The Role of Histamine H1-Receptors in the Anticonvulsive Effect of Morphine against Maximal Electroconvulsive Shock in Mice†

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ABSTRACT—Morphine is known to release histamine from mast cells. It is also known that histamine receptors mediate some of morphine's effects on the central nervous system. The contribution of H1- and H2-receptors to the effect of morphine on maximal electroconvulsive shock in mice was investigated in the present experiments. Morphine showed a dose-dependent anticonvulsive effect, but produced spontaneous clonic convulsions at higher doses (100 mg/kg, i.p.). The anticonvulsive effect of morphine (1 mg/kg, i.p.) was antagonized by histamine H1-receptor antagonists, dimethindene (0.1 mg/kg, i.p.), promethazine (0.4 mg/kg, i.p.) and pheniramine (30 mg/kg, i.p.), and naloxone (10 mg/kg, i.p.), but not by the H2-receptor antagonist ranitidine (10–50 µg, i.c.v.). These results show that morphine has an anticonvulsive effect via histamine H1-receptors against maximal electroconvulsive shock in mice.

Keywords: Morphine, Anticonvulsive effect, Histamine, Histamine H1-receptor, Maximal electroconvulsive shock

Brain histamine is localized in both neurons and mast cells (1–3). It has been suggested that mast cell stores of histamine contribute significantly to brain histamine levels (1–3). Evidence also suggests that histamine and other amines stored and released by mast cells, serve physiological roles as neuromodulators of brain functions (4–6). It has been suggested that the central histaminergic system plays an inhibitory role in convulsions (7–10).

Acute morphine treatment is known to increase the turnover of neuronal histamine (11). Moreover, morphine's effect on mast cells in the central nervous system should also be taken into consideration as a target of morphine action, since it is known to release histamine from mast cells in peripheral tissues (12, 13); On the other hand, histamine receptors are known to play important roles in morphine antinociception and morphine-stimulated locomotion (14, 15). It is also suggested that morphine has both convulsant and anticonvulsant effects, depending on the dose, the species, the route of administration and the method (16).

In the present study, we observed the role of histamine H1- and H2-receptors in the anticonvulsive effect of morphine against maximal electroconvulsive shock (MES) in mice.

MATERIALS AND METHODS

Animals
Male albino mice (Eczacibasi, Istanbul, Turkey) weighing 25–30 g were used. The animals were housed at a constant temperature (22±1°C), with food and water ad lib, and a 12-hr light/dark cycle (lights on at 6:00 a.m. and off at 6:00 p.m.).

The experiments had been approved by the “Center of the Laboratory Animals-Animal Care Ethics Committee” of our faculty.

Maximal electroshock seizures
MES seizures were induced through ear clip electrodes by a current generator (ECT Unit, 7801; Ugo Basile, Varese, Italy). The mice were stimulated with a 0.4-msec pulse width, 0.2-sec duration, 60 Hz square wave current. Tonic hind-limb extension (THE) was accepted as a MES seizure. Mice that did not show THE were considered to be protected from MES.

Experimental procedure
To estimate the current that produced MES seizure in half of the animals, MES50, 5 groups of mice (n=20) were...
subjected to electroshock of 30, 40, 50, 60 and 70 mA.

Various doses of morphine (ranging from 0.001 to 200 mg/kg, i.p.) were tested with MES50 in seven groups of mice (n=20), and the dose-response curve was obtained.

Naloxone, histamine H1-receptor antagonists, dimethindene, promethazine and pheniramine, and the histamine H2-receptor antagonist ranitidine were tested with MES50 in different groups of mice (n=20). Ranitidine was injected by the intracerebroventricular (i.c.v.) route. Under ether anesthesia, a 22 ga. cannula was implanted using the following coordinates: 0.8 mm anterior to bregma, 0.8 mm lateral to midline zero and 3.0 mm ventral to the skull surface. Other drugs were administered intraperitoneally in a volume of 0.1 ml/10 g body weight. The control group received only 0.1 ml/10 g saline intraperitoneally. All chemicals were dissolved in isotonic NaCl. The animals were used only once. Injections were made 1 hr before the test. All experiments were carried out during 2:00–5:00 p.m.

**Drugs**

Morphine hydrochloride (Haver, Istanbul, Turkey), dimethindene maleate (Fenistil®; Ciba-Geigy, Istanbul, Turkey), pheniramine maleate (Avil®, Hoechst, Istanbul, Turkey), promethazine hydrochloride (Sigma, St. Louis, MO, USA), ranitidine hydrochloride (Ulcuran®; Abfar-Zyma, Istanbul, Turkey) and naloxone hydrochloride (Sigma) were used.

**Statistical analyses**

MES50 was calculated by the method of Litchfield-Wilcoxon (17) using the computer program described by Tallarida and Murray (18), and comparisons among the groups were made by the Chi-square and Fisher exact test.

**RESULTS**

**Calculation of MES50**

In different groups of mice subjected to an electroshock of 30, 40, 50, 60 or 70 mA, the calculated MES50 current was 50 mA (73.37–56.65 mA).

**Dose-response relationship of morphine on MES50 seizure**

Morphine produced a dose-dependent anticonvulsant effect at low doses and completely protected against MES seizure at 1 and 50 mg/kg, i.p. (P<0.001) (Fig. 1); this effect was antagonized by naloxone (10 mg/kg, i.p.) (P<0.001) (Table 1). The protective effect of morphine against MES50 diminished at higher doses (100 and 200 mg/kg, i.p.; P<0.01 and P<0.05, respectively) (Fig. 1).

**Effects of H1 and H2-antagonists**

When used alone, dimethindene (0.1 mg/kg, i.p.), promethazine (0.4 mg/kg, i.p.), pheniramine (30 mg/kg, i.p.) and ranitidine (50 μg, i.c.v.) had no significant effect on MES seizures (Table 1). However, the anticonvulsive effect of morphine (1 mg/kg, i.p.) was antagonized by dimethindene, promethazine and pheniramine dose-dependently (Fig. 2, Table 1), but not by ranitidine (Table 1).

**DISCUSSION**

It has been widely reported that morphine has anticonvulsant and proconvulsant effects in various species depending on the dose, route of administration and the method (16). In the present study, we observed that morphine has a dose-dependent protective effect on MES seizures at lower doses and that this effect diminishes at higher doses. The lessening of the anticonvulsant effect at
higher doses may be due to its proconvulsant property behind its anticonvulsant effects.

Histamine receptors, especially H₂-receptors, are known to play important roles in morphine’s effects (14, 15). It has been reported that morphine antinociception is mediated by activation of brain histamine H₂-receptors in

Table 1. The effects of histamine receptor antagonists and morphine on MES

| Treatment                        | % seizure | P                |
|----------------------------------|-----------|------------------|
| Saline                           | 55        |                  |
| Morphine (1 mg/kg, i.p.)         | 0         | \( P < 0.001 \) vs saline, Chi square test |
| Dimethindene (0.1 mg/kg, i.p.)   | 40        |                  |
| Promethazine (0.4 mg/kg, i.p.)   | 45        |                  |
| Pheniramine (30 mg/kg, i.p.)     | 55        |                  |
| Ranitidine (10 µg, i.c.v.)       | 50        |                  |
| Ranitidine (25 µg, i.c.v.)       | 55        |                  |
| Ranitidine (50 µg, i.c.v.)       | 45        |                  |
| Morphine (1 mg/kg, i.p.) +       |           |                  |
| Dimethindene (0.01 mg/kg, i.p.)  | 10        |                  |
| Dimethindene (0.05 mg/kg, i.p.)  | 25        | \( P < 0.01 \) vs morphine, Fisher exact test |
| Dimethindene (0.1 mg/kg, i.p.)   | 50        | \( P < 0.01 \) vs morphine, Chi square test |
| Morphine (1 mg/kg, i.p.) +       |           |                  |
| Promethazine (0.1 mg/kg, i.p.)   | 5         |                  |
| Promethazine (0.2 mg/kg, i.p.)   | 25        | \( P < 0.05 \) vs morphine, Fisher exact test |
| Promethazine (0.4 mg/kg, i.p.)   | 45        | \( P < 0.01 \) vs morphine, Fisher exact test |
| Morphine (1 mg/kg, i.p.) +       |           |                  |
| Pheniramine (10 mg/kg, i.p.)     | 10        |                  |
| Pheniramine (20 mg/kg, i.p.)     | 30        | \( P < 0.05 \) vs morphine, Fisher exact test |
| Pheniramine (30 mg/kg, i.p.)     | 45        | \( P < 0.01 \) vs morphine, Fisher exact test |
| Morphine (1 mg/kg, i.p.) +       |           |                  |
| Ranitidine (25 µg, i.c.v.)       | 0         |                  |
| Morphine (1 mg/kg, i.p.) +       |           |                  |
| Ranitidine (50 µg, i.c.v.)       | 0         |                  |
| Morphine (1 mg/kg, i.p.) +       |           |                  |
| Naloxone (10 mg/kg, i.p.)        | 55        | \( P < 0.001 \) vs morphine, Chi square test |

Fig. 2. Effects of histamine H₁-receptor antagonists, dimethindene (▲), promethazine (□) and pheniramine (▲), in combination with morphine (1 mg/kg, i.p.) on MES₅₀ seizure. *\( P < 0.05 \), **\( P < 0.01 \) vs morphine (1 mg/kg, i.p.), Fisher exact test; **\( P < 0.01 \) vs morphine (1 mg/kg, i.p.), Chi-square test.
rats (14), and morphine-stimulated locomotion of the C57BL/6J mouse may be partially mediated by histamine H2-receptors of the nucleus accumbens (15). Morphine and other opioids with μ-agonistic activity increase brain histamine turnover in mice (11, 19). Footshock-induced enhancement of brain histamine turnover in mice is mediated partly by activation of opioid-related mechanisms (20). Our results show that the anticonvulsant effect of morphine is mediated by histamine H1-receptors, since H1-antagonists, dimethindene, promethazine and pheniramine, antagonized this effect, but ranitidine did not.

It was reported that i.c.v. histamine injections or endogenous histamine release in mouse brain exerts anticonvulsant effect against electrically induced convulsions, which is antagonized by histamine H1-receptor antagonists, but not by centrally acting histamine H2-receptor antagonists (8–10). It has been suggested that elevated brain histamine concentration by histidine or metoprine leads to an increase of the pentetrazole-induced seizure threshold (but not of the electroconvulsive threshold) which is antagonized by dimethindene and promethazine (7). On the contrary, Tuomisto and Tacke showed that elevation of brain histamine concentrations by metoprine inhibits maximal hindleg extension after MES and suggested that histaminergic neurons are involved in mechanisms that inhibit generalizations of epileptic discharges in rat brain (21). These reports indicate that the anticonvulsant effect of morphine may be mediated by activation of brain histamine H1-receptors.

Our results support earlier reports indicating that morphine induces histamine release in mice brain; moreover, data suggest that morphine exerts anticonvulsant effects via histamine H1-receptors. Further experiments are required to delineate the site of morphine’s action on MES seizure, whether it acts on mast cells, neurons or both.

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