Modulation of motor functions involving central dopaminergic system by L-histidine

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There exists a possibility of interactions of histaminergic system with other neurotransmitters and their receptors in the central nervous system. Experimental evidences suggest a possible inhibitory influence of histaminergic system on the dopaminergic system. To elucidate the possible interaction between the histaminergic and dopaminergic pathways, we devised a strategy to study their effects on locomotor function and stereotypy behaviour. We investigated the effect of L-histidine, the precursor of histamine, on apomorphine-induced stereotypy and perphenazine-induced catalepsy. Histidine antagonised apomorphine-induced stereotypy. This inhibitory effect of histidine was abolished by both H1- and H2-receptor antagonists, chlorpheniramine and cimetidine, respectively. Perphenazine-induced catalepsy was potentiated by histidine and this effect was inhibited by chlorpheniramine alone but not by cimetidine. These results confirm a possible histamine-dopamine interaction in the modulation of motor functions by the central nervous system.

The nigrostriatal dopaminergic pathway has been long implicated in motor functioning1. It is generally accepted that dopamine is present in the region of nucleus accumbens and is responsible for locomotor activity, while stereotypy is mediated by striatal dopaminergic neurons2,3. Stereotyped behaviour may operate via a reciprocal balance between the dopaminergic and cholinergic inhibitory systems, in favour of dopaminergic dominance5, while cholinergic system is positively implicated in motor dysfunction7. Agents that activate the histaminergic system enhance drug-induced catalepsy. Moreover, histaminergic neurons might have an inhibitory effect on dopaminergic system in the striatum and/or nucleus accumbens5,7. The present work was, therefore, planned to elucidate the possible role of histamine in the modulation of motor functions involving dopamine using apomorphine-induced stereotypy and perphenazine-induced catalepsy.

Materials and Methods

Animals — Albino mice (BALB/c, 20-25 g, either sex) and Wistar rats (200-250 g, males) bred in central animal house facility of Panjab University were used. The animals were housed under standard laboratory conditions (12 hr/12 hr light/dark cycle) with free access to food (Hindustan lever products, Calcutta, India) and water; food being withdrawn 3 hr prior to experimentation. All experiments were performed between 10:00 hrs and 17:00 hrs.

Apomorphine-induced stereotypy — Mice were placed individually in glass containers. Sniffing, rearing, licking and grooming were observed as stereotypic behaviours at 0, 5, 10, 15, 30, 45 and 60 min after apomorphine administration. The intensity of stereotypy was recorded as described by Costall and Naylor8, i.e., 1+=presence; 2+=moderately severe, and 3+=intense and continuous action. The cumulative score at each time interval was calculated by adding all the scores for the purpose of comparison8. L-Histidine was administered (100, 200 and 500 mg/kg, i.p.) 30 min prior to injection of apomorphine (2.5 mg/kg, i.p.). Dopamine receptor antagonist, haloperidol, was injected (0.5 and 1 mg/kg, i.p.) 30 min prior to apomorphine injection. Histamine H1 and H2 receptor antagonists, chlorpheniramine and cimetidine, respectively were injected (10 and 100 mg/kg, i.p. respectively) immediately prior to histidine treatment.

Perphenazine-induced catalepsy — Catalepsy was induced in rats with perphenazine. The development and severity of catalepsy was scored according to the method described6. Stage 1: rat moves freely when placed on the table (Score = 0); stage 2: rat moves only when touched or pushed (score = 0.5); stage 3: rat fails to correct posture in 10 sec when front paws are placed alternately on a 3 cm high wooden block.
(score = 0.5 for each paw with a total score of 1.0 for this stage); stage 4: rat fails to correct posture in 10 sec when front paws are placed alternately on a 9cm high wooden block (score = 1.0 for each paw with a total score of 2.0 for this stage). Thus a complete cataleptic response was described when the score was 3.5. A lower score meant an apparently lesser degree of catalepsy. The scoring of cataleptic response was done at 0, 15, 30, 60, 90, 120, 180 and 240 min after perphenazine administration. L-Histidine was administered (500 mg/kg, i.p.) 60 min prior to the injection of perphenazine (0.5, 1 and 5 mg/kg, i.p.). Histamine receptor antagonists, chlorpheniramine and cimetidine, were injected (10 and 100 mg/kg, i.p. respectively) immediately prior to histidine treatment. Scopolamine, muscarinic receptor antagonist, was injected (5 mg/kg, i.p.) immediately prior to histidine treatment.

**Statistical analysis** — Results expressed as mean ± SE of cumulative stereotypy and catalepsy score were subjected to Analysis of Variance (one-way ANOVA) followed by Dunnet's t-test. P-values less than 0.05 (P < 0.05) were considered as statistically significant.

**Results**

L-Histidine produced a dose dependent (100, 200, 500 mg/kg i.p.) decreases in stereotypy induced by apomorphine (2.5 mg/kg i.p.) (Fig.1). Histamine H₁ receptor antagonist, chlorpheniramine (10 mg/kg i.p.), as well as H₂ receptor antagonist, cimetidine (100 mg/kg i.p.) significantly reversed the inhibitory effect of histidine on apomorphine-induced stereotypy (Fig.2). Further, cimetidine (100 mg/kg i.p.) increased the intensity of apomorphine-induced stereotypy, the effect being significant at 5 minutes (Fig. 2) and statistically insignificant at other time intervals. Haloperidol, a dopamine receptor antagonist attenuated apomorphine-induced stereotypy in a dose-dependent manner (0.5-1 mg/kg i.p.) (Fig. 3). Co-administration of histidine (500 mg/kg i.p.) with haloperidol (0.5 mg/kg i.p.) significantly potentiated the inhibitory effect of either drugs alone on apomorphine-induced stereotypy (Fig. 3).

Perphenazine (0.5-5 mg/kg i.p.) produced a dose-dependent increase in catalepsy score (Fig. 4). Maximum catalepsy score was attained using perphenazine (5 mg/kg i.p.). At a much lower dose (0.5 mg/kg i.p.) perphenazine produced minimal catalepsy score. Pretreatment with histidine (500 mg/kg i.p.) did not modify the perphenazine (5 mg/kg i.p.) induced catalepsy but significantly potentiated the catalepsy produced by lower dose of perphenazine (0.5 mg/kg i.p.) (Fig. 4). The potentiating effect of histidine on perphenazine-induced catalepsy was markedly attenuated by H₁ receptor antagonist, chlorpheniramine (10 mg/kg i.p.) but not by H₂ receptor antagonist cimetidine (100 mg/kg i.p.) (Fig. 5). Scopolamine (2 mg/kg i.p.) completely abolished the effect produced by histidine pretreatment on perphenazine-induced catalepsy (Fig. 5).

**Discussion**

The dopaminergic system is invariably associated with motor function. The inhibitory influence of histaminergic neurons on dopaminergic system is supported by the finding that tyramine-induced release of (³H) dopamine from striatal slices was inhibited by preincubation of the slices with histamine and methamphetamine-induced hyperactivity was reduced by histamine. Systemic administration of L-histidine also reduced the hyperactivity induced by amphetamine. These studies showed the inhibitory effect of histidine on indirectly active sympathomimetic amines.

We have shown the inhibitory effect of histidine on directly acting dopamine agonist, apomorphine. Our results indicate that histamine receptors are involved in the inhibition of apomorphine-induced stereotypy by histidine, since this effect is reversed by histamine antagonists. Moreover, potentiation of sub-effective dose of haloperidol by histidine indicates the interplay of dopaminergic system with the histaminergic system. Thus it could be possible that the metabolite of histidine, i.e., histamine, exerts an inhibitory effect on the postsynaptic dopaminergic receptors. This is in good agreement with a recent finding that inhibition of methamphetamine-induced stereotyped behaviour by histidine may be due to the involvement of central histaminergic system through dopamine D₂ receptors.

Apomorphine-induced compulsive behaviour (stereotypy) is an established model for schizophrenia. Several lines of evidence suggest the role of histamine in the pathogenesis of schizophrenia. Association of histidinemia with schizophrenia increased levels of N'-methyl histamine, a metabolite of histamine, in CSF of schizophrenic and reduced density of H₁ receptors in the post-mortem frontal cortex of schizophrenic patients indicate a vital role of central histaminergic
Fig. 1 — Effect of histidine on apomorphine induced stereotypy. The doses shown within the parenthesis are expressed as mg/kg (i.p.). Each group consisted of at least 5 animals. *P < 0.05 compared to apomorphine (2.5) treated group at the corresponding time intervals.

Fig. 2 — Effect of histamine receptor antagonists (chlorpheniramine and cimetidine) on the attenuation of apomorphine-induced stereotypy by histidine. The doses shown within the parenthesis are expressed as mg/kg (i.p.). Each group consisted of at least 5 animals. *P < 0.05; **P < 0.05 compared to apomorphine (2.5) and histidine (500) + apomorphine (2.5) treated group respectively at the corresponding time intervals.

Fig. 3 — Effect of haloperidol on apomorphine-induced stereotypy and on attenuation of apomorphine induced stereotypy by histidine. The doses shown within the parenthesis are expressed as mg/kg (i.p.). Each group consisted of at least 5 animals. *P < 0.05; **P < 0.05 compared to histidine (500) + apomorphine (2.5) and haloperidol (0.5) + apomorphine (2.5) treated group respectively at the corresponding time intervals.
system in schizophrenia, thereby suggesting a possible interaction with the dopaminergic system.

Histaminergic receptors are also widely distributed in the basal ganglia. Lesions in the substantia nigra (SN) and tuberomammillary nucleus (TM) have opposite effect on scanning behaviour thereby suggesting the existence of a reciprocally acting regulatory system in terms of sensorimotor process, possibly involving dopamine and histamine there by suggesting a functional link between the tuberomammillary-striatal (HAergic) and nigrostriatal (DAergic) system is very likely.

Intracerebroventricular administration of HA elicits biphasic changes in spontaneous locomotor activity which may be mediated separately by H1 and H2 receptor mechanisms and catalepsy is observed following high dose of histamine. Cholinergic mechanisms are also involved in catalepsy. Perphenazine has shown to increase the brain ACh and HA levels. HA causes an increase in the cholinergic activity of the brain. High dose of perphenazine increases histamine turnover in the

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**Fig. 4** — Perphenazine-induced catalepsy in rats and effect of histidine (500 mg/kg, i.p.) pretreatment on perphenazine (0.5 mg/kg, i.p.) induced catalepsy. *P < 0.05 compared to perphenazine (0.5) treated group. The doses shown within the parenthesis are expressed as mg/kg (i.p.). Each group consisted of at least 5 animals.

**Fig. 5** — Effect of antihistaminics (cimetidine and chlorpheniramine) and anticholinergic drug (scopolamine) on potentiation of perphenazine-induced catalepsy by histidine. The doses shown within parenthesis are expressed as mg/kg (i.p.). Each group consisted of at least 5 animals. *P < 0.05; *P < 0.05 compared to histidine (500) + perphenazine (0.5); and scopolamine (5) + histidine (500) + perphenazine (0.5) treated group respectively at the corresponding time intervals.
whole brain of mice and rats. The increase of histamine turnover is related to brain dysfunction of chronic schizophrenia and enhanced antipsychotic-induced catalepsy. H₃-antagonists block catalepsy induced by haloperidol, opioids and perphenazine; the anti-cataleptic effect assumed to be mediated through the blockade of H₃-receptors. Since many H₃-antagonists also have anti-cholinergic activity, it may be this action which is responsible for their anti-cataleptic effect in these studies.

Our results suggest that histidine may be converted to HA and the increased brain levels of the amine mediates the cataleptic response through the H₃-receptors. Involvement of dopaminergic system in catalepsy is well established. Impairment of dopamine inputs by neuroleptics produce catalepsy in animals and extrapyramidal side-effects in humans. It has been reported that HA may exert an inhibitory effect on the DAergic neurons. Increased inhibition of DA system due to rise in brain levels of HA by histidine could also contribute to the potentiation of perphenazine-induced catalepsy by histidine. The results obtained show that chlorpheniramine reversed the potentiation of perphenazine-induced catalepsy by histidine while cimetidine did not. Neurochemical evidences indicate that H₃-antagonists inhibit the neuronal uptake of DA in vivo and in vitro and thus enhance the function of DAergic system in brain. Potentiation of L-dopa-induced behavioural excitement by histamine H₃-receptor antagonists in mice further provide the behavioural evidence for the inhibition of dopamine uptake by H₃-antagonists.

Thus the potentiation of catalepsy seen with histidine does not necessarily involve the HA ergic system alone and the involvement of other neurotransmitter system is speculated. The central dopaminergic facilitatory and anticholinergic activity of H₃-antagonists may account for the anticaetalgeic effect of chlorpheniramine.

The inhibitory effect of histaminergic neurons on the dopaminergic system can be incriminated in the attenuation of apomorphine-induced stereotypy and potentiation of perphenazine-induced catalepsy by histidine, there by further substantiating the role of histaminergic system in the modulation of dopaminergic motor function.

References


