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Effects of Centrally Administered H2 Antagonists on Motor Activity

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O'NEILL, K. A. AND S. B. GERTNER. *Effects of centrally administered H2 antagonists on motor activity*. PHARMACOL BIOCHEM BEHAV 26(4) 683–686, 1987.—Two structurally distinct H2 antagonists, cimetidine and BMY 25,368, were injected into the cerebral ventricles of mice. Both drugs produced reductions in locomotor activity and rotorod latencies. The effects of the H2 antagonists on locomotor activity were attenuated by the H2 agonist, impromidine, as well as by the H1 antagonist, chlorpheniramine. When given alone, chlorpheniramine had no effect on locomotor activity, while impromidine reduced locomotion. These data suggest that histaminergic receptors may mediate important actions on arousal and sedation mechanisms.

Histamine Locomotion Behavior Intraventricular

A growing body of evidence suggests that histamine is a transmitter within the CNS. Pharmacological, anatomical and physiological data indicate that histaminergic nuclei and fiber systems are widely distributed in the brain, and two histaminergic receptors have been identified, but not clearly characterized (see [14] for review).

In previous studies, it has been shown that histamine itself given into the cerebral ventricles has sedative [12], and in very large doses, cataleptic effects in rats [11]. Others have demonstrated that central histaminergic systems exert control over fluid balance [10], cardiovascular function [9], temperature regulation [3], and nociceptive processing [4]. However, the significance of central histaminergic systems for the control of behavior has not been extensively explored. With the advent of new specific agonists and antagonists for H1 and H2 receptors, it has become possible to investigate the functional significance of some of these systems. Thus, the purpose of these experiments was to determine the effects of central H2 receptor blockade on gross locomotor function, using two structurally distinct H2 antagonists, cimetidine and BMY 25,368.

METHOD

CD-1 male mice (Charles River), weighing approximately 20 g served as subjects. Mice were housed under standard laboratory conditions (12 hour light/12 hour dark cycle), 10 per cage, with food and water available ad lib, and were allowed to acclimate for 3–5 days prior to experiments.

Twenty-four hours prior to the experiment, mice were lightly anesthetized with ether, and a small part of the scalp was removed, exposing the skull. Drugs were injected intracerebroventricularly (ICV), using a modification of the method of Haley and McCormick [7]. Using a 27 gauge needle, cut to a length of 3 mm, the needle was inserted through the skull, 2 mm lateral to bregma, on the coronal suture.

All drugs were dissolved in a vehicle of distilled water, and brought to a pH of 7.4 with HCl and NaOH. Pilot studies showed no significant difference between the activity of mice injected with distilled water or artificial cerebrospinal fluid. All drugs were delivered in a volume of 5 μl. The compounds used in these experiments were the generous gifts of Schering Corporation (chlorpheniramine), Smith Kline (cimetidine, impromidine) and Bristol-Myers (BMY 25,368).

An Opto-Varimex activity monitor (Columbus Instruments, OH) was used to monitor horizontal activity (locomotion). Activity was measured for a 30 min period immediately following ICV injections, and data were recorded at 5 min intervals. In all experiments, pairs of mice were tested, so that all Ns refer to numbers of pairs.

Motor deficits were assessed by the rotorod test [6]. Mice were trained to walk on a rod rotating at 12 rpm for 120 sec in 3 daily training trials for 3 days prior to drug testing. Mice which failed to remain on the rotorod for 120 sec during all of the last 3 training trials were excluded from the experiment. On the test day, latencies to fall from the rotorod were measured at 5, 15 and 30 min after drug treatment.

Data were analyzed by repeated measures analysis of variance, using the least squares solution [15]. Significant differences between specific groups were determined by Newman-Keuls tests.

RESULTS

As shown in Fig. 1, cimetidine treatment significantly reduced locomotor activity, $F(2,22)=71.92$, $p<0.001$. This ef-

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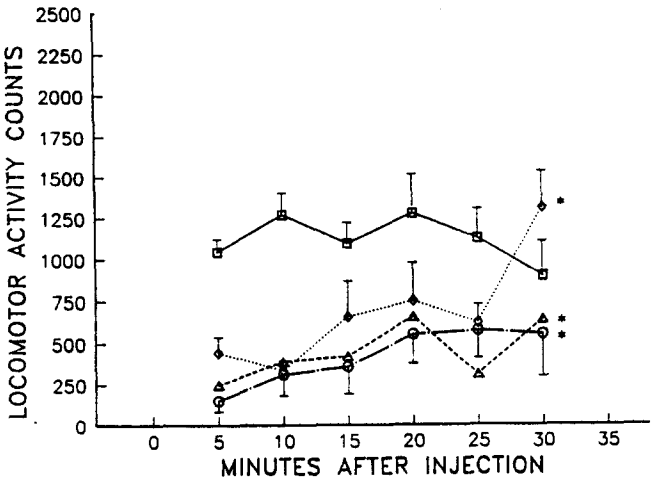

FIG. 1. The dose and time related effects of ICV cimetidine on locomotor activity. Values represent means and standard errors of horizontal activity counts of (N) pairs of mice. *=$p<0.05$, significant treatment effect across the 30 min period. (○) CIM 50 μg (5); (△) CIM 25 μg (4); (◇) CIM 10 μg (4); (□) control (11).

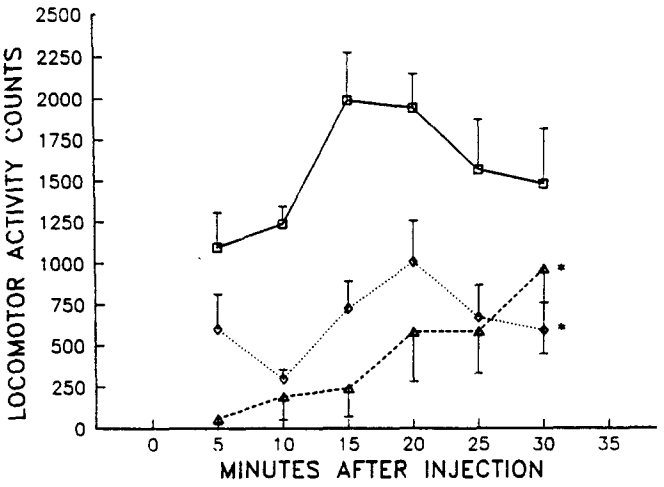

FIG. 2. The dose and time related effects of ICV BMY 25,368 on locomotor activity. Values represent means and standard errors of horizontal activity counts of (N) pairs of mice. *=$p<0.05$, significant treatment effect across the 30 min period. (△) BMY 50 μg (3); (◇) BMY 20 μg (4); (□) control (6).

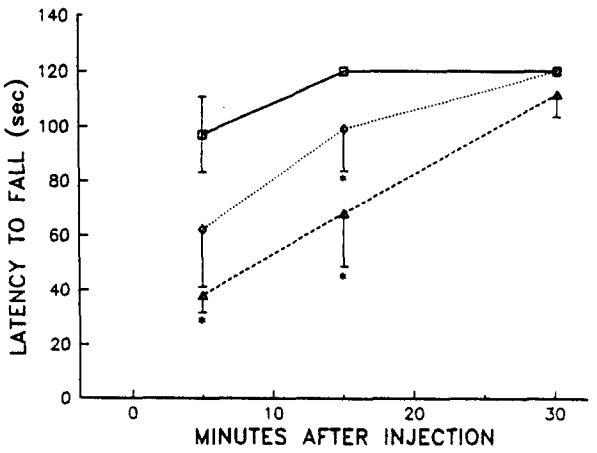

FIG. 3. The dose and time related effects of ICV cimetidine and BMY 25,368 on rotorod performance. Values represent means and standard errors of latencies of (N) mice to fall from rod rotating at 12 rpm after ICV drug treatment. *=$p<0.05$, significant reduction in latency at specific time point. (△) BMY 25 μg (7); (◇) CIM 25 μg (7); (□) control (5).

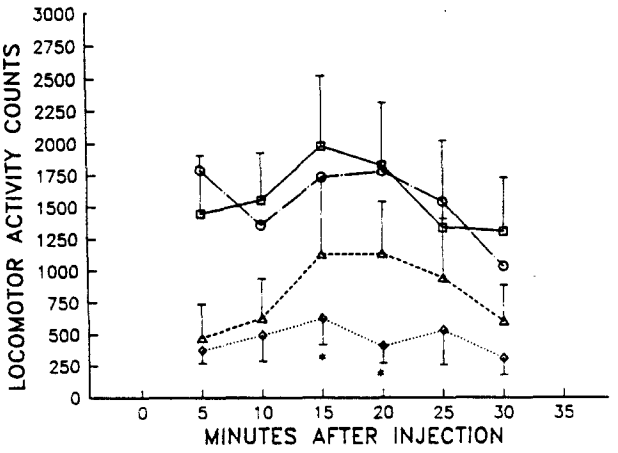

FIG. 4. The effect of ICV impromidine on cimetidine and BMY 25,368 induced reduction in locomotor activity. Values represent means and standard errors of horizontal activity counts of (N) pairs of mice. *=$p<0.05$, significant reduction in locomotor counts at specific time point, compared to control. (○) IMP 50 μg and BMY 25 μg (3); (△) IMP 50 μg and CIM 50 μg (4); (◇) IMP 50 μg (5); (□) control (6).

fect was consistent across the entire 30 min testing period ($p<0.05$). Locomotor activity was significantly reduced by the dose of 10 μg, ($p<0.05$). Further, at a dose of 25 μg cimetidine significantly reduced locomotion, as compared with both control animals and mice treated with the 10 μg dose ($p<0.05$). At 50 μg, the effect of cimetidine on locomotion appeared to reach a plateau. Mice treated with 50 μg showed significantly less activity than the control or 10 μg groups ($p<0.05$), but no significant decrease, compared with the 25 μg group ($p<0.05$). Treatment with BMY 25,368 also produced a significant reduction in locomotion, $F(2,11)=7.04$, $p<0.05$, as shown in Fig. 2. The effect of BMY 25,368 was also consistent across the 30 min period ($p<0.05$), and there was no significant difference between the effects of 20 and 50 μg. Both cimetidine and BMY 25,368 significantly impaired rotorod performance, $F(2,16)=21,16$, $p<0.001$, in a time related manner, $F(2,4)=9.69$, $p<0.005$, as seen in Fig. 3. BMY 25,368 significantly reduced rotorod latencies at 5 and 15 min after treatment ($p<0.05$). Cimetidine significantly reduced rotorod latencies at 15 min after administration. Neither drug had any effect on rotorod performance by 30 min after administration.

Figure 4 shows the effect of the H2 agonist, impromidine, given alone, or with the H2 antagonists, on locomotor activ-

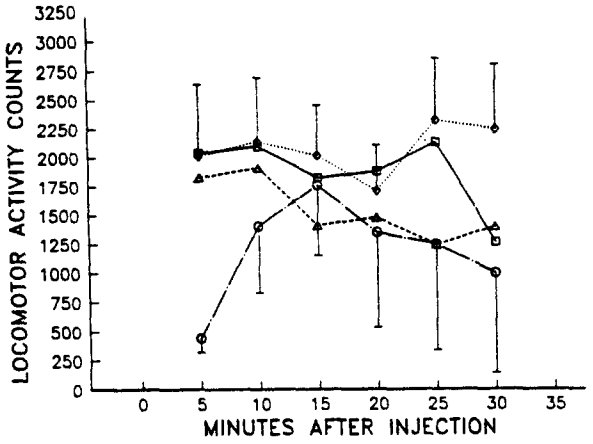

FIG. 5. The effect of ICV chlorpheniramine on cimetidine and BMY 25,368 induced reduction in locomotor activity. Values represent means and standard errors of horizontal activity counts of (N) pairs of mice. (○) CHLOR 50 μg and BMY 25 μg (5); (△) CHLOR 50 μg and CIM 25 μg (4); (◇) CHLOR 50 μg (8); (□) control (10).

ity. Results of an analysis of variance showed a significant drug treatment effect, $F(3,14)=3.34$, $p<0.05$, which did not vary across time ($p<0.05$). At 15 and 30 min after treatment, impromidine itself significantly reduced locomotor activity ($p<0.05$). Further analysis revealed that the locomotor activity of mice which received impromidine and cimetidine or BMY 25,368 did not differ significantly from controls ($p<0.05$). Thus, impromidine given alone reduced locomotion, but when given with an H2 antagonist, impromidine attenuated the H2 antagonist reduction in locomotion, resulting in activity levels similar to those of control animals.

Treatment of mice with chlorpheniramine either alone or in combination with the H2 antagonists had no significant effect on locomotor activity, $F(3,23)=2.699$, $p<0.05$, as shown in Fig. 5. Thus, chlorpheniramine attenuated the motor depressant effects of both cimetidine and BMY 25,368 on locomotion at a dose which by itself had no effect on locomotion.

DISCUSSION

The results of these studies show that two structurally distinct H2 antagonists significantly reduced motor activity and impaired rotorod performance after ICV administration. Similar effects (depression, sedation and confusion) have been reported after the clinical use of cimetidine [8,13]. These activity-reducing effects would appear to be related to the actions of the H2 antagonists on H2 receptors, since the drugs are structurally unrelated, and because the specific H2 agonist, impromidine, attenuated the reductions in locomotor activity seen after H2 antagonists. However, the finding that impromidine given alone also resulted in a significant reduction in locomotion is puzzling. It appears contradictory that H2 antagonists and an H2 agonist each reduce activity when given alone, but together have no effect. One property which the H2 antagonists and the H2 agonist used in these experiments may have in common is the antagonism of the putative H3 autoreceptor. Recently, Arrang *et al.* [1] have reported evidence which supports the existence of an H3 presynaptic autoreceptor, which mediates the release of histamine. These investigators have shown that in the brain, histamine attenuated its own release. This auto-inhibitory effect is blocked by a number of H2 antagonists as well as by the H2 agonist, impromidine. Therefore, both cimetidine and impromidine are potent H3 antagonists. It is tempting to speculate that the actions of both H2 agonists and antagonists on the presynaptic autoreceptors (H3 receptors) may underly the reduction on motor activity, while effects on post-synaptic H2 receptors may reverse these actions. Thus, antagonism of H3 receptors (resulting in increased histamine release) may be the mechanism underlying the activity reducing effects of these three compounds. Indeed, other have reported similar activity reducing effects of ICV histamine [12]. Blockade of post-synaptic H2 receptors (preventing post-synaptic effects from greater HA release) might underly the apparent antagonism between H2 agonist and antagonist effects on locomotion.

The attenuation of H2 sedation by the H1 antagonist, chlorpheniramine, is somewhat surprising, although others have shown that H1 antagonists possess stimulatory actions in rodents [2]. Whether the antagonism of H2 antagonist hypoactivity by chlorpheniramine is due to direct actions on H1 receptors (inducing stimulation), or some kind of complex interaction between different histaminergic receptors remains to be determined. Nevertheless, the data presented here indicate that central histaminergic systems are implicated in the control of some gross behavioral states, and are worthy of further study in this regard. However, it should be noted that to date, most of the H2 antagonists have very poor penetrability into the CNS, and must be given ICV. H2 or H3 antagonists that penetrate well into the CNS may have intriguing actions on behavior. As a new group of centrally acting agents, such compounds could have several potential clinical applications, such as in the treatment of anxiety and psychosis.

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