CATALEPTIC EFFECT OF HISTAMINE INDUCED BY INTRAVENTRICULAR INJECTION IN MICE

Chiaki KAMEI, Tatsuro DABASAKI and Kenji TASAKA
Department of Pharmacology, Faculty of Pharmaceutical Sciences, Okayama University, Okayama 700, Japan
Accepted May 27, 1983

It has been shown that histamine (Hi) induces various alterations in animal behavior when injected into the appropriate regions of the brain. Feldberg and Sherwood (1), for instance, reported that injection of Hi at doses of 100–200 µg into the lateral ventricle of a cat caused muscle weakness, decrease of spontaneous activity and sleepiness. In rats, intraventricular application of Hi induced cataleptic behavior (2). Heath and de Balbian (3) described that 5–20 µg of Hi produced a cataleptic state and reduced activity when injected into the septal region of monkeys. The present study was carried out to investigate if Hi application into a mouse brain would induce behavior changes relating to catalepsy and to study the influence of some drugs on such Hi-induced catalepsy.

Male ddY strain mice, weighing 25–30 g, were used; and at least 10 animals were employed in each of the 20 groups. Catalepsy was determined according to the method of Oka et al. (4). In brief, mice were forced to take an awkward and bizarre posture by having their forepaws grasp a stainless steel bar of 4 mm diameter, set horizontally at the height of 5.5 cm. The mice not removing their forepaws from the bar within 30 sec were considered to be cataleptic. Intraventricular injection was carried out according to the method of Haley and McCormick (5). A drug dissolved in saline was injected with a constant volume of 5 µl. To confirm whether the drug given intraventricularly reached the ventricular system or not, 5 µl of India ink was injected after the experiment was concluded in some cases, and the brain was sectioned and examined histologically. In all test cases of injecting India ink, it was found in the lateral ventricle or even in the third ventricle. Statistical analysis for testing the drug effect was done by the Fisher exact probability test (6).

At doses of 20 µg or more, Hi induced a cataleptic state in all the mice tested, and the intensity and duration of catalepsy were exhibited in a dose-dependent fashion (Table 1). A significant effect was obtained at doses of 20 µg or more, and the maximal effect was observed at 8–15 min after the application of effective doses of Hi. Hi produced an obviously cataleptic effect at 100 µg without any other signs of neurotoxicity. Therefore, this dose was employed in the following experiments. Table 2 shows the effect of various drugs on Hi-induced catalepsy. The test drug was administered intraventricularly or intraperitoneally. In the intraventricular administration, each drug was applied simultaneously with Hi; and in the intraperitoneal injection, drugs were given 30 min before Hi. Pyrilamine (20 µg, i.vent. and 5–20 mg/kg, i.p.) and diphenhydramine (5–20 mg/kg, i.p.) clearly reduced the intensity of Hi-induced catalepsy. Cimetidine (5 µg, i.vent. and 5–20 mg/kg, i.p.), on the contrary, did not significantly affect the intensity of Hi-induced catalepsy. Atropine (2 and 5 mg/kg, i.p.), scopolamine (0.5 and 1 mg/kg, i.p.), biperiden (1 and 2 mg/kg, i.p.) and L-DOPA
Table 1. Cataleptogenic effect of histamine in mice

| Drugs     | Dose (µg/body) | 0  | 3   | 8   | 15  | 30  | 60  | 120 min |
|-----------|----------------|----|-----|-----|-----|-----|-----|---------|
| Saline    |                | 0/10| 0/10| 0/10| 0/10| 0/10| 0/10| 0/10    |
| Histamine | 10             | 0/10| 2/10| 2/10| 0/10| 0/10| 0/10| 0/10    |
|           | 20             | 0/10| 3/10| 5/10*| 5/10*| 3/10| 2/10| 2/10    |
|           | 50             | 0/10| 5/10*| 5/10*| 6/10*| 1/10| 1/10| 0/10    |
|           | 100            | 0/10| 4/10*| 6/10*| 7/10*| 3/10| 1/10| 0/10    |
|           | 200            | 0/10| 8/10*| 8/10*| 8/10*| 7/10*| 4/10*| 3/10    |

*P<0.05 with the Fisher exact probability test, compared to the saline-treated group.

Table 2. Influence of certain drugs on Hi-induced catalepsy

| Drugs     | Dose (µg, i.vent.) | 0  | 3   | 8   | 15  | 30  | 60  | 120 min |
|-----------|--------------------|----|-----|-----|-----|-----|-----|---------|
| Hi        | 100                | 0/10| 4/10| 6/10| 7/10| 3/10| 1/10| 0/10    |
| Hi + Pyr  | 20 (µg, i.vent.)   | 0/10| 2/10| 3/10| 2/10*| 1/10| 0/10| 0/10    |
| Pyr       | 5                 | 0/10| 3/10| 3/10| 1/10*| 0/10| 0/10| 0/10    |
| Hi + Diphen | 10        | 0/10| 1/10| 1/10*| 0/10*| 0/10| 0/10| 0/10    |
| Diphen    | 20                | 0/10| 8/10*| 8/10*| 7/10*| 4/10*| 3/10| 1/10    |
| Hi + Cim  | 5 (µg, i.vent.)    | 0/10| 4/10| 4/10| 3/10| 0/10| 0/10| 0/10    |
| Cim       | 5                 | 0/10| 5/10| 4/10| 3/10| 1/10| 0/10| 0/10    |
| Hi + Cim  | 10                | 0/10| 5/10| 3/10| 2/10| 0/10| 0/10| 0/10    |
| Cim       | 20                | 0/10| 5/10| 5/10| 5/10| 1/10| 0/10| 0/10    |
| Hi + Atr  | 2                 | 0/10| 2/10| 2/10| 2/10*| 0/10| 0/10| 0/10    |
| Atr       | 5                 | 0/10| 1/10| 1/10*| 1/10*| 0/10| 0/10| 0/10    |
| Hi + Scop | 0.5               | 0/10| 4/10| 1/10*| 2/10*| 1/10| 0/10| 0/10    |
| Scop      | 1                 | 0/10| 1/10| 1/10*| 1/10*| 0/10| 0/10| 0/10    |
| Hi + Biper| 1                 | 0/10| 0/10*| 1/10*| 1/10*| 0/10| 0/10| 0/10    |
| Biper     | 2                 | 0/10| 0/10*| 1/10*| 1/10*| 0/10| 0/10| 0/10    |
| Hi + L-DOPA | 50          | 0/10| 3/10| 8/10| 5/10| 4/10| 3/10| 1/10    |
| L-DOPA    | 200              | 0/10| 1/10| 3/10| 2/10*| 1/10| 0/10| 0/10    |

Abbreviations: Hi, Histamine; Pyr, Pyrilamine; Diphen, Diphenhydramine; Cim, Cimetidine; Atr, Atropine; Scop, Scopolamine; Biper, Biperiden. *P<0.05, with the Fisher exact probability test, compared to the histamine-treated group.

(200 mg/kg, i.p.) were all effective in reducing both the intensity and the period of Hi-induced catalepsy.

Although there are some reports describing the cataleptogenic activity of Hi in cats (1) and monkeys (3), the results shown in those papers merely describe the administration of a single dose of Hi. There is no qualification of participation by either the receptor for H₁ or H₂. In the report of Nowak et al. (2), the dose...
of Hi employed to produce catalepsy in approx. 70% of the tested rats was 1000 μg; at this dose, acute toxicity signs such as flaccidity of the body and occasional respiratory disturbances were observed. In mice, the dose of Hi required to produce the same extent of catalepsy was 100 μg, about one-half the dose based on the organ weight in each species. At this dose, no signs of acute toxicity, as seen in the rats, were revealed. From these findings, it seems likely that mice are not only more sensitive to Hi than rats, but also catalepsy in mice induced by Hi causes no toxic reaction. It has been reported that cataleptic symptoms can be induced by an imbalance of cholinergic and dopaminergic functions in the central nervous system (CNS) (7), and it is generally considered that catalepsy induced by neuroleptics can be ascribed to an increase of dopamine turnover (8). Nowak et al. (2, 9) reported that Hi produced a rise in the concentration of homovanillic acid in the striatum without a decrease of dopamine content, suggesting an increase of dopamine turnover. Based on the same assumption, the inhibitory effect of L-DOPA on Hi-induced catalepsy can be understood. Nowak et al. (9) also reported that atropine inhibits both Hi-induced catalepsy and an increase of homovanillic acid. From these findings, it is reasonable to assume that the cataleptic effect of Hi is rather indirectly related to the cholinergic or dopaminergic mechanisms, but not directly associated with a histaminergic mechanism.

There are some findings suggesting the possibility that Hi itself produces catalepsy. For instance, Maśliński et al. (10) reported that high doses of histidine (i.p.) consequently increasing Hi level in the brain caused catalepsia-like symptoms in rats. Chopra and Dandiya (11) also reported that the administration of 4 mg/kg of perphenazine, causing catalepsy in rats, resulted in simultaneous increases of the brain acetylcholine and Hi; especially, the Hi content was increased by 18-fold compared with its normal level. They concluded that Hi content is a better indicator of catalepsy than acetylcholine content. In addition, they reported that an increase of Hi content induced by perphenazine was counteracted by diphenhydramine. Adam and Hey (12) also reported that chlorpromazine and trifluperazine significantly increased Hi content in the hypothalamus. H1 blockers are known to exert some anticholinergic action, and it has been suggested in some studies that the anticholinergic property may be responsible in some part of the effect of H1 blockers in the CNS (13). However, Subramanian and Mulder (14) reported that Hi did not produce the efflux of 14C-acetylcholine from striatal and hypothalamic slices. Therefore, it can be presumed that Hi-induced catalepsy may occur not only by imbalance between the dopaminergic and cholinergic systems, but also directly by the histaminergic mechanism. It has been recognized that not only H1 but also H2 receptors participate in the CNS action of Hi (15). However, it becomes apparent from the present study that catalepsy provoked by Hi in mice is associated only with the H1 receptor.

References

1) Feldberg, W. and Sherwood, S.L.: Injections of drugs into the lateral ventricle of the cat. J. Physiol. (Lond.) 123, 148–167 (1954)
2) Nowak, J.Z., Pilc, A., Lebrecht, U. and Maśliński, C.: Does histamine interact with cholinergic neurones in its cataleptogenic action in the rat? Neuropharmacology 16, 841–847 (1977)
3) Heath, R.G. and de Balbian, V.F.: Effects of chemical stimulation to discrete brain areas. Am. J. Psychiatry 117, 980–989 (1961)
4) Oka, M., Yamada, K., Kamei, C., Yoshida, K. and Shimizu, M.: Differential antagonism of antiavoidance, cataleptic and ptotic effects of neuroleptics by biperiden. Japan. J. Pharmacol. 29, 435–445 (1979)
5) Haley, T.J. and McCormick, W.G.: Pharmacological effects produced by intracerebral injection of drugs in the conscious mouse. Br. J. Pharmacol. 12, 12–15 (1957)
6) Siegel, S.: Nonparametric Statistics for the Behavioral Sciences, p. 96-104, McGraw-Hill Inc., New York (1956)

7) Bowers, M.B., Jr. and Roth, R.H.: Interaction of atropine-like drugs with dopamine-containing neurones in rat brain. Br. J. Pharmacol. 44, 301-306 (1972)

8) Costall, B. and Naylor, R.J.: Neuroleptic and non-neuroleptic catalepsy. Arzneimittelforsch. 23, 674-683 (1973)

9) Nowak, J.Z. and Maśliński, Cz.: Cholinergic link in the histamine-mediated increase in homovanillic acid in the rat striatum. Agents Actions 7, 27-30 (1977)

10) Maśliński, Cz., Lebrecht, U., Nowak, J.Z., Pilc, A. and Wieczorek-Fila, Z.: Catalepsia-like symptoms produced by histidine in rats. Agents Actions 3, 185-186 (1973)

11) Chopra, Y.M. and Dandiya, P.C.: The relative role of brain acetylcholine and histamine in perphenazine catatonia and influence of anti-depressants and diphenhydramine alone and in combination. Neuropharmacology 14, 555-560 (1975)

12) Adam, H.M. and Hye, H.K.A.: Concentration of histamine in different parts of brain and hypophysis of cat and its modification by drugs. Br. J. Pharmacol. 28, 137-152 (1966)

13) Wyngaarden, J.B. and Seegers, M.H.: The toxic effects of antihistaminic drugs. JAMA 145, 277-282 (1951)

14) Subramanian, N. and Mulder, A.H.: Modulation by histamine of the efflux of radiolabeled catecholamines from rat brain slices. Eur. J. Pharmacol. 43, 143-152 (1977)

15) Schwartz, J.C.: Minireview: Histamine receptors in brain. Life Sci. 25, 895-912 (1979)