Trakya Üniversitesi Tıp Fakültesi
Dergisi: 12(1,2,3): 17-19, 1995

The Role of H2 Receptors in the Nociceptive Effect of Compound 48/80 in Mice*

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SUMMARY

Contribution of H1 and H2 receptors to the effect of compound 48/80, a potent histamine releaser, on nociceptive responses was evaluated in mice. Compound 48/80 produced nociceptive effects in hot-plate test. Both the H1 receptor antagonist, dimethindene (0.1 mg/kg, i.p.), and H2 receptor antagonist, ranitidine (4 mg/kg, i.p.), were ineffective in preventing the nociceptive effect of compound 48/80, whereas a large peripheral dose of ranitidine (100 mg/kg, i.p.) antagonized it, since ranitidine is a poorly brain penetrating compound. These results indicate that compound 48/80 has nociceptive effects, mediated via central H2 receptors, in hot-plate test in mice.

Key Words: *Compound 48/80, nociceptive effect, H1 receptor antagonist, H2 receptor antagonist*

ÖZET

48/80 MADDESİNİN SIÇANLARDAKİ NOSİSEPTİF ETKİSİNDE H2 RESEPTÖRLERİNİN ROLÜ

Bilinen en güçlü histamin salıverici maddelerden biri olan 48/80 maddesinin sıçanlardaki nosiseptif yanıtlar üzerine etkisine, H1 ve H2 reseptörlerinin katılımı incelendi. 48/80 maddesi "hot-plate" testinde belirgin derecede nosiseptif etki oluşturdu. Hem H1 reseptör antagonisti dimetinden (0.1 mg/kg, i.p.), hem de H2 reseptör antagonisti, ranitidin (4 mg/kg, i.p.), 48/80 maddesinin nosiseptif etkisini önlemede etkisizdi. Buna karşın, beyine oldukça az geçen bir bileşik olan ranitidin, çok yüksek dozda kullanıldığında (100 mg/kg, i.p.), bu etkiyi antagonize etti. Bu sonuçlar, sıçanlarda "hot-plate" testinde, 48/80 maddesinin nosiseptif etkilerine santral H2 reseptörlerin aracılık ettiğini göstermektedir.

Anahtar Kelimeler: *48/80 maddesi, nosiseptif etki, H1 reseptor antagonisti, H2 reseptor antagonisti*

Brain histamine is localized in both neurons and mast cells and there is direct biochemical evidence for a contribution by mast cells to brain histamine levels (1, 2, 3). Evidence also suggests that biogenic amins such as histamine, serotonin and dopamine, which are stored and released by mast cells, serve physiological roles as neuromodulators of brain functions (2, 4, 5).

Although histamine is now widely accepted as a transmitter or modulator in the central nervous system, it is only recently that some investigations on its role in nociception has been done; however there is conflicting evidence (2, 6, 7, 8).

In the present study, we observed the role of histamine, stored in brain mast cells, on nociception.

METHOD

Animals. Male albino mice (Eczacıbaşı) weighing 25-30 g were used. The animals were housed at constant room temperature (22 ± 1 °C),

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* Presented in 1th European Congress of Pharmacology, Milano, ITALY
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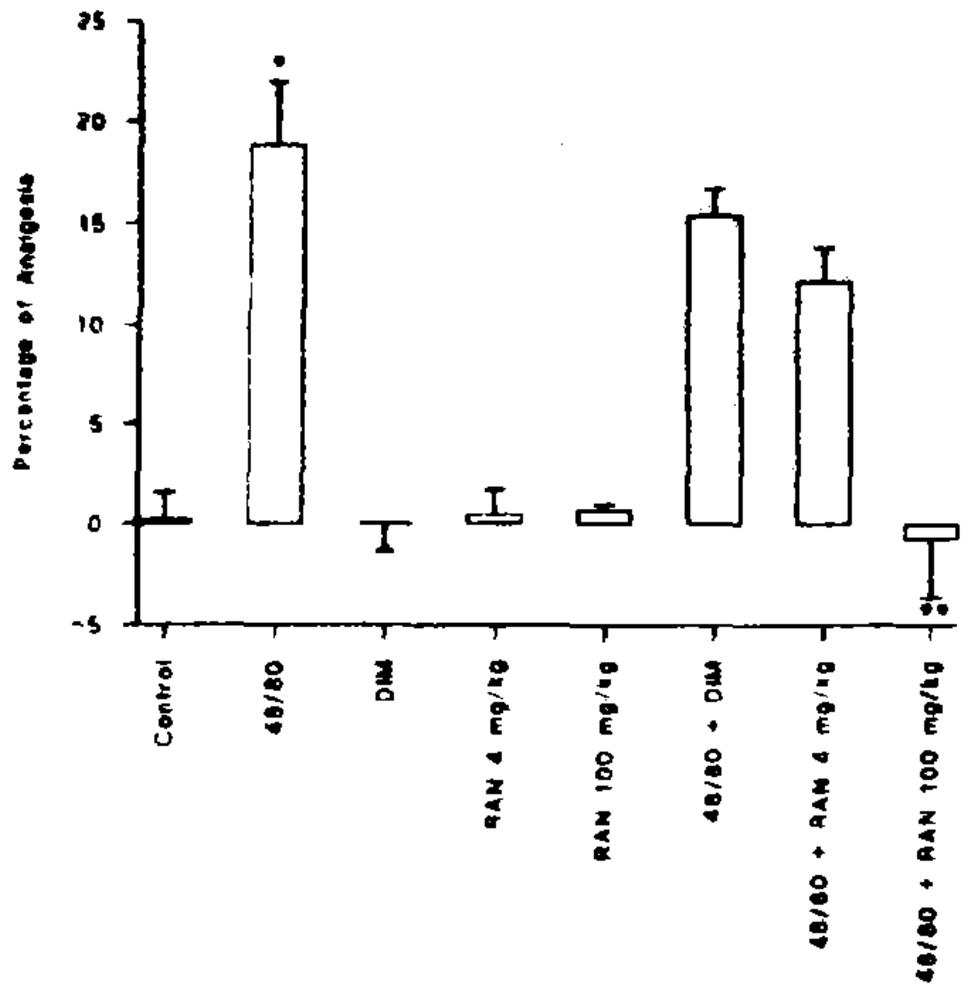

FIGURE I. Percentage of analgesia of all groups

with food and water *ad libitum*, and a 12 hr light/dark cycle (lights on at 6:00 a.m., and off at 6:00 p.m.).

Hot plate test in mice. A glass cylinder (16 cm high, 16 cm diameter) was used to keep the mouse on the heated surface of the plate, which was kept at a temperature of 55±0.5 °C using a thermo-regulated water-circulating pump. A latency period until the mouse jumped was registered by a means of a stopwatch (cut-off time 60 sec). Control values for each animal were determined before drug administration. Mice were re-tested 30 min after drug injection. The responses were expressed as a percentage of analgesia using the following equation:

$$\text{Percentage of analgesia} = \frac{(\text{test latency} - \text{control latency})}{(\text{cut - off time} - \text{control latency})} \cdot 100$$

Drugs. Dimethindene (Fenistil®, Ciba-Geigy) and ranitidine (Ulcuran®, Abfar-Zyma) were diluted from commercial preparations. Compound 48/80 was a gift from Prof. Dr. A. Akçasu, Department of Pharmacology, Cerrahpaşa Medical Faculty of İstanbul University.

Statistical analysis. Results were evaluated by ANOVA followed by the Newman-Keuls test. Values are expressed as means ± S.E.M.

RESULTS

Our results indicate that compound 48/80 produces antinociceptive responses ($p < 0.05$). High dose of ranitidine inhibited compound 48/80 antinociception ($p < 0.05$), whereas dimethindene and low dose of ranitidine had no effect (Table I, *Figure 1*).

DISCUSSION

It is suggested that mast cells stores of histamine contribute significantly to the overall histamine content of the brain (1, 2, 3). On the other hand, the transmitter role of histamine in the mammalian brain is widely accepted in recent years (2, 8). The histaminergic system neuron system regulates various activities of the brain, such as the arousal state, brain energy metabolism, locomotor activity, neuroendocrine, autonomic and vestibular functions, feeding, drinking, sexual behavior, and analgesia (7).

The role of histamine and histamine receptor antagonists in nociception has been studied extensively; however there is conflicting evidence. Although most of these findings suggest that histamine and histamine receptors, especially histamine H2 receptors, are involved in the antinociceptive activity (9, 10, 11). Malmberg Aiello P. *et al* showed that low doses of histamine was hyperalgesic both in rats and mice (12), and Koch J.E. *et al* showed the pro-nociceptive effects of histamine H2 receptors (13). Moreover, the antinociceptive effects of H1 and H2 antihistaminics have also been shown (14, 15). On the other hand, it is suggested that histamine H2 receptor antagonists

TABLE I. Percentage of analgesia of all groups

Groups	Percentage of analgesia
Control	-0.20 ± 1.38
Dimethindene (0.1 mg/kg, ip)	0.02 ± 1.38
Ranitidine (4 mg/kg, ip)	-0.46 ± 1.24
Ranitidine (100 mg/kg, ip)	-0.68 ± 0.29
48/80 (2 mg/kg, ip)	-18.86 ± 3.12*
48/80 (2 mg/kg, ip) + Dimethindene (0.1 mg/kg, ip)	-15.27 ± 1.32*
48/80 (2 mg/kg, ip) + Ranitidine (4 mg/kg, ip)	-12.04 ± 1.69*
48/80 (2 mg/kg, ip) + Ranitidine (100 mg/kg, ip)	0.72 ± 2.90**

* $p < 0.05$ vs control (ANOVA, Newman-Keuls test)

** $p < 0.05$ vs 48/80 alone (ANOVA, Newman-Keuls test)

have inhibitory effects in opioid antinociception (16, 17, 18, 19, 20).

Present data suggests that compound 48/80, a potent histamine releaser from mast cells, possess an analgesic effect in rats, and H_2 receptors mediate compound 48/80 antinociception. Our findings, indicating the nociceptive effects of histamine are in line with those of Malmberg Aiello P. *et al* and Koch J.E. *et al* (12, 13). Probably, compound 48/80 released a small amount of histamine from brain mast cells with the dose used in our experiments.

A large peripheral dose of ranitidine antagonized the nociceptive effect of compound 48/80 in our study, since ranitidine is a poorly brain penetrating compound. These results correlate with the findings suggesting that histamine H2-receptors mediate histamine's nociceptive effects. However, further experiments are needed to delineate the mechanisms of the nociceptive or antinociceptive properties of histamine and histamine antagonists.

ACKNOWLEDGEMENT

We thank Eczacıbaşı-Turkey for mice and Prof. Dr. A. Akçasu for the generous supply of compound 48/80.

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