin. Psychiatry*, **65**: 25-28.

Farde L, Nordstrom AL and Wiesel FA (1992). Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: Relation to extra-pyramidal side effects. *Arch. Gen. Psychiatry*, **49**: 538-544.

Haleem DJ (1992). Repeated corticosterone treatment attenuates behavioral and neuroendocrine responses to 8-hydroxy-2-(di-n-propylamino) tetralin in rats. *Life Sci.* **51**: 225-230.

Haleem DJ (2014). 5-HT-1A receptor-dependent control of nigrostriatal dopamine neurotransmission in the pharmacotherapy of Parkinson's disease and schizophrenia. *Behav. Pharmacol.*, **26**: 45-58.

Haleem DJ, Samad N and Haleem MA (2007a). Reversal of haloperidol-induced tardive vacuous chewing movements and supersensitive somatodendritic serotonergic response by buspirone in rats. *Pharmacol. Biochem. Behav.*, **87**: 115-121.

Haleem DJ, Samad N and Haleem MA (2007b). Reversal of haloperidol-induced extra pyramidal symptoms by buspirone: A time-related study. *Behav. Pharmacol.*, **18**: 147-53.

Haleem DJ and Parveen T (1994). Brain regional serotonin synthesis following adaptation to repeated restraint. *Neuroreport*, **5**: 1785-1788.

Haleem DJ and Khan NH (2003). Enhancement of serotonin-1A receptor dependent responses following withdrawal of haloperidol in rats. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **27**: 645-651.

Haleem DJ, Shireen E and Haleem MA (2004). Somatodendritic and postsynaptic serotonin-1A receptors in the attenuation of haloperidol-induced catalepsy. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **28**: 1323-1329.

Halperin R, Gueri JJ Jr and Davis KL (1989). Regional differences in the induction of behavioral supersensitivity by prolonged treatment with atypical neuroleptics. *Psychopharmacology (Berl).* **98**: 386-391.

Jacob BL and Azmitia EC (1992). Structure and function of brain serotonin system. *Physiol. Rev.*, **72**: 165-229.

Kapur S (1996). 5-HT2 antagonism and EPS benefits: is there a causal connection? *Psychopharmacology (Berl).* **124**: 35-39.

Karl T, Duffy L, O'brien E, Matsumoto I and Dedova I (2006). Behavioral effects of chronic haloperidol and risperidone treatment in rats. *Behav. Brain. Res.*, **171**: 286-294.

Kelland MD, Freeman AS and Chiodo LA (1990). Serotonergic afferent regulation of the basic physiology and pharmacological responsiveness of nigrostriatal dopamine neurons. *J. Pharmacol. Exp. Ther.*, **253**: 803-811.

Klawans HL Jr. Rubovits (1972). An experimental model of tardive dyskinesia. *J. Neural. Transm.,* **33**: 235-346.

Lau YS, Petroske E, Meredith GE and Wang JQ (2003). Elevated neuronal nitric oxide synthase expression in chronic haloperidol-treated rats. *Neuropharmacology*, **45**: 986-94.

Lister J, Andreazza AC, Navaid B, Wilson VS, Teo C, Nesarajah Y, Wilson AA, Nobrega JN, Fletcher PJ and Remington G (2017). Lipoic acid and haloperidol-induced vacuous chewing movements: Implications for prophylactic antioxidant use in tardive dyskinesia. *Prog Neuropsychopharmacol. Biol. Psychiatry,* **4**(72): 23-29.

Lucki I, Singh A and Kreiss DS (1994). Antidepressant-like behavioral effects of serotonin receptor agonists. *Neurosci. Biobehav. Rev.,* **18**: 85-95.

Nascimento JO, Kikuchi LS, de Bortoli VC, Zangrossi H Jr and Viana MB (2014). Dorsomedial hypothalamus serotonin 1A receptors mediate a panic-related response in the elevated T-maze. *Brain Res. Bull*, **109**: 39-45.

Neal-Beliveau BS, Joyce JN and Lucki I (1993). Serotonergic involvement in haloperidol-induced catalepsy. *J. Pharmacol. Exp. Ther.,* **265**: 207-217.

Prommer E. (2015) Aripiprazole: A New Option in Delirium. *Am. J. Hosp. Palliat. Care,* doi:10.1177/1049909115612800

Rogóz Z, Skuza G and Legutko B (2007). Repeated co-treatment with imipramine and amantadine induces hippocampal brain-derived neurotrophic factor gene expression in rats. *J. Physiol. Pharmacol.,* **58**: 219-234.

Samad N (2015). Rice bran oil prevents neuroleptic-induced extra pyramidal symptoms in rats: Possible antioxidant mechanisms. *J. Food Drug Analysis,* **23**: 370-375.

Samad N and Haleem DJ (2014). Haloperidol-induced extra pyramidal symptoms attenuated by imipramine in rats. *Pak. J. Pharm. Sci.,* **27**: 1497-1501.

Samad N, Haleem MA and Haleem DJ (2016). Protective effects of rice bran oil in haloperidol-induced tardive dyskinesia and serotonergic responses in rats. *Pak. J. Pharm. Sci.,* **29**: 1467-1471.

Samad N, Khan A, Perveen T, Haider S and Abdul Haleem M (2007). Increase in the effectiveness of somatodendritic 5-HT-1A receptors in a rat model of tardive dyskinesia. *Acta. Neurobiol. Exp.*, **67**: 389-397.

Savitz J, Lucki I and Drevets WC (2009). 5-HT_{1A} receptor function in major depressive disorder. *Prog. Neurobiol.,* **88**: 17-31.

Scheggi S, Marchese G, Grappi S, Secci ME and De Montis MG (2011). Cocaine sensitization models an anhedonia-like condition in rats. *Int. J. Neuropsychopharmacol.*, 14: 333-346.

Shireen E (2016). Experimental treatment of antipsychotic-induced movement disorders. *J. Exp. Pharmacol.,* **8**: 1.

Shireen E and Haleem DJ (2005). Motor effects of buspirone: Relationship with dopamine and serotonin in the striatum. *J. Coll. Physicians Surg. Pak,* **15**: 753-756.

Shireen E and Haleem DJ (2011). Reversal of haloperidol-induced motor deficits by mianserin and mesulergine in rats. *Pak J Pharm Sci,* 24: 7-12.

Turrone P, Remington G, Kapur S and Nobrega JN (2003). Differential effects of within-day continuous vs. transient dopamine D2 receptor occupancy in the development of vacuous chewing movements (VCMs) in rats. *Neuropsychopharmacology,* **28**: 1433-1439.

Ugedo L, Grenhoff J and Stevensson TH (1989). Ritanserin, a 5-HT2 receptor antagonist, activates midbrain dopamine neurons by blocking serotonergic inhibition. *Psychopharmacology (Berl).* **98**: 45-50.

Wąsik A, Możdżeń E, Romańska I, Michaluk J and Antkiewicz-Michaluk L (2013). Antidepressant-like activity of the endogenous amine, 1-methyl-1,2,3,4-tetrahydroisoquinoline in the behavioral despair test in the rat, and its neurochemical correlates: a comparison with the classical antidepressant, imipramine. *Eur. J. Pharmacol.*, **700**: 110-117.

Wedenberg ML (1996). Serotonergic mechanism in neuroleptic-induced catalepsy in the rat. *Neurosci. Biobehav. Rev.,* **20**: 325-339.

Woźniak M, Gołembiowska K, Noworyta-Sokołowska K, Acher F, Cieślik P, Kusek M, Tokarski K, Pilc A and Wierońska JM (2016). Neurochemical and behavioral studies on the 5-HT_{1A}-dependent antipsychotic action of the $mGlu_4$ receptor agonist LSP4-2022. *Neuropharmacology,* Pii: S0028-3908(16)30278-7.