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Neuropharmacology of the Histaminergic system in the brain

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Histamine is now recognized as a neurotransmitter or a neuromodulator in the brain, as many scientific investigations have been carried out since the 1980's, especially in Japan. Two major findings have contributed to understanding the possible functions of central histamine, as follows. Immunohistochemical findings that the cell bodies of histaminergic system located in the tuberomammullary nucleus of lateral hypothalamus in the brain and efferent fibers projected widely from the olfactory bulb to the spinal cord (Wada's group). Thus, it is recognized that the central histaminergic neuron system is a regulatory center for whole brain activity. Another finding is the existence of histamine H3 receptors in the presynapse of histaminergic neuron system in addition to the postsynaptic H1 and H2 receptors. Arrang et al. demonstrated the existence of presynaptic histamine H_3 receptors controlling the release of neuronal histamine as autoreceptors. A few years later, this idea was further confirmed by the introduction of the first selective ligands for study of the function of histamine H_3 receptors, such as *(R)*-α-methylhistamine, an agonist of these receptors, and thioperamide, an antagonist of them. Histamine H3-receptor antagonists, such as thioperamide, clobenpropit and FUB 181 can activate the central histaminergic system inducing enhanced histamine release from nerve terminals.

Recently, much evidence has been provided that the central histaminergic system plays an important role in learning and memory in rodents. For example, activation of the histaminergic system by intracerebroventricular treatment with

histamine or intraperitoneal administration of histidine leads to improved learning and memory in rodents. Inhibition of the central histaminergic system, by blocking the H1 receptors or histamine synthesis, disrupts learning and memory. Betahistine, a partial H1-receptor agonist and H3-receptor antagonist improved a scopolamine-induced learning deficit in rat.

These findings suggest the possibility that histamine H_3-receptor antagonists may be useful for treatment of learning and memory deficits such as those of Alzheimer's disease. In fact, we confirmed this by studying the effect of FUB 181 in the elevated plus-maze test. Treatment with scopolamine (0.5 mg/kg) 15 min before an acquisition trial significantly prolonged transfer latency on the retention trial compared with that of the vehicle-treated group. Pretreatment with FUB 181 alone (2.5 and 5 mg/kg) 60 min before the acquisition trial counteracted the scopolamine-induced prolongation of transfer latency on the retention trial. FUB 181 alone at the doses tested did not affect transfer latency. The ameliorating effect of FUB 181 (2.5 mg/kg) on scopolamine-induced prolongation of transfer latency on the retention trial was blocked by pretreatment with a histamine H3 agonist, BP 2.94 (10 mg/kg). The effect of FUB 181 was also antagonized by pretreatment with ketotifen (4 mg/kg), but not by pretreatment with terfenadine (10 mg/kg,) or zolantidine (20 mg/kg). Even a low dose of FUB 181 (1.3 mg/kg) in combination with zolantidine (20 mg/kg) counteracted the scopolamine induced prolongation of transfer latency on the retention trial. None of BP 2.94, ketotifen, terfenadine, and zolantidine given alone 70 min before the acquisition trial resulted in significant differences in transfer latency on the retention trial from that in the vehicle-treated group. Thus, FUB 181, a novel 4-(3-(ω-(aryl)alkyloxy)propyl)-1*H*-imidazole derivative alone (2.5 and 5 mg/kg) significantly improved the scopolamine-induced learning deficit in the elevated plus-maze test in mice. Since this ameliorating effect of FUB 181 was antagonized by

pretreatment with BP 2.94 (10 mg/kg), a prodrug of *(R)*-α-methylhistamine, a histamine H_3-receptor agonist, it was probably due to the increased release of endogenous histamine *via* autoreceptors on histaminergic neurons. This hypothesis is supported by our previous finding in an *in vitro* study that the antagonist activity of FUB 181 for histamine H_3 receptors was at least 250 times higher than that for other receptors including histamine H_1 and H_2 receptors, muscarinic (M_3), serotonergic (5-HT_{2A} and 5-HT_3), and adrenergic (α_1 and β_2) receptors. However, the cholinergic system may have played a role in the ameliorating effect of histamine H_3-receptor antagonists on learning and memory, since there is a close relationship between the cholinergic and histaminergic system in learning and memory. One possibility is that FUB 181 increases the release of acetylcholine through histamine H_3 heteroreceptors.

Moreover, the possibility of the use of histamine H3 receptor antagonists in the treatment of Parkinson's disease, epilepsy, motion sickness, narcolepsy, diabetes etc. has been suggested in addition to the useful for treatment of Alzheimer's disease.

On the other hand, antihistamines (H1 receptor antagonists) are widely prescribed for treatment of various allergy symptoms. Currently, central effects such as sedation, enhanced convulsion in young epileptic patients, enhanced rewarding effect of morphine-like drugs are known as the common side effects of antihistamines treatment. Therefore, a newer class of H1 receptor antagonists has been developed with an improved balance between central nervous system and peripheral effects. It is now established that epinastine, cetirizine, ebastine, astemizole fall into this new category of antihistamines. Here, we can show you an example as follows.

Effects of second generation of histamine H_1 receptor antagonists, cetirizine and ebastine, on the antitussive and rewarding effects of dihydrocodeine in mice were studied. Little information is available about the interaction between dihydrocodeine and second-generation antihistamine drugs such as ebastine and cetirizine, with

particular reference to the rewarding effect of dihydrocodeine. In this study, the effects of second generation of histamine H_1 antagonists such as, ebastine and cetirizine on the antitussive and rewarding effects of dihydrocodeine were examined in mice. Male ICR Mice (6 weeks old) were exposed to a nebulized solution of capsaicin (30 micro-mol/l) under conscious and identical conditions, using a body plethysmograph. The coughs produced during a 3-min exposure period were counted. Effects of H_1 antagonists on the reinforcing effect of dihydrocodeine were assessed by using the conditioned place preference procedure in mice. Dihydrocodeine, at doses of 3, 30 mg/kg, p.o., dose-dependently inhibited the number of capsaicin-induced coughs when the antitussive effect was examined 60 min after administration. The ED_{50} of dihydrocodeine was determined to be 9.6 mg/kg. The dose-response curve of the antitussive effect of dihydrocodeine was shifted to the left under the p.o. co-administration of ebastine or cetirizine. The potentiation of the antitussive effect of dihydrocodeine by ebastine was similar to that obtained with cetirizine. Dihydrocodeine (3 mg/kg, i.p.) ebastine (1 mg/kg, s.c.) and cetirizine (1 mg/kg, s.c.) by themselves, did not produce a significant preference or aversion for the drug-associated place. Concurrent dosing of dihydrocodeine and ebastine produced a significant place preference. However, dihydrocodeine combined with cetirizine didn't produce a significant place preference. Significant place preference induced by concurrent dosing of dihydrocodeine and ebastine was abolished when SCH23390 (3 mg/kg, s.c.) was given as pretreatment 30 min before each conditioning session. Concurrent dosing of dihydrocodeine (3 mg/kg, i.p.) and ebastine (1 mg/kg, s.c.), but not cetirizine (1 mg/kg, s.c.) produced a marked increase in dopamine turnover ratio (DOPAC+HVA/DA) in the limbic forebrain. There was no statistical difference between the ED_{50} of dihydrocodeine in combination with ebastine and that of dihydrocodeine in combination with cetirizine. Concurrent dosing of dihydrocodeine and ebastine produced a

significant place preference. This behavioral potentiation was antagonized by SCH23390, a dopamine D_1 antagonist. Moreover, ebastine enhanced the central dopamine turnover ratio, but cetirizine did not, in this study. Taken together, the potentiation of place preference of dihydrocodeine with ebastine may be due, at least in part, to stimulations of the central dopaminergic system via D_1 receptors. However, combination of dihydrocodeine with cetirizine dose not potentiate place preference at all, nor does it potentiate the central dopaminergic system. Thus, it is likely that cetirizine may be a useful constituent in opioid-containing, antitussive preparations that would not potentiate the development of psychological dependence.