

Effects of H₁-receptor antagonists in antidepressant tests in rats

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Abstract: Considering the vast data suggesting the role of brain histamine(HA) in behaviour, emotions, anxiety and depression; four H₁-receptor antagonists; promethazine, diphenhydramine, cyclizine and pheniramine were subjected to antidepressant tests in rats. All H₁ – antagonists behaved like antidepressants in animal tests. They antagonized reserpine induced catalepsy, potentiated methamphetamine induced stereotypy and reduced the period of immobility in Porsolt's behavioural despair test. It is suggested that H₁- antagonists might be inhibiting the modulating effect of endogenous brain HA on the brain monoamines. Thus H₁- antagonists might be useful in a certain class of depressed patients.

Keywords: Histamine, H₁-antagonist, reserpine, methamphetamine, catalepsy, stereotypy, Porsolt's behavioural despair test.

Introduction

Histamine (HA) is recently included in the list of central neurotransmitters. HA is found to fulfill many classic criteria for a neurotransmitter substance [1]. Brain HA is suggested to have physiological role in thermoregulation, body fluid balance, sleep and wakefulness and release of certain hormones [2,3]. Brain HA appears to play some role in control of mood, emotions and other behavioural functions also. Isao Inoue et al in 1996[4], demonstrated that the H₁ – receptor knock out mutant mice show augmented locomotor activity during light period. They also suggested that HA may be involved in circadian rhythm of locomotor activity, exploratory behaviour and control of emotions. Zarrindast MR et al[5] have demonstrated anxiogenic effect of HA injected in amygdala in rats. This effect was antagonized by H₁-antagonist pyrilamine. HA injected in nucleus accumbens of rats was shown to reduce exploration and produce H₁ -receptor mediated anxiogenic effect.[6]. Similar effects were demonstrated in another study by Ruarte MB et al 1997 [7]. Ito C et al in 1999 [8] have demonstrated that both acute and chronic restraint stresses increase the brain HA turnover, which may partly relate to the vulnerability to stress-induced anxiety and depression. Ito C in 2000 [9] documents that acute stress increases HA turnover in diencephalon which can be partly related to anxiety and chronic stress increases HA turnover in nucleus accumbens and striatum which would have role in preventing stress vulnerability. Intraperitoneal L-histidine produces decreased

exploration and angiogenesis in mice. This is attenuated in a dose-dependent manner by H_1 – antagonist, pyrilamine [10]. This vast inconclusive data suggests that disturbance in central HA neuronal system may be one etiology of behavioural disorders. Prousky et al (2002)[11] have stated that histadelics (i.e. patients with high HA levels) are depressed and histapenics (i.e. patients with low HA levels) are nervous, anxious and paranoid. Kano M et al [12], have shown that HA H_1 – receptor binding was significantly decreased in frontal, prefrontal cortex and cingulate gyrus in 10 depressed patients. They have suggested that HA neuronal system might be playing an important role in pathophysiology of depression and modulation of central HA neuronal system may prove to be useful in the treatment of depression. Considering these reports it was thought worthwhile to subject the classical H_1 –receptor antagonist drugs (antihistaminics) to antidepressant tests in animals.

Materials and Methods:

Animals – Male albino Wistar rats weighing 150-200 g were used for all tests. They were given food and water ad libitum upto 30 minutes before the tests. All the experiments were performed between 10 and 16 hours in a noiseless, diffusely illuminated room. Animals were allowed to adapt to the new environment for 30 minutes prior to starting experimental procedure. All animals were used only once. The drug solutions were freshly prepared using distilled water as solvent.

Drugs – Four classical H_1 – receptor antagonists were studied in two different doses in each test. All drugs were administered intraperitoneally. The drugs used were Promethazine hydrochloride (**PMZ**, Inj. Phenergan, May & Baker Ltd., Bombay) 10 & 15 mg/kg, Diphenhydramine hydrochloride (**DPH**, Pure powder, Parke Davis (India) Ltd.) 10 & 20 mg/kg, Cyclizine hydrochloride (**CCZ**, Pure powder, Burroughs Wellcome (India) Ltd.) 10 & 20 mg/kg and Pheniramine maleate (**PM**, Inj. Avil, Hoechst India Ltd.) 10 & 15 mg/kg.

Antidepressant Tests :For all tests, animals were divided in 9 groups each of ten animals. In each test one group was kept as control and received normal saline (NS) intraperitoneally as pretreatment. Remaining 8 groups were pretreated with H_1 -antagonist (two different doses of four drugs).

All the “Principles of laboratory animal care” were practiced meticulously during experiments

Tests :

1) Initially effects of both doses of H_1 -antagonists on general behaviour of animals were observed, keeping one group as control.

2) *Reserpine (RES) induced catalepsy* :30 minutes after pretreatment with H_1 -antagonists or normal saline animals received RES 2.5 mg/kg intraperitoneally. All animals were tested for presence of catalepsy at ½h, 1h, 2h, 3h, 4h intervals. Animals were placed with their front paws on a 8 cm high wooden block. Catalepsy was scored by method of Ahtee L. and Buncombe G. (1974)[13]. If animal maintains the imposed posture for 20 seconds, it was given one point. Thus 2 points for 40 sec, 3 points for 60 sec. and so on. Maximum 6 points were given. Mean catalepsy scores of groups were calculated.

2) *Methamphetamine (MAMP) induced stereotypy* : 30 minutes after the pretreatment with H₁-antagonist or normal saline, all animals received MAMP 1mg/kg intraperitoneally. Animals were kept individually in perspex cages and observed for development of stereotypy at ½, 1, 2, 3 and 4 hour interval. Stereotypy was scored by the method of Costal et al (1972)[14]. The mean scores of stereotypy for different groups at each time interval were calculated.

3) *Porsolt Behavioural Despair Test* : The test was carried out by the method of Porsolt et al (1979)[15]. The rats were forced to swim inside a vertical cylindrical container (height 40cm, diameter 18 cm), containing water (15 cm height) at 25°C. After initial vigorous attempt to escape, rats attained an immobility. After 15 minutes swimming, rats were removed from water and allowed to dry in a heated enclosure for 15 minutes. At the end of this drying period they were given the drug or saline intraperitoneally. Then the rats were returned to their home cages. For next 24 hours rats were allowed to take food and water ad libitum. After 24 hours all rats received again same dose of same drug or saline as given on previous day. 30 minutes after this second injection the rats were again forced to swim in the cylinder for 5 minutes, one at a time. The total duration of immobility during this 5 minutes swim was calculated. A rat was judged to be immobile whenever it remained floating, motionless in the water, in a slightly hunched back but upright posture, the head being kept just above the water surface. The mean period of immobility for each group was calculated.

Statistics :In all tests mean scores of test groups were compared with mean score of control group and results were analysed by Mann-Whitney U-test. P<0.05 was considered statistically significant.

Results:

Effect on general behaviour : No change in general behaviour was observed in rats treated with DPH 10 mg/kg, CCZ 10 mg/kg & 20 mg/kg and PM 10 mg/kg & 15 mg/kg. No drug could itself induce stereotypy or catalepsy in both the doses. PMZ in both doses 10 mg/kg & 15 mg/kg, produced decrease in locomotor activity and with PMZ 15 mg/kg sedation was induced at the end of one hour. DPH 20 mg/kg induced excitation and increased locomotor activity for initial one hour; which later on subsided.

Effect on Reserpine induced catalepsy (Table 1):All the H₁-antagonists inhibited the reserpine induced catalepsy. PMZ 10 &15 mg/kg and CCZ. 10 mg/kg inhibited it significantly, at most of the time intervals. (P<0.05). Inhibition by CCZ 20 mg/kg, DPH 10 & 20 mg/kg, PM 10 & 15 mg/kg was highly significant (P<0.01) at most of the time intervals. DPH and PM not only decreased the score but also delayed the onset of catalepsy.

Table No.1 : Effect Of H₁ - Antagonists On Reserpine Induced Catalepsy

Drug R _x	MEAN CATALEPSY SCORE ± S.E.M.				
	½ h	1 h	2 h	3 h	4 h
NS + RES 2.5	0 ± 0	0.8 ± 0.6	2.4 ± 0.8	3.3 ± 0.6	4.9 ± 0.8
PMZ 10 + RES 2.5	0 ± 0	0 ± 0	1.3 ± 0.2 *	2.5 ± 0.3	4.0 ± 0.6
PMZ 15 + RES 2.5	0 ± 0	0 ± 0	1.0 ± 0.2 *	1.9 ± 0.2 *	2.5 ± 0.2 *
DPH 10 + RES 2.5	0 ± 0	0 ± 0 **	0 ± 0 **	0 ± 0 **	1.5 ± 0.2 **
DPH 20 + RES 2.5	0 ± 0	0 ± 0 **	0 ± 0 **	0 ± 0 **	0.2 ± 0.1 **
CCZ 10 + RES 2.5	0 ± 0	1.8 ± 0.3	2.5 ± 0.6	2.4 ± 0.2	1.7 ± 0.2 **
CCZ 20 + RES 2.5	0 ± 0	0 ± 0 **	0.9 ± 0.2 **	1.0 ± 0.2 **	1.0 ± 0.2 **
PM 10 + RES 2.5	0 ± 0	0 ± 0 **	0 ± 0 **	0.9 ± 0.2 **	1.7 ± 0.3 **
PM 15 + RES 2.5	0 ± 0	0 ± 0 **	0 ± 0 **	0 ± 0 **	0.9 ± 0.2 **

* denotes P<0.05, ** denotes P<0.01.(Mann Whitney's U-test)

Total 9 groups of rats(n=10) were used for this test.

The control group was pretreated with normal saline(NS) and remaining groups were pretreated with one H₁-antagonist given i.p. viz. promethazine(PMZ 10 or 15 mg/kg), diphenhydramine(DPH 10 or 20 mg/kg), cyclizine(CCZ 10 or 20 mg/kg), pheniramine(PM 10 or 15 mg/kg). 30 min after pretreatment all groups received reserpine (RES) 2.5 mg/kg i.p.

*Effect on Methamphetamine induced stereotypy (Table 2):*All the four H₁ – antagonists potentiated the stereotypy significantly (P<0.05) at most of the time intervals. The potentiation by PMZ 10 & 15 mg/kg, DPH 20 mg/kg, CCZ 20 mg/kg, was highly significant (P<0.01) at 4 hours interval.

Table No. 2 : Effect Of H₁ - Antagonists On Methamphetamine Induced Stereotypy

Drug R _x	MEAN STEREOTYPY SCORE ± S.E.M.				
	½ h	1 h	2 h	3 h	4 h
NS + MAMP 1	1.4 ± 0.2	2.2 ± 0.3	2.4 ± 0.4	1.9 ± 0.5	1.1 ± 0.4
PMZ 10 + MAMP 1	1.9 ± 0.2	2.0 ± 0.3	2.8 ± 0.3	2.6 ± 0.2	2.6 ± 0.2 **
PMZ 15 + MAMP 1	2.2 ± 0.2*	3.0 ± 0.3 *	3.4 ± 0.2 *	3.2 ± 0.2 *	2.8 ± 0.2 **
DPH 10 + MAMP 1	2.3 ± 0.3*	3.0 ± 0.2 *	3.0 ± 0.2 *	3.0 ± 0.4 *	2.2 ± 0.5 *
DPH 20 + MAMP 1	2.3 ± 0.3*	3.2 ± 0.3 *	3.2 ± 0.3 *	3.5 ± 0.2 **	3.2 ± 0.4 **
CCZ 10 + MAMP 1	2.2 ± 0.3*	2.6 ± 0.2 *	3.2 ± 0.2 *	3.3 ± 0.2 *	2.7 ± 0.2 **
CCZ 20 + MAMP 1	2.8 ± 0.5*	3.8 ± 0.2 *	3.8 ± 0.2 *	3.6 ± 0.2 **	3.6 ± 0.2 **
PM 10 + MAMP 1	2.2 ± 0.2*	3.0 ± 0.2 *	3.0 ± 0.1 *	3.0 ± 0.1 *	3.0 ± 0.1 **
PM 15 + MAMP 1	2.5 ± 0.2*	2.9 ± 0.2 *	3.2 ± 0.2 *	3.5 ± 0.2 **	3.3 ± 0.3 **

* denotes P<0.05, ** denotes P<0.01.(Mann Whitney's U-test)

Total 9 groups of rats(n=10) were used for this test.The control group was pretreated with normal saline(NS) and remaining groups were pretreated with one H₁-antagonist given i.p. viz. promethazine(PMZ 10 or 15 mg/kg), diphenhydramine(DPH 10 or 20 mg/kg), cyclizine(CCZ 10 or 20 mg/kg), pheniramine(PM 10 or 15 mg/kg). 30 min after pretreatment all groups received methamphetamine(MAMP)1mg/kg.

Effect on the period of immobility in Porsolt Test (Fig.1): All the four H₁ – antagonists reduced the mean total period of immobility. This inhibition was dose dependent and highly significant with both doses of all drugs. (P<0.01). In the rats treated with DPH 20 mg/kg and CCZ 20 mg/kg, vigorous escape directed activity was observed along with reduction in the mean period of immobility.

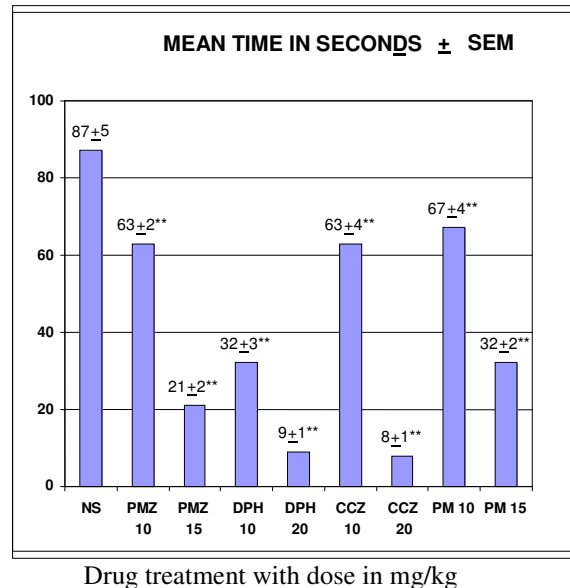
Effect Of H₁ - Antagonists On Period Of Immobility In Porsolt Test.

Fig. 1:** denotes $P < 0.01$ (Mann Whitney's U-test)

Total 9 groups of rats ($n=10$) were used for this test. The control group was treated with normal saline (NS) and remaining groups were treated with one H₁-antagonist given i.p. viz. promethazine (PMZ 10 or 15 mg/kg), diphenhydramine (DPH 10 or 20 mg/kg), cyclizine (CCZ 10 or 20 mg/kg), pheniramine (PM 10 or 15 mg/kg). All groups received same treatment again after 24 h. 30 min after second dose test was performed.

Discussion

In the doses used, H₁-antagonists did not produce significant change in the general behaviour of rats. Only DPH (20 mg/kg) produced a short lasting increase in locomotor activity, and CCZ (20 mg/kg) produced short lasting tremor. These observations are consistent with those quoted by Lewis and Isaac (1977)[16]. Nowak JZ[17] has shown that H₁-antagonists are shown to increase levels of noradrenaline and serotonin in hypothalamus and striatum of rat brain, which can explain this effect. Karamanakos PN et al[18] have suggested that the central serotonergic system may play a key role in the locomotor stimulant effects of chlorpheniramine in rats. They suggest that, this action is mediated via postsynaptic 5-HT_{1A} receptors. They have also shown the significant correlation between chlorpheniramine induced increased locomotor activity and increase in brain serotonin levels. Lal and Sourkes [19], have mentioned that DPH in high doses, produced stereotyped sniffing in rats. But in our study stereotypy was not induced by any of the H₁-antagonists, even with higher doses. Our results clearly show that H₁ – antagonists behave as antidepressants in animal models of depression. H₁ – antihistaminics significantly inhibited reserpine induced catalepsy.

Reserpine induces catalepsy due to depletion of catecholamines from presynaptic nerve terminals. The catalepsy produced by reserpine is suggested to be mediated via histaminergic mechanism also [20]. It is stated that reserpine inhibits histaminolytic properties of diamine oxidase, resulting in increased histamine levels. This increased histamine may be producing modulation of striatal catecholamines, mainly dopamine. This modulating effect might be mediated by H_1 -receptors, therefore H_1 – antagonists inhibited the reserpine induced catalepsy. Our results are supported by observations of Pawlowski and Sidorowicz [21]. We observed that H_1 -antihistaminics significantly potentiated the methamphetamine induced stereotyped behaviour in rats. These results are similar to the observations of Muley et al [22], Joshi et al[23] and Ito C et al[24] . This effect may be also explained on the basis that H_1 -antagonists inhibit the modulating effect of histamine on central monoamines. Brain histamine is said to have inhibitory effect on methamphetamine induced stereotypy and locomotor hyperactivity through H_1 and H_2 – receptors[24 , 25]. The forced swimming test is suggested to be a primary screening test for antidepressant drugs [26]. The state of immobility in the rat, induced due to failure to escape is very much similar to endogenous depression in human beings. We observed that all four H_1 – antagonists reduced this period of immobility in a highly significant manner ($p < 0.01$). These results are consistent with those obtained by Wallach and Hedley in 1979[27]. Kitada Y et al[28] observed that single injection of DPH reduced time of immobility but this effect disappeared after chronic treatment of DPH. We have not observed effect of chronic treatment of DPH. Luttinger D et al [29] have suggested that activity of mianserin ,an atypical antidepressant, in behavioural despair test is best explained by its antihistaminergic potency. Chlorpheniramine is shown to have antidepressant like effect in the mouse tail suspension test[30]. This effect of chlorpheniramine was significantly inhibited by D_1 – dopaminergic antagonist and α_1 – antagonist, prazosin. Hirano S et al (2007)[30] have suggested that antidepressant like effect of chlorpheniramine might be mediated by activation of D_1 – and α_1 receptors. We suggest that this effect might be due to antagonism of modulatory effect of histamine on brain catecholaminergic system by chlorpheniramine. Carlsson and Lindqvist [31] have postulated that antihistaminics effectively block the noradrenaline and serotonin neuronal uptake, like tricyclic antidepressant drugs. In the mutant mice lacking H_1 – receptors, serotonin release was significantly increased in brain [32]. Son L Z et al [33] have postulated that, endogenous HA, by acting through H_1 -receptors, facilitate release of GABA which in turn inhibits serotonin release. Prolonged treatment (2 weeks) with H_1 – antagonists and tricyclic antidepressants is shown to produce significant decrease in the brain histamine level in rats [34]. In one study chlorpheniramine is found to increase activity of brain histamine N- methyl transferase; the histamine metabolizing enzyme in rats[35]. Thus H_1 – antagonists might be inhibiting the modulatory effect of brain histamine on brain monoaminergic system by H_1 – receptor blockade or decrease in histamine release or by increase in histamine metabolism. Inhibition of modulating effect of histamine may lead to increase in monoamine levels in brain. Many tricyclic antidepressants are potent H_1 – receptor

antagonists; even more potent than conventional H₁ – antagonists like DPH [36,37]. Many antidepressant drugs, including atypical drugs, are observed to inhibit histamine sensitive adenylyl cyclase like H₁ – antagonists[38]. Therefore it is suggested that the blockade of histamine sensitive adenylyl cyclase may account at least partly for clinical efficacy of antidepressant drugs and that some disturbance of histaminergic neurons may contribute to aetiology of endogenous depression[38]. Recently it was demonstrated that, H₁ – receptor binding in frontal, prefrontal cortex and cingulate gyrus was significantly reduced in brains of 10 depressed patients[12]. In other study it was observed that histadelics i.e. patients with increased histamine levels, have less serotonin level and they were depressed[39,40]. Therefore we suggest that decreased H₁ – receptor binding in depressed patients might be due to down regulation of H₁ – receptors which might be a result of persistently increased histamine levels in these patients. This increased histamine modulates catecholaminergic neuronal system, leading to decreased levels of serotonin, noradrenaline and probably dopamine, which manifests as depression. A report of one clinical study says that, 77% (10 out of 13) of a group of patients who were depressed but not psychotic had significant improvement while receiving DPH [36]. Thus modulation of histaminergic neuronal system may prove to be a novel approach to the treatment of depression, and H₁-antihistaminic drugs or centrally acting histamine synthesis inhibitors may be useful in at least a selected class of depressed patient.

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