Original article

Effect of Mirtazapine, a 5-$HT_{2A/2C}$Antagonist Pre-treatment on Stereotyped Behaviour Induced by Apomorphine and Dexamphetamine in Albino Wistar Rats

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Abstract:

Background - Mirtazapine is a unique, atypical antidepressant with 5-$HT_{2A/2C}$ receptor antagonistic activity. Many studies have shown that serotonin (5-HT) acts through 5-HT receptors in the different areas of brain and modulates dopaminergic neuronal activity as well as dopamine release from nigrostriatal dopaminergic neurons. There are established 14 subtypes of 5-HT receptors from which central 5-HT_{2A}receptors have facilitatory effect whereas 5-HT_{2C} receptors have inhibitory effect on nigrostriatal dopaminergic neurons. The aim of study is to evaluate effect of mirtazapine (MIR) 5-$HT_{2A/2C}$ antagonist pre-treatment on Stereotyped Behaviour (SB) induced by Apomorphine (APO) and Dexamphetamine (DAM) in rats.

Material and Methods–Rats divided in 4 main groups and then each group was further subdivided further into 4 subgroups(n = 6). In each main group, one subgroup received dimethyl sulfoxide (DMSO) and other subgroups received 5, 10 and 20 mg/kg mirtazapine pre-treatment intraperitoneally respectively. Then after one hour animals received the respective dose of APO /DAM then we scored SB in each rat at every 10 min testing time intervals for 90 and 180 min respectively. Control group values were compared with different doses valuesof MIR.

Results - Pre-treatment with 5, 10 and 20 mg/kg mirtazapine did not show significant influence on 1.5 and 3 mg/kg apomorphine induced SB in rats but these doses showed significant potentiation of 5 and 10 mg/kg dexamphetamine induced SB in rats.

Conclusion - Mirtazapine did not show significant influence APO induced SB in rats indicates that MIR does not have direct DA receptor agonistic or antagonistic activity but these doses showed significant potentiation of DAM induced SB. Mirtazapine removes the inhibitory control of 5-HT on nigrostriatal dopaminergic neurons by blocking central 5-HT_{2C} receptors predominantly and results in potentiation of DAM induced SB.

Keywords: Mirtazapine Apomorphine Dexamphetamine Stereotyped Behaviour (SB)

Introduction

Serotonergic neurons originate from midbrain raphe nuclei and innervate the Substantia Nigra (SN), Ventral Tegmental Area (VTA) and the striatum[1,2,3,4]. Many studies have shown high density of 5-HT fibers inSNc (Substantia Nigra pars compacta), SNr (Substantia Nigra pars reticularis) and VTA[1,2,3,4]. In SNc, SNr and VTA these serotonergic neurons make synaptic connections with dopaminergic and nondopaminergic neurons i.e. Gamma Amino Butyric Acid (GABA) neurons[1,2,3,5]. SN contains highest 5-HT concentration. SNr receives a high dense 5-HT input than SNc. Futher the terminal areas of SN, VTA, striatum and nucleus accumbens receive serotonergic neuron input from raphe nuclei[1,2,3,4,6]. It has been established and proved that there are high to moderate levels of 5-HT_{2A} and 5-HT_{2C} receptor binding and corresponding messenger ribonucleic acid (mRNA) in basal ganglia, forebrain and limbic system[3,5,7,8]. The central serotonergic system exerts inhibitory control and facilitatory control on nigrostriatal and mesolimbic dopaminergic pathway activity through 5-HT_{2A} and5-HT_{2C} respectively[9,10]. Data from various studies indicates that 5-HT_{2A} agonism increases nigrostriatal dopaminergic pathway activity and dopamine release whereas antagonism decreases the same. In vivo microdialysis studies have established that systemic administration of SR46349B, the 5-HT_{2A} receptor antagonist inhibits haloperidol-induced DA release in the striatum[11]. 5-HT_{2A} antagonist M100907 blocked 3,4-methylenedioxymethamphetamine (MDMA) induced DA efflux in the striatum[12]. The 5-$HT_{2A/2C}$ receptor agonist, 2,5-Dimethoxy-4-iodoamphetamine hydrochloride (DOI) potentiated amphetamine-stimulated DA outflow[13]. The 5-$HT_{2A/C}$ receptor antagonist ritanserin infusions into the striatum or SN attenuated MDMA-induced DA release. Above data suggests the important role of striatal and nigral 5-HT_2 receptors in MDMA-evoked nigrostriatal DA release.

The 5-HT_{2C} receptor inverse agonist SB 206553 given systemically increases the firing of DA neurons in the SNc[10]. Although systemic administration of 5-HT_{2C} receptor agonists for e.g. selective agonist Ro 60-0175 decreases DA release in the striatum[14,15,16]. Systemic administration of antagonists (SB 242084)[15]and inverse agonists (SB 206553) at 5-HT_{2C} receptors increases DA efflux in the nigrostriatal region[10,15,17,18]. Above observations suggest that 5-HT_{2C} receptors mediate the tonic inhibition of the nigrostriatal pathway.

The Stereotyped Behaviour (SB) manifests as sniffing behaviour and of the oral movement variety (OMV) characterized by biting, gnawing and licking behaviour in rats.

Apomorphine, direct acting DA agonist in high doses produces the OMV of SB in rats by directly stimulating striatal postsynaptic D2 and D1DA receptors[19].The intensity of apomorphine induced SB therefore depends on the functional status of the postsynaptic striatal D2 and D1 DA receptors.The SB induced by apomorphine is quick in onset and short lasting because of its rapid metabolism. Dexamphetamine, indirect acting DA agonist produces SB of OMV indirectly in rats i.e. by releasing DA from the nigrostriatal dopaminergic neurons with resultant stimulation of striatal postsynaptic D2 and D1 receptors by released DA. The intensity of SB produced by dexamphetamine depends on the synthesis and intraneuronal stores of DA available for release as well as on the functional status of postsynaptic striatal D2 and D1 DA receptors[19,20].

Materials and Methods

Animals

Albino Wistar rats of either sex weighing 100-200 gm were used for all experiments. Animals were bred in Central Animal House of Krishna Institute of Medical

Sciences Karad. They were allowed free access to food and water up to the time of experimentation and kept under standard conditions. The animals were brought to the experimental lab one hour before experiment and kept in laboratory. Each group consisted six animals and each animal was used only once. All observations were made blind with respect to the treatments used. The 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), dexamphetamine sulphate (Sigma), apomorphine hydrochloride (Sigma) in pure powder form. Dimethyl sulfoxide (DMSO) was used as vehicle for mirtazapine. Apomorphine was dissolved in distilled water containing 0.2 mg/ml ascorbic acid while dexamphetamine was dissolved in distilled water. All drug solutions were prepared freshly and immediately before use and injected intraperitoneally. The volume of injection for all drugs was 2 ml/kg body weight. Doses referred to the drugs mentioned and are selected on the basis of previous studies conducted in our laboratory and those reported in literature. Perse effects of Mirtazapine in doses 5,10,20 and 40 mg/kg were studied in rats.

Stereotyped Behaviour (SB) Testing Induced by DA Agonists in Rats –

For observation of SB, rats were placed in individual cages made of wire netting, measuring 30×20×20cm, 30 min before drug treatment to allow adaptation to the new environment. Intensity of SB was assessed over a 30 sec observation period at 10 min intervals throughout its duration, using the scoring system of Costall and Naylor[21] in which animal showing periodic sniffing was scored 1, continuous sniffing was scored 2, periodic biting, gnawing or licking was scored 3 and continuous biting, gnawing or licking was scored 4. SB score of each animal in the group was taken at 10 min testing time interval to compute the mean value of the group for that particular timing. Mirtazapine was injected 1 hr before APO or DAM treatment. Control groups received vehicle (2 ml/kg body weight ip) 1 hr before receiving APO or DAM.

Group I	Treatment used
1.	DMSO (2 ml/kg) + APO 1.5 mg/kg
2.	MIR 5 mg/kg + APO 1.5 mg/kg
3.	MIR 10 mg/kg + APO 1.5 mg/kg
4.	MIR 20 mg/kg + APO 1.5 mg/kg
Group II	Treatment used
1.	DMSO (2 ml/kg) + APO 3 mg/kg
2.	MIR 5 mg/kg + APO 3 mg/kg
3.	MIR 10 mg/kg + APO 3 mg/kg
4.	MIR 20 mg/kg + APO 3 mg/kg
Group III	Treatment used
1.	DMSO (2 ml/kg) + DAM 5 mg/kg
2.	MIR 5 mg/kg + DAM 5 mg/kg
3.	MIR 10 mg/kg + DAM 5 mg/kg
4.	MIR 20 mg/kg + DAM 5 mg/kg

Group IV	Treatment used
1.	DMSO (2 ml/kg) + DAM10 mg/kg
2.	MIR 5 mg/kg + DAM 10 mg/kg
3.	MIR 10 mg/kg + DAM 10 mg/kg
4.	MIR 20 mg/kg + DAM 10mg/kg

Observations and Results

In preliminary experiments mirtazapine 2.5 to 20 mg/kg did not produce any gross behavioral changes viz dopaminergic receptor (D2DA) mediated stereotyped behaviour. Mirtazapine 40 mg/kg dose had produced shivering, sniffing and hypotonia in all animals. So, for subsequent studies, Mirtazapine was used in the dose range of 5 to 20 mg/kg.

Effect of Mirtazapine Pretreatment on Apomorphine Induced SB in Rats

The results are given in Table 1& 2. Pretreatment with mirtazapine (5 to 20 mg/kg) did not showed significant influence on apomorphine (1.5 and 3mg/kg) induced SB in rats.

Table1: Effect of Mirtazapine Pretreatment on Apomorphine Induced SB in Rats

Group **Testing Time Interval min**	**Control** **+** **APO 1.5 mg/kg** **Mean ± SD**	**MIR5** **+** **APO 1.5 mg/kg** **Mean ± SD**	**MIR10** **+** **APO 1.5 mg/kg** **Mean ± SD**	**MIR20** **+** **APO 1.5 mg/kg** **Mean ± SD**
10	2.16 ± 0.40	2 ± 0.00	1.83 ± 0.40	1.66 ± 0.51
20	2.16 ± 0.40	1.83 ± 0.75	1.83 ± 0.40	2.33 ± 0.51
30	2.16 ± 0.40	1.83 ± 0.40	2.16 ± 0.40	1.66 ± 0.51
40	2.16 ± 0.75	2 ± 0.0	2.16 ± 0.40	1.83 ± 0.75
50	2.16 ± 0.75	1.83 ± 0.40	2 ± 0.63	1.66 ± 0.51
60	1.33 ± 0.51	1.33 ± 0.81	1.66 ± 0.51	1.66 ± 0.51
70	1.5 ± 0.83	1 ± 0.63	1.66 ± 0.51	1 ± 0.63
80	1 ± 0.89	0.66 ± 0.81	1.33 ± 0.51	0.83 ± 0.98
90	0.66 ± 0.81	0.16 ± 0.40	0.5 ± 0.54	0.66 ± 1.03

Table 2: Effect of Mirtazapine Pretreatment on Apomorphine Induced SB in Rats

Group Testing Time Interval in min	Control + APO 3mg/kg Mean ± SD	MIR 5 + APO 3mg/kg Mean ± SD	MIR 10 + APO 3 mg/kg Mean ± SD	MIR 20 + AP0 3 mg/kg Mean ± SD
10	2±1.26	2±0.00	1.83±0.40	2±0.00
20	3±0.63	3±0.00	2±0.00*	2.33±0.51
30	3.5±0.54	3±0.00	3.16± 0.40	3±0.00
40	3.33±0.51	3.33±0.51	2.83±0.40	3±0.00
50	3±0.63	3.33±0.51	3±0.63	2.83±0.40
60	3.16±0.40	2.83±0.40	3±0.89	2.33±0.81
70	2.66±0.51	3±0.00	2±0.63	2.33±0.51
80	2±0.00	2.66±0.51	1.83±0.75	1.16±0.98
90	1.5±0.54	2.33±0.51	1±0.89	0.16±0.40

Table 3: Effect of Mirtazapine Pre-treatment on Dexamphetamine Induced SB in Rats

Group Testing Time Interval in min	Control + DAM 5 mg/kg Mean ± SD	MIR5 + DAM 5 mg/kg Mean ± SD	MIR10 + DAM 5 mg/kg Mean ± SD	MIR20 + DAM 5 mg/kg Mean ± SD
10	2.33 ± 0.51	2.83 ± 0.40 (21.45)	3 ± 0 (28.75)	2 ± 0 (14.16)
20	2.33 ± 0.51	2.83 ± 0.40 (21.45)	2.5 ± 0.54 (7.29)	3 ± 0.63 (28.75)
30	2.33 ± 0.51	2.83 ± 0.40 (21.45)	**4 ± 0***** (71.67)	3.33 ± 0.51 (41.63)
40	2.33 ± 0.51	3.16 ± 0.00 (35.62)	**4 ± 0***** (71.67)	**3.66 ± 0.51***(57.08)
50	2.16 ± 0.40	3.0 ± 0.40 (38.88)	**3.66 ± 0.51****(69.44)	**3.5 ± 0.54****(62.03)
60	2.33 ± 0.51	3.16 ± 0.40 (35.62)	3.5± 0.54 (50.21)	**4 ± 0***** (71.67)
70	2.33 ± 0.51	3.0 ± 0.00 (28.75)	**3.66 ± 0.51***(57.08)	**3.83 ± 0.40****(64.37)
80	2.0 ± 0.00	**3.5± 0.54*** (75)	**3.33 ± 0.51***(65)	**3.83 ± 0.40****(91)
90	2.16 ± 0.40	3.5 ± 0.54 (62.03)	**3.66 ± 0.51***(69.44)	**3.83 ± 0.40****(77.31)
100	2.16 ± 0.40	**3.66 ± 0.51***(69.44)	**3.66 ± 0.51***(69.44)	**3.83 ± 0.40****(77.31)
110	2.16 ± 0.40	3.16 ± 0.40 (46.29)	**3.5 ± 0.54*** (62.03)	**3.5 ± 0.54**** (62.03)
120	2.16 ± 0.40	3.33 ± 0.51 (54.16)	**3.66 ± 0.51****(69.44)	**3.5 ± 0.54*** (62.03)
130	2.16 ± 0.40	**3.5 ± 0.54*** (62.03)	3.33 ± 0.51 (54.16)	**3.5 ± 0.54*** (62.03)
140	2 ± 0	**3.33 ± 0.51****(66.50**)**	**3.16 ± 0.40*** (58)	**3.5 ± 0.54**** (75)
150	2 ± 0	2.83 ± 0.40 (41.50)	**3.16 ± 0.40*** (58)	**3.83 ±0.40*****(91.5)
160	1.5 ± 0.54	2.66 ± 0.51 (77.33)	3 ± 0 (100)	**3.83 ±0.40*****(155)
170	1.33 ± 0.51	2.5 ± 0.54 (87.96)	**3.33 ± 0.51**** (150)	**3.5 ± 0.54**** (163.15)
180	1.33 ± 0.51	2.33 ± 0.51 (75.18)	**3 ± 0*** (100)	**3.66 ±0.51*****(144)

TAB. 4 Effect of Mirtazapine Pre-treatment on Dexamphetamine Induced SB in Rats

Group Testing Time Interval in min	Control + DAM 10mg/kg Mean ± SD	MIR5 + DAM 10mg/kg Mean ± SD	MIR10 + DAM 10mg/kg Mean ± SD	MIR20 + DAM 10mg/kg Mean ± SD
10	1.33 ± 0.51	2 ± 0 (50.37)	1.83 ± 0.40 (37.59)	1.5 ± 0.54 (12.78)
20	2 ± 0	2 ± 0 (00)	2.66 ± 0.81(33)	2.16 ± 0.40 (08)
30	2.33 ± 0.51	2 ± 0 (25.56)	3.33 ± 1.21 (42.91)	2.83 ± 0.40 (21.45)
40	2.66 ± 0.51	2.66 ± 0.51 (00)	**3.5± 1.22*(31.57)**	3.5 ± 0.54 (31.57)
50	2.83 ± 0.40	3 ± 0 (06)	3.33 ± 1.21 (17.66)	**4 ± 0****(41.34)
60	3 ± 0	**3.83 ± 40***(27.66)	3.33 ± 1.21 (11)	**4 ± 0****(33.33)
70	2.66 ± 0.51	**4 ± 0**** (50.37)	3.33 ± 1.21 (25.18)	**4 ± 0****(50.37)
80	2.66 ± 0.81	**4 ± 0***(50.37)	3.33 ± 1.21 (25.18)	**4 ± 0***(50.37)
90	2.5 ± 0.54	**4 ± 0****(60)	3.33 ± 1.21 (33.20)	**4 ± 0****(60)
100	2.83 ± 0.40	**4 ± 0****(41.34)	3.33 ± 1.21 (17.66)	**4 ± 0****(41.34)
110	2.66 ± 0.51	**3.83 ± 0.40***(43.98)	3.16 ± 1.32 (18.79)	**4 ± 0****(50.37)
120	2.66 ± 0.51	3.66 ± 0.51 (37.59)	3.16 ± 1.32 (18.79)	**4 ± 0****(50.37)
130	2.5 ± 0.54	3.33 ± 1.21 (33.20)	3.16 ± 1.32 (12.64)	**4 ± 0****(60)
140	2 ± 0.63	3.33 ± 1.21 (66.50)	3.16 ± 1.32 (58)	3.66 ± 0.51 (83)
150	2.16 ± 0.75	3.5 ± 1.22 (62.03)	3.16 ± 1.32 (46.29)	3.5 ± 0.83 (62.03)
160	2.5 ± 1.04	3.5 ± 1.22 (40)	3 ± 1.5 (20)	3.33 ± 1.21 (13.32)
170	2.16 ± 0.98	3.5 ± 1.22 (62.03)	3 ± 1.5 (38.38)	3.16 ± 1.32 (46.29)
180	2.33± 1.03	3 ± 1.26 (28.75)	3 ± 1.5 (28.75)	3 ± 1.26 (28.75)

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.

Percentage Change in SB of 5, 10, and 20 mg /kg Mirtazapine Pre-treatment + DAM 10 mg/kg at Different Testing Time Intervals with respect to DAM 10 mg/kg is given in bracket.

Discussion

Mirtazapine at 5, 10 and 20 mg/kg did not significantly influence 1.5 and 3 mg/kg apomorphine induced SB in rats. Mirtazapine did not produce any effect on apomorphine induced stereotyped behavior. This indicates that mirtazapine doesnot have any inhibitory or facilitatory effect on central D1 and D2 receptors.

Pretreatment with 5, 10 and 20 mg/kg mirtazapine significantly potentiated the dexamphetamine SB in rats and also prolonged the duration of SB beyond 180 min up to 240 min. Amphetamine induces SB by releasing dopamine from the nigrostriatal dopaminergic neurons with resultant stimulation of the postsynaptic striatal D_1 and D_2 dopamine receptors by the released dopamine[18,19].

In our study, pretreatment with 5, 10 and 20 mg/kg mirtazapine did not potentiate apomorphine stereotypy. It suggests that the potentiation of dexamphetamine stereotyped behaviour by 5, 10 and 20mg/kg mirtazapine is not due to any facilitatotry effect of these doses of mirtazapine at or beyond the post synaptic nigrastriatal D_1 and D_2 dopamine receptors. This potentiation of 5 and 10 mg/kg dexamphetamine stereotypy by 5, 10 and 20mg/kg doses of mirtazapine is explained as given below

Many studies have found that high densities of mRNA for 5-HT_{2C} receptors and low densities 5-HT_{2A} binding sites in SN 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. In our study we have confirmed that mirtazapine is a unique atypical antidepressant having $5HT_{2A/2C}$ blocking activity at 5,10 and 20 mg/kg[22]. Mirtazapine is more likely to produce facilitatory effect on nigrostriatal dopaminergic transmission due to blockade of central 5-HT_{2C} receptors predominantly and removes inhibitory control of 5-HT on nigrostriatal dopaminergic neurons. As a result there is an increase in synthesis as well as intraneuronal stores of DA therefore more DA is available for release due to dexamphetamine with resultant potentiation of dexamphetamine stereotypy in rats. Our results are in agreement with previous study of Thorat et al[22] that mirtazapine at 5,10 and 20 mg/kg doses significantly antagonised haloperidol induced catalepsy in rats by increasing synthesis and release of dopamine in nigrostriatal area due to predominant blockage of central 5-HT_{2C} receptors.

Our findings suggest that Mirtazapine induced significant blockade of central 5-HT_{2C} receptor at 5, 10 and 20 mg/kg had significantly potentiated dexamphetamine induced stereotyped behaviour.

Conclusion

Mirtazapine did not significantly influence apomorphine induced SB in rats as it does not have direct DA receptor agonistic or antagonistic activity but it had significantly potentiated dexamphetamine induced SB by blocking central $5HT_{2C}$ receptors , which removes the inhibitory control of 5-HT on nigrostriatal dopaminergic neurons and resulting in potentiation of dexamphetamine induced stereotyped behaviour.

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