Original Article

EFFECT OF RISPERIDONE, AN ATYPICAL ANTIPSYCHOTIC ON CENTRAL DOPAMINE-D_2 AND SEROTONIN- $5HT_2$ RECEPTOR MEDIATED BEHAVIOURS IN RATS AND MICE

Chandrakant Sahebrao Waghmare[1], Sachin Kore[2]

ABSTRACT

Recent evidence suggests that overactivity of central serotonin 5- HT_2 and dopamine D_2 receptors is involved in the pathogenesis of schizophrenia and that central serotonin 5 HT2 receptor antagonism has been associated with efficacy against negative symptoms of schizophrenia and a lower propensity to cause extrapyramidal side effects. Risperidone, an atypical antipsychotic agent has both dopamine D_2 and serotonin 5- HT_2 antagonistic activity. To demonstrate dopamine D_2 receptor antagonism, risperidone was studied for its effect on apomorphine and methamphetamine induced stereotyped behavior in rats. Risperidone was also studied for its effect on 5- hydroxytryptophan induced head twitch activity in mice, a central serotonin 5- HT_2 mediated behavior for demonstrating central 5-HT_2 receptor antagonism. It was observed that risperidone antagonized the apomorphine and methamphetamine induced stereotyped behavior in rats as well as the 5-hydroxytryptophan (5-HT) induced head twitch activity in mice, in a dose dependent manner which shows that risperidone combines both central dopamine D_2 and serotonin 5-HT_2 receptor antagonism.

Key words

Schizophrenia D_2 antagonism 5- HT_2 antagonism

Negative symptoms Extrapyramidal side effects

INTRODUCTION

Risperidone, a benzisoxazole derivative is an atypical antipsychotic agent which exhibits both central dopamine D_2 and serotonin 5-HT_2 receptor antagonism[1]. While the diagnostic symptoms of schizophrenia are now well established, the etiology and pathophysiology of the disease remain unclear. There is emerging evidence for specific neuronal deficits in schizophrenia which may result in secondary dysfunction of central neurotransmitter systems including among others, dopamine and serotonin[2].

Thus while the clinical potency of typical antipsychotics is correlated with their in vitro affinity for dopamine D_2 receptors [3], serotonin $5HT_2$ antagonistic activity has been associated with efficacy against the negative symptoms of schizophrenia and a lower propensity to cause extrapyramidal side effects [4].

Therefore taking into account above reports, the present study was conceived so as to study the effect of risperidone on central dopamine D_2 and serotonin 5-HT_2 receptor mediated behaviours in rats and mice.

OBJECTIVES

To investigate the effect of risperidone pretreatment on:

a. Apomorphine induced stereotyped behavior in rats.

b. Methamphetamine induced stereotyped behavior in rats.

c. 5-hydroxytryptophan induced head twitch activity in mice.

MATERIALS AND METHODS

Preparation of solutions:

Drug used Solvent

1. Apomorphine HCl Distilled water containing 0.2 mg/ml ascorbic acid
2. Methamphetamine HCl Diluted to required strength with distilled water

   (Methedrine inj, Borroughs Welcome & Co, 30 mg/1.5 ml)
3. 5-Hydroxytryptophan (Sigma) 0.9% Saline
4. Carbidopa (Sigma) 0.9% Saline
5. Risperidone (Sun) 0.9% Saline

The strengths of the solution were so adjusted that the required dose of the drug was present in a volume of 0.1 ml/10gm body weight in mice and 0.2 ml/100 gm body weight in rats.

All the drugs were injected intraperitoneally.

For studying the effects of risperidone on stereotyped behavior, male albino rats weighing between 120-200 gm with free access to a standard diet and tap water were used. Each animal was used only once.

All observations were made between 10 and 16 hours at 27^0-30^0 C in a noiseless, diffusely illuminated room. For observations, the animals were placed in individual cages made of wire netting with a floor of 30 cm X 20 cm X 20 cm. The animals were placed in observation cages 30 minutes before drug treatment so as to allow adaptation to the new environment.

The intensity of stereotyped behavior was assessed over an observation period at 10 min. intervals throughout its duration using the scoring system of Costall and Naylor [5] where,

Periodic sniffing = score - 1
Continuous sniffing = score - 2
Periodic biting
gnawing or licking, = score- 3
Continuous gnawing, = score- 4
licking or bitting

The maximum intensity of stereotyped behavior scored by each rat in the group was taken to compute the mean value of the group.

Drugs were injected intraperitoneally (i.p). For each dose 10 animals were used. Risperidone was injected 45 minutes before apomorphine /methamphetamine injection. Control groups received requisite volume of distilled water i.p. before receiving apomorphine / methamphetamine.

The results were statistically analyzed by the Student's unpaired 't' test.

For studying effect of risperidone on head twitch activity in mice, male albino mice weighing between 20-30 gm were used. They were allowed food and water ad libidium upto the time of experimentation. Each animal was used only once. All observations were made between 10 and 16 hours at 24^0 -26^0 c in a noiseless, diffusely illuminated room. For observation animals were placed in open topped transparent plastic cages measuring 30 X 20 X 20 cms.

The mice were divided in groups of 6 each. The control group received carbidopa 25 mg/kg i.p. followed 15 minutes later by 5- hydroxytryptophan 100 mg/kg i.p. The test group in addition received risperidone 60 minutes before. The assessment of head twitch activity was done by method of Guy M. Gudwin, Richard Green et al, (1985)[6].

In both groups, 15 minutes after 5-hydroxytryptophan injection, total no. of head twitches in a 2 minute period were noted. The results were statistically analyzed by Mann Whitney rank order test.

OBSERVATIONS & RESULTS

1. Risperidone pretreatment antagonized the apomorphine induced stereotyped behavior in rats in a dose dependent manner. (Table 1)
2. Risperidone pretreatment antagonized the methamphetamine induced stereotyped behavior in rats in a dose dependent manner. (Table 2)
3. Risperidone pretreatment antagonized the head twitch activity in mice induced by 5 HTP in a dose dependent manner. (Table 3)

Treatment dose (mg/kg)	Intensity S.B. score Mean ± SEM	'P' value
I)		
1. APO 0.5	1.0 ± 0.00	P>0.05
2. RIS 0.25 + APO 0.5	0.9 ± 0.10	P< 0.001
3. RIS 0.5 + APO 0.5	0.5 ± 0.17	P< 0.001
4. RIS 1 + APO 0.5	0.3 ± 0.16	P< 0.001
5. RIS 2 + APO 0.5	0 ± 00	
II)		
1. APO 1	2.0±0.00	P<0.05
2. RIS 0.25 + APO 1	1.6±0.28	P<0.05
3. RIS 0.5 + APO 1	1.2±0.34	P<0.001
4. RIS 1 + APO 1	0.4±0.17	P<0.001
5. RIS 2 + APO 1	0±00	

Table 1 : Effect of risperidone pretreatment on apomorphine induced stereotyped behavior in rats

Treatment dose (mg/kg)	Intensity S.B. score Mean ± SEM	'P' value
I)		
1. MAM 2.5	1.2 ± 0.13	
2. RIS 0.25 + MAM 0.5	1 ± 0.00	P>0.05
3. RIS 0.5 + MAM 0.5	0.7 ± 0.16	P< 0.05
4. RIS 1 + MAM 0.5	0.4 ± 0.17	P< 0.01
5. RIS 2 + MAM 0.5	0 ± 00	P< 0.001
II)		
1. MAM 5	2.2±0.20	
2. RIS 0.25 + MAM 5	1.5±0.24	P>0.05
3. RIS 0.5 + MAM 5	1.2±0.30	P<0.05
4. RIS 1 + MAM 5	0.5±0.18	P<0.001
5. RIS 2 + MAM 5	0±00	P<0.001

Table 2 : Effect of risperidone pretreatment on methamphetamine induced stereotyped behavior in rats:

Treatment dose mg/kg	No. of head twitches per 2 minutes
1. Carbidopa 25 + 5 HTP 100	**10**
2. RIS 0.25 + Carbidopa 25 + 5HTP 100	**07** *
3. RIS 0.25 + Carbidopa 25 + 5 HTP 100	**05** *
4. RIS 1 + Carbidopa 25 + 5 HTP 100	**02** *
5. RIS 2 + Carbodopa 25 + 5HTP 100	**00**

Table 3 : Effect of risperidone pretreatment on 5 -Hydroxytryptophan induced head twitch activity in mice:

* P <0.001 (Highly significant)

Abbreviations:
SB – Stereotyped behavior
RIS - Risperidone
Carbi – Carbidopa
MAM – Methamphetamine
APO - Apomorphine

DISCUSSION

The ability of the drugs to ameliorate changes in SB induced by apomorphine or methamphetamine is a standard test of potential antipsychotic activity [7].

Methamphetamine induced SB results from activation of postsynaptic dopamine D_2 receptors by the released dopamine [8].

Apomorphine is believed to act directly on dopamine D_2 receptors which results in SB in rats [9,10]. In the present study, risperidone pretreatment antagonized the apomorphine and methamphetamine induced SB in rats in a dose dependent manner which indicates that risperidone possesses central dopamine D_2 receptor antagonism.

The serotonin 5-HT_2 receptor antagonistic activity has been associated with efficacy against negative symptoms of schizophrenia and a low propensity to cause extrapyramidal side effects [11,12].

The head twitch response evoked in mice occurs as a result of increased activity of central 5 - hydroxytryptamine (5-HT) neuronal systems[13,14]. This behavior appears to be mediated by 5-HT_2 receptors[15,16]. The head twitch is produced by 5- HTP which acts as a precursor of 5- HT. Carbidopa prevents peripheral decarboxylation of 5-hydroxytryptophan and increases its absorption in central nervous system which in turn is converted into serotonin (5 -HT).

In the present study risperidone pretreatment antagonized the head twitch activity in mice induced by 5 HTP in a dose dependent manner which shows that risperidone has central 5- HT_2 receptor antagonistic activity[17].

CONCLUSION

Risperidone, the atypical antipsychotic exhibits both central serotonin $5HT_2$ and dopamine D_2 receptor antagonism and may have advantage over typical neuroleptics of a lower incidence of extrapyramidal symptoms, a reduced requirement for anti parkinsonian medication and a tendency towards greater efficacy in controlling negative symptoms of schizophrenia.

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1. **Chandrakant Sahebrao Waghmare**
Professor & Head, Dept. of Pharmacology,
Ashwini Rural Medical College & Hospital,
Solapur. (Corresponding Author)

2. **Sachin Kore,**
Assistant Professor, Dept. of Skin & V.D.,
KBN Institute of Medical Sciences,
Gulbarga. (Co- Author)