ORIGINAL ARTICLE

Effect of Mirtazapine Pre-treatment on Haloperidol, Ergometrine and Fluoxetine Induced Behaviours in Albino Rats

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Abstract:

Background: Central 5-HT_{2A} and 5-HT_{2C} serotonergic receptors are mainly involved in the control of nigrostriatal and mesolimbic dopaminergic neuronal activity has been well proved and established. 5-HT has facilitatory effect on stimulated dopamine release by stimulating central 5-HT_{2A} receptors and inhibitory effect by stimulating 5-HT_{2C} receptors. *Aim and Objectives:* To evaluate 5-HT_{2A} and 5-HT_{2C} receptor blocking activity of Mirtazapine (MIR) and the effect of mirtazapine pre-treatment on Ergometrine (ERG) induced behaviours, Fluoxetine (FLU) induced penile erections and Haloperidol (HAL) induced catalepsy in rats. *Material and Methods*: Each group was subdivided into different subgroups consisting 6 animals in each. Control group received Dimethyl Sulfoxide (DMSO) and other groups received different doses of mirtazapine one hour before ERG/FLU/HAL. Values obtained from control group were compared with all remaining groups pre-treatment with different doses of MIR. *Results*: MIR (MIR) at 2.5, 5, 10 and 20 mg/kg intraperitoneally (i.p) did not produce any *per se* effects. Pre-treatment with 5, 10 and 20 mg/kg i.p. MIR significantly antagonised ERG induced behaviours. 5 mg/kg i.p. MIR significantly antagonised whereas 10 and 20 mg/kg i.p. MIR abolished FLU (10 mg/kg) induced penile erections in rats. MIR 5 and 20 mg/kg i.p. significantly antagonised HAL (1mg/kg) induced catalepsy at 1 hr testing time interval while 10 and 20 mg/kg MIR significantly antagonised HAL (1 mg/kg) induced catalepsy at 2 hr testing time interval. *Conclusion*: Our results indicate that MIR at 5, 10 and 20 mg/kg possesses 5-HT_{2A} and 5-HT_{2C} receptors blocking activity. At 5, 10 and 20 mg/kg MIR, by blocking central 5-HT_{2C} receptors predominantly, causes release of dopamine from nigrostriatal dopaminergic neurons and therefore antagonizes HAL induced catalepsy.

Keywords: Mirtazapine, Ergometrine, Fluoxetine, Haloperidol, Catalepsy, Penile Erections

Introduction:

Many studies have established an anatomical connection between the central serotonergic pathway and nigrostriatal dopaminergic pathway. 5-HT neurons originate from midbrain raphe nuclei and innervate the Substantia Nigra (SN), Ventral Tegmental Area (VTA), the striatum, nucleus accumbens and the frontal cortex [1, 2] In the SN the serotonergic terminals make synaptic connections with both dopaminergic and non dopaminergic neurons i.e. Gamma Amino Butyric Acid (GABA) neurons [1, 3, 4]. Many studies have established the presence of 5-HT_2 receptors in the cell bodies and terminal area of the nigrostriatal dopaminergic system. The presence of 5-HT_{2A} and 5-HT_{2C} receptors with their messenger ribonucleic acid (mRNA) in the SN, VTA, striatum, nucleus accumbens in rat brain have been established by different radiographic and histochemistry studies

[1, 4, 5]. The involvement of central serotonergic receptors, mainly 5-HT_{2A} and 5-HT_{2C} in the control of nigrostriatal and mesolimbic dopaminergic neurotransmission is well established [6-8]. It has been accepted that 5-HT_{2A} and 5-HT_{2C} receptors exert opposite effect on dopamine release. 5-HT produces facilitatory effect on stimulated dopamine release by stimulating central 5-HT_{2A} receptors [9]. 3-4 methylenedioxymethamphetamine, a 5-HT_{2A} receptor agonist increases DA release [10] and 5-HT_{2A} receptor antagonists decrease dexamphetamine mediated DA release in striatum and nucleus accumbens [11-12]. On the other side central 5-HT_{2C} receptor agonist decreases and its antagonist increases dopamine release from nigrostriatal, mesolimbic and mesocortical dopaminergic neurons [7, 13-19]. From these observations it has been proved that 5-HT has a facilitatory and inhibitory control on the dopaminergic neurotramission in nigrostriatal, mesolimbic and mesocortical dopaminergic pathway through stimulation of 5-HT_{2A} and 5-HT_{2C} receptors respectively. In the present study we have determined the dosage range at which Mirtazapine (MIR) has 5-HT_{2A} and 5-HT_{2C} receptor blocking activity, by studying the effect of MIR pre-treatment on Ergometrine (ERG) induced behaviours and Fluoxetine (FLU) mediated penile erections in albino rats. The serotonergic behaviours viz head and whole body shakes, reciprocal forepaw treading, lateral head weaving, flat body posture and hind limb abduction and the Head-Twitch Response (HTR) in mice are due to central 5-HT_{2A} and 5-HT_{1A} receptor stimulation. ERG produces serotonergic behaviours in rats and HTR in mice by its direct action i.e. through stimulation of central 5-HT_{2A} receptors [20, 21]. Penile erections in rats are produced due to direct as well as indirect stimulation of central 5-HT_{2C} receptors [22-24]. FLU induces penile erections in male rats by directly stimulating central 5-HT_{2C} receptors [23, 25-29]. Catalepsy , a state in which animal is unable to correct externally imposed posture, is due to functional lack of dopamine at postsynaptic striatal dopaminergic D_2 and D_1 receptors in striatum [30, 31]. Based on above observations, we aimed with objectives to study the effect of 5, 10, 20 mg/kg MIR pre-treatment on ERG induced behaviours, FLU induced penile erections and HAL induced catalepsy in rats.

Material and Methods:

Animals:

Albino Wistar rats of either sex weighing 100-200 g were used for all study groups except for the FLU study group, where we used only male albino rats. They were bred in Central Animal House, Krishna Institute of Medical Sciences Karad. The animals were kept under standard conditions and allowed free access to food and water up to the time of experimentation. The animals were brought to the department and kept in laboratory, at least 1 hr before the experiments for acclimatization to the laboratory environment. Six animals were included in each group. Each animal was used only once. All observations were made blind with respect to the treatments used. The experimental protocol was approved by the Institutional Animal Ethics Committee and conducted according to Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines.

Drugs:

Drugs used were Mirtazapine (Cipla, Panvel, India), Ergometrine maleate (Boehringer, Germany), fluoxetine hydrochloride (Sun Pharmaceuticals, Baroda, India) in pure powder form and Haloperidol (RPG Life Sciences, Ankleshwar, India) was used in injection form. MIR was dissolved in Dimethyl Sulfoxide (DMSO). HAL injection solution was diluted to required strength with Distilled Water (DW). All drug solutions were prepared freshly and immediately before use and injected intraperitoneally (i. p.). The volume of injection for all drugs was 2 ml/kg body weight. About 5, 10, 20 and 40 mg/kg of MIR doses were studied in rats to rule out *per se* effects of it.

ERG Induced Behavioural Syndrome in Rats

Animals were placed for observation individually in Perspex cages (30×20×20cm) immediately after the injection of 10 mg/kg ERG. Each rat was observed for 1 min, once after every 5 min, between 10 and 125 min timing after injection of ERG (i.e. for 20 scoring periods, each period of 1 min duration). Animal behaviours were assessed by the method of Sloviter *et al*. [32].

Five individual 5-HT mediated behaviours viz. head and whole body shakes, reciprocal forepaw treading, lateral head weaving, flat body posture and hind limb abduction were observed. Every animal was scored separately 0 or 1 i.e. absence or presence of that particular behaviour. Each animal was tested for 20 testing time intervals. The maximum possible score per animal at each testing time interval will be 5. MIR was injected 1 hr before ERG.

Group	Treatment used
1.	DMSO (2 ml/kg) + ERG10 (10 mg/kg)
2.	MIR5 (5 mg/kg) + ERG10 (10 mg/kg)
3.	MIR10 (10 mg/kg) + ERG10 (10 mg/kg)
4.	MIR20 (20 mg/kg) + ERG10 (10 mg/kg)

FLU Induced Penile Erections (PEs) in Rats

We followed the methodology of Berendsen and Broekkamp [22]. For the observations of vehicle (2 ml/kg ip, control group) and FLU (10 mg/kg) induced PEs, the rats were placed in individual perspex cages (30×20×20cm) immediately after the injection of vehicle and FLU. MIR was injected 1 hr before FLU. Control group received vehicle (2 ml/kg i.p.) 1 hr before receiving FLU. Total numbers of PEs were counted between 5 and 60 min observation period. The total number of PEs scored by each rat in the group was taken to compute the mean value of the group.

Group	Treatment used
1.	DMSO (2 ml/kg) only
2.	DMSO + FLU10 (10 mg/kg)
3.	MIR5 (5 mg/kg) + FLU10 (10 mg/kg)
4.	MIR10 (10 mg/kg) + FLU10 (10 mg/kg)
5.	MIR20 (20 mg/kg) + FLU10 (10 mg/kg)

Catalepsy Testing in Rats

Rats were placed for observation and measurement of catalepsy in individual perspex cages (30×20×20cm), 30 min before drug treatment to allow adaptation to the new environment. Catalepsy was evaluated by placing both front limbs of the animal over an 8 cm high wooden block and the time for which the animal maintains the imposed posture was measured. Scoring was done according to Costall and Naylor [18]. Animal maintaining the imposed posture for 0 to 10 sec was scored 0; 11 to 30 sec was scored 1; 31 to 60 sec was scored 2; 61 to 120 sec was scored 3; and 121 sec and above was scored 4. Animals were tested and scored for catalepsy at 1 and 2 hrs after HAL treatment. Catalepsy score of each animal in the group was taken at the respective testing time intervals to compute the mean value of the group for that particular timing. MIR was injected 1 hr before HAL and the control group received vehicle (2 ml/kg i.p.) 1 hr before receiving HAL.

Group	Treatment used
1.	DMSO (2 ml/kg) + HAL 1 (1mg/kg)
2.	MIR5 (5 mg/kg) + HAL 1 (1mg/kg)
3.	MIR10 (10 mg/kg) + HAL 1 (1mg/kg)
4.	MIR20 (20 mg/kg) + HAL 1 (1mg/kg)

Data Analysis:

Data was analysed using non-parametric ANOVA, Kruskal Wallis test followed by post hoc Dunn's multiple comparison test (Graph pad Instat). p value of less than 0.05 ($p < 0.05$) was taken as statistically significant.

Results:

In preliminary experiments 2.5 to 20 mg/kg of MIR did not produce any gross behavioural changes viz. dopaminergic receptor (D_2 and D_1) mediated stereotyped behaviour or serotonergic receptor mediated behaviours (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}). MIR 40 mg/kg dose had produced shivering, sniffing and hypotonia in all animals. For subsequent studies, MIR was therefore used in the dose range of 5 to 20 mg/kg.

Effect of MIR Pre-treatment on ERG induced Behavioural Syndrome in Rats

The results are given in Table 1 and 2. Rats pretreated with 10 mg/kg ERG had induced the 5-HT_{2A} receptor mediated behavioural syndrome viz. head and whole body shakes, reciprocal forepaw treading, lateral head weaving, flat body posture and hind limb abduction. Pre-treatment with 5, 10 and 20 mg/kg MIR significantly decreased the intensity of the behavioural syndrome induced by 10 mg/kg ergometrine.

Table 1: Mean ± SD of 5, 10, and 20 mg /kg MIR Pre-treatment at Different Testing Time Intervals as Compared with ERG Induced Behaviours in Rats

Testing Time Interval in (min)	Control + ERG 10 Mean ± SD	Study Groups		
		MIR5 + ERG 10 Mean ± SD	MIR10 + ERG 10 Mean ± SD	MIR20 + ERG 10 Mean ± SD
10	2.50 ± 0.54	2.16 ± 0.40•	**0.00 ± 0.00*** **	**0.33 ± 0.51** **
16	2.00 ± 0.63	1.33 ± 0.51•	0.83 ± 0.40•	**0.16 ± 0.40*** **
22	2.33 ± 0.51	1.33 ± 0.51•	**0.66 ± 0.51***	**0.16 ± 0.40*** **
28	2.16 ± 0.40	0.66 ± 0.51•	**0.50 ± 0.54***	**0.16 ± 0.40*** **
34	2.50 ± 0.54	1.00 ± 0.00•	**0.66 ± 0.81***	**0.00 ± 0.00*** **
40	2.33 ± 0.51	**0.50 ± 0.54***	**0.16 ± 0.40** **	**0.50 ± 0.54***
46	2.50 ± 0.54	0.83 ± 0.40•	**0.50 ± 0.83** **	**0.50 ± 0.54** **
52	2.16 ± 0.75	0.83 ± 0.40•	**0.33 ± 0.51** **	**0.50 ± 0.54***
58	2.50 ± 0.54	**0.50 ± 0.54***	**0.33 ± 0.51** **	**0.50 ± 0.54***
64	2.33 ± 0.81	**0.33 ± 0.51***	**0.00 ± 0.00** **	**0.00 ± 0.00** **
70	2.33 ± 0.81	**0.16 ± 0.40** **	**0.33 ± 0.51** **	**0.00 ± 0.00** **
76	2.16 ± 0.40	**0.00 ± 0.00*** **	**0.16 ± 0.40** **	**0.00 ± 0.00*** **
82	2.16 ± 0.40	**0.00 ± 0.00*** **	**0.16 ± 0.40** **	**0.00 ± 0.00*** **
88	1.83 ± 0.75	**0.00 ± 0.00*** **	**0.16 ± 0.40** **	**0.00 ± 0.00*** **
94	1.66 ± 0.51	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **
100	2.00 ± 0.00	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **
106	1.66 ± 0.51	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **
112	1.66 ± 0.51	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **
118	2.00 ± 0.63	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **
124	1.66 ± 0.51	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **	**0.00 ± 0.00*** **

*Statistically Significance level at 5, 10 and 20 mg/kg Mirtazapine for different testing time intervals as compared to control group ***p<0.001, **p<0.01, *p<0.05, •Non significant with control group*

Table 2: Percentage Change of 5, 10, and 20 mg/kg MIR Pre-treatment + ERG 10 mg/kg at Different Testing Time Intervals with respect to ERG Induced Behaviours in Rats

Testing Time Interval in (min)	Study Groups		
	MIR5 + ERG10	MIR10 + ERG10	MIR20 + ERG10
10	-13.60	-100.00	- 86.80
16	-33.50	-58.50	-92.00
22	-42.91	-71.67	-93.13
28	-69.44	-76.85	- 92.59
34	-60.00	-73.60	-100.00
40	-78.54	-93.13	-86.33
46	-66.80	-80.00	-80.00
52	-61.57	-84.72	-76.85
58	-80.00	-86.80	-80.00
64	-85.83	-100.00	-100.00
70	-93.13	-85.83	-100.00
76	-100.00	-92.59	-100.00
82	-100.00	-92.59	-100.00
88	-100.00	-91.25	-100.00
94	-100.00	-100.00	-100.00
100	-100.00	-100.00	-100.00
106	-100.00	-100.00	-100.00
112	-100.00	-100.00	-100.00
118	-100.00	-100.00	-100.00
124	-100.00	-100.00	-100.00

Effect of MIR Pre-treatment on FLU induced Penile Erections in Male Rats

The results are given in Table 3 and Fig 1. FLU (10 mg/kg) treated group pre-treated with DMSO exhibited a significant increase in the number of PEs as compared to control (DMSO 2ml/kg i.p treated) group. Pre-treatment with 5 mg/kg MIR had significantly decreased where as 10 and 20 mg/kg MIR abolished PEs induced by 10 mg/kg FLU in male rats.

Table 3: Mean ± SD of 5, 10, and 20 mg/kg MIR Pre-treatment + 10 mg/kg FLU as Compared with 10 mg/kg FLU Induced Penile Erections of Male Rats in 1 hour

Mean ± SD	DMSO	DMSO + FLU10	Study Groups		
			MIR5 + FLU10	MIR10 + FLU10	MIR20 + FLU10
1 Hour	0.33± 0.51	3.33± 1.50*	0.16 ± 0.40**	0***	0***

**P < 0.05 as compared to the vehicle (DMSO, 2 ml/kg ip) treated control group. Statistically significance level at 5, 10 and 20 mg/kg MIR + FLU as compared to DMSO+ FLU 10mg/kg group. ***p<0.001, **p<0.01*

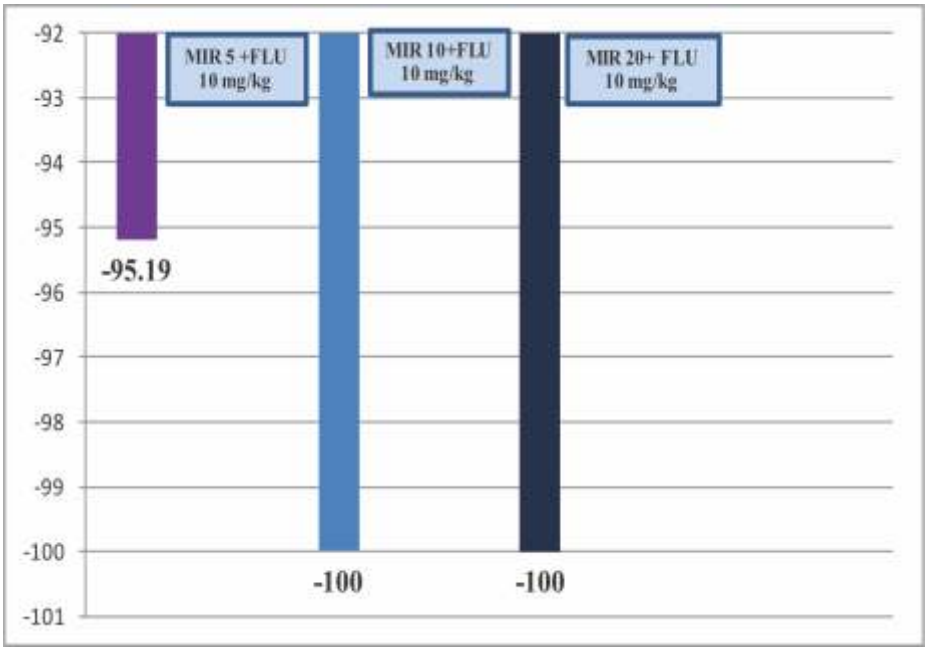

Fig. 1: Percentage Change of 5, 10, and 20 mg/kg MIR Pretreatment + 10 mg / kg FLU with respect to 10 mg/kg FLU Induced Penile Erections in Male Rats in 1 hour

Effect of MIR Pretreatment on HAL induced Catalepsy in Rats

The results are given in Table 4 and Fig 2. Pre-treatment with 5 and 20 mg/kg MIR significantly decreased cataleptic effect of 1 mg/kg HAL at 1 hour testing time interval. Pre-treatment with 10 and 20 mg/kg had very significantly decreased the cataleptic effect of 1mg/kg HAL at 2 hour testing time interval.

Table 4: Mean ± SD of 5, 10, and 20 mg/kg MIR Pretreatment + 1mg/kg HAL as Compared with 1mg/kg HAL Induced Catalepsy of Rats at 1 hour and 2 hours

Mean ± SD	Control + HAL 1	Study Groups		
		MIR5 + HAL 1	MIR10 + HAL 1	MIR20 + HAL 1
1 Hour	2.83 ± 0.75	0.66 ± 0.51*	1.0 ± 0.63	0.33 ± 0.51**
2 Hours	2.83 ± 0.98	1.0 ± 0.63	0.83 ± 0.75*	0.5 ± 0.54**

Statistically significance level at 5, 10 and 20 mg/kg MIR + HAL 1mg/kg as compared to control group
***p<0.01, *p<0.05*

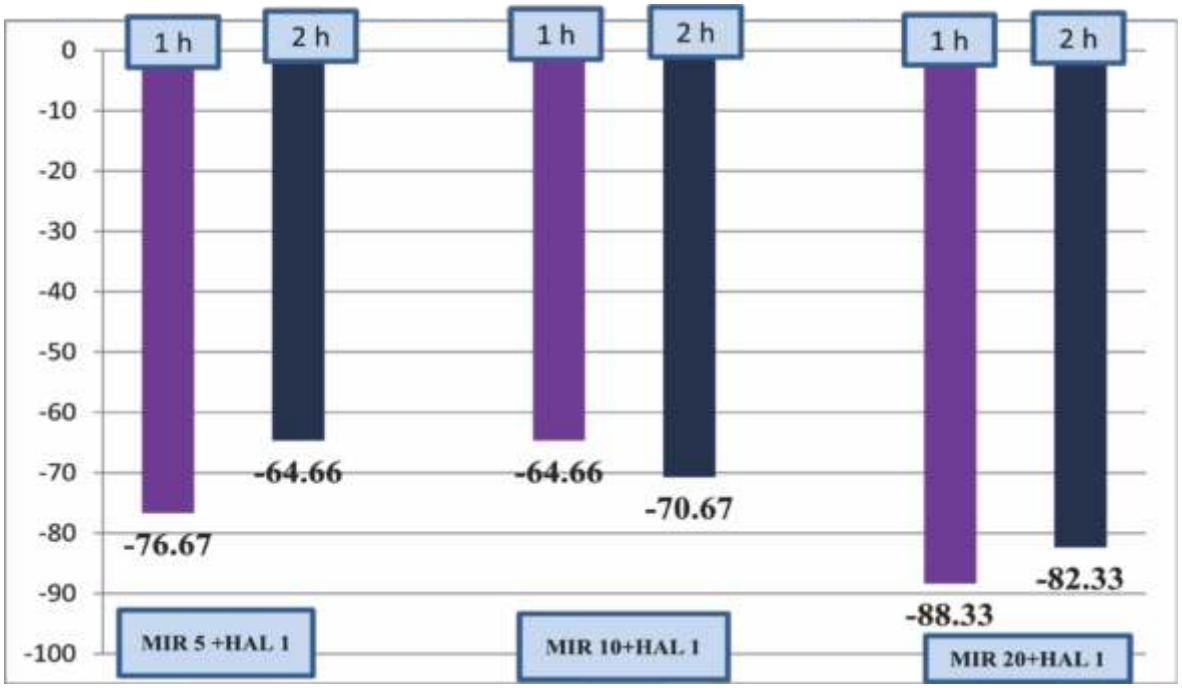

Fig. 2: Percentage Change of 5, 10, and 20 mg/kg MIR Pretreatment + 1mg/kg HAL with respect to 1mg/kg HAL Induced Catalepsy of Rats at 1 hour and 2 hours

Discussion:

In our study, pre-treatment with 5, 10 and 20 mg/kg MIR had significantly antogonised 5-HT_{2A} receptor mediated behaviours induced by ERG in rats. 5 mg/kg MIR had significantly decreased where as 10 and 20 mg/kg MIR had abolished PEs induced by FLU. Above results suggest that at these doses MIR act as 5-HT_{2A} and 5-HT_{2C} receptor antagonist.

MIR 5 mg/kg and 20 mg/kg i.p. had significantly antagonised HAL (1mg/kg) induced catalepsy at 1 hr testing time interval while 10 and 20 mg/kg MIR had significantly antagonised HAL (1 mg/kg) induced catalepsy at 2 hr testing time intervals. As it was already observed 5, 10 and 20 mg/kg MIR had exerted 5-HT_{2A} and 5-HT_{2C} blocking activity. Antagonism of HAL induced catalepsy by MIR pretreatment is explained as given below.

HAL induces catalepsy by blocking the nigrostriatal postsynaptic striatal D_2 and D_1 dopamine receptors [33]. In addition, following the blockade of the pre and postsynaptic striatal D_2DA receptors by HAL, there is a compensatory feed-back increase of nigrostriatal dopaminergic neuronal activity, which is associated with an allosteric activation of tyrosine hydroxylase enzyme and there is an increase in synthesis and release of dopamine from nigrostriatal dopaminergic neurons which counteracts to some extent the HAL induced catalepsy i.e. HAL induced blockade of the postsynaptic striatal D_1 and D_2 dopamine receptors [7,34]. 5-HT_{2A} receptors are located on the nigrostriatal dopaminergic neurons. Activation of these receptors by 5-HT or 5HT_{2A} agonists increases the release of dopamine from nigrostriatal dopaminergic neurons [35]. In contrast, 5-HT_{2C} receptors are located on the striatonigral, striatal and nigral GABAergic neurons. Their activation by 5-HT or 5-HT_{2C} receptor agonists causes release of GABA in the SN and striatum. The released GABA stimulates the $GABA_B$ receptors located on the nigrostriatal dopaminergic neurons and inhibits the activity of the nigrostriatal dopaminergic neurons [35]. Therefore 5-HT_{2A} receptor activation increases where as 5 HT_{2C} receptor activation decreases the HAL induced dopamine release which occurs during compensatory "feed–back" increase of the nigrostriatal dopaminergic neuronal activity due to HAL induced blockade of the pre and post synaptic striatal D_2 dopamine receptors. Therefore 5HT_{2A} receptor activation, by increasing the release of dopamine from nigrostriatal dopaminergic neurons, will counteract the HAL induced blockade of the post synaptic striatal D_1 and D_2 dopamine receptors with resultant antagonism of HAL catalepsy. But 5-HT_{2C} receptor activation, by decreasing the release of dopamine from the nigrostriatal dopaminergic neurons will enhance HAL induced blockade of the post synaptic striatal D_1 and D_2 dopamine receptors with resultant potentiation of HAL catalepsy. MIR induced blockade of central 5-HT_{2C} receptors removes inhibitory control of 5-HT on nigrostriatal dopaminergic neurons. As a result there is an increase in synthesis as well intraneuronal stores of DA therefore more DA is available for release during HAL induced compensatory feedback increase of nigrostriatal dopaminergic neuronal activity. As a result HAL induced blockade of postsynaptic striatal D1 and D2 DA receptors is counteracted to the greater extent with resultant antagonism of HAL induced catalepsy. In addition

many studies have found high densities of mRNA for 5-HT_{2C} receptors and low densities of mRNA for 5-HT_{2A} binding sites in substantia nigra and nucleus accumbens[1].The 5-HT_{2C} receptor mediated inhibitory effect is likely to predominate over 5-HT_{2A} receptor mediated facilitatory effect of 5-HT on nigrostriatal dopaminergic transmission. This suggests that 5-HT_{2C} receptor antagonistic effect of MIR on nigrostriatal dopaminergic transmission had predominated over 5-HT_{2A} receptor antagonism.

This observation is in agreement with the finding of Balsara *et al.* [36] and Reavill *et al.* [37] that HAL induced catalepsy was reversed by pre-treatment with trazadone, a 5-$HT_{2A/2C}$ receptor antagonist and SB228357, a 5-HT_{2C} receptor antagonist respectively. In addition, our results are supported by the findings in another study that in vivo SB06553, a 5-HT_{2C} antagonist increased accumbal and striatal dopamine release in a dose dependent manner [35, 38]. Again, according to Berendsen *et al*. [39], MIR attenuated HAL induced catalepsy maximum at 90 mins after its treatment in rats. MIR had showed therapeutic potency in MPTP induced mice model of Parkinson's disease [40]. HAL induced catalepsy is an animal model for evaluation of drugs effective in treatment of Parkinson's disease, Extrapyramidal Side Effects (EPS) and tardive dyskinesia produced by typical antipsychotics. So we can hypothesize that MIR may be beneficial in Parkinson's disease patient having associated depression, drug induced parkinsonism as well as in schizophrenic patient having negative symptoms and showing EPS to typical antipsychotics .

Conclusion:

MIR at 5, 10 and 20 mg/kg possesses 5-HT_{2A} and 5-HT_{2C} receptors blocking activity. At these doses of MIR, by blocking central 5-HT_{2C} receptors removes inhibitory control of 5-HT on nigrostriatal dopaminergic system. Therefore there was increase in synthesis and release of dopamine which resulted into antagonism of HAL induced catalepsy.

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