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## INFORMATION

Hokkaido University granted the Doctor of Veterinary Medical Science Degree to the following researcher on December 25, 1996, under the regulation (1962) authorizing the granting of the Doctor's degree to qualified researchers who was not graduate of the Graduate School of Veterinary Medicine.

The title of the thesis and other information are as follows :

### BEHAVIORAL AND NEUROCHEMICAL STUDY OF EFFECT OF MCI-225, A NOVEL PSYCHOACTIVE COMPOUND, ON ATTENTION, LEARNING AND MEMORY

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The effect of MCI-225, a novel synthesized thienopyrimidine analog on attention, learning and memory was studied in comparison with those of tacrine, an acetylcholinesterase (AChE) inhibitor and desipramine, a noradrenaline (NA) uptake inhibitor. The mechanism of action of MCI-225 was also investigated.

Dorsal noradrenergic bundle (DNB) lesion with 6-hydroxydopamine caused both resistance to the extinction of food-rewarded runway response and a marked decrement in cortical NA content in rats. MCI-225 (10 and 30 mg/kg, PO) and desipramine (30 mg/kg, PO) reduced the resistance to the extinction in DNB-lesioned rats but tacrine (1 and 3 mg/kg, PO) did not reduce the resistance. N-(2-chloroethyl)-N-ethyl-2-bromo-benzylamine (DSP-4), a neurotoxin of noradrenergic neurons, (50 mg/kg, IP) decreased both the investigatory response to a novel stimulus and cortical NA content in mongolian gerbils. MCI-225 (1-10 mg/kg, PO) and desipramine (3 mg/kg, PO) ameliorated the decrement in the investigatory response in DSP-4 treated gerbils. Tacrine did not change the response.

Basal forebrain (BF)-lesion with ibotenic acid impaired the retention of passive avoidance response (PAR) and decreased both cortical choline acetyltransferase (ChAT) activity and local cerebral glucose utilization (LCGU) in rats. Repeated administration of MCI-225 (0.3 and 1 mg/kg, PO) reversed the PAR failure but did not change the cortical ChAT activity. MCI-225 (1 mg/kg, PO) ameliorated the reduction of LCGU in the parietal cortex. Repeated administration of tacrine (0.3 mg/kg, PO) reversed the PAR failure but failed to prevent the decrement in both ChAT activity

and LCGU. In Morris water maze task, MCI-225 (1–10 mg/kg, PO) reversed the learning impairment caused by scopolamine (0.5 mg/kg, IP) in rats. Tacrine (0.1–3 mg/kg, PO) tended to reverse the impairment.

In midpontine pretrigeminal (PTG) feline preparation, MCI-225 (1 and 3 mg/kg, IV) enhanced the tracking eye movements induced by a moving visual stimulus with negligible effects on both spontaneous eye movements and the electrocorticogram (ECoG). Tacrine (0.3 mg/kg, IV) enhanced both types of eye movements with a tendency to induce ECoG arousal. Desipramine (3 mg/kg, IV) did not change tracking eye movements but slightly increased the spontaneous eye movements with a tendency to induce ECoG drowsy.

MCI-225 (1–30 mg/kg, PO) did not change gross behavior and spontaneous motor activity in rats. MCI-225 (30 mg/kg, PO) slightly increased the arousal electroencephalogram (EEG) pattern in rats. MCI-225 inhibited von-Bezold Jarisch reflex induced by 5-hydroxytryptamine (5-HT) in rats ( $ED_{50}=42$  mg/kg, PO).

In rat brain synaptosomes, MCI-225 inhibited uptake of NA ( $IC_{50}=1.8\times 10^{-8}$ M) and 5-HT ( $IC_{50}=1.7\times 10^{-6}$ M). MCI-225 ( $1\times 10^{-7}$ – $1\times 10^{-5}$  M) did not show any effects on ChAT activity, AChE activity and high affinity choline uptake in rat brain. MCI-225 showed the highest affinity to 5-HT<sub>3</sub> receptor in rat cortex ( $IC_{50}=8.1\times 10^{-8}$  M) among the receptors tested.

These results show that MCI-225 reverses the behavioral changes caused by central noradrenergic or cholinergic disruption and suggest that MCI-225 may ameliorate the impairment in attention, learning, and memory. In PTG preparation, in which neither noradrenergic nor cholinergic neurons is lesioned, MCI-225 may also enhance attention. It is suggested that NA uptake inhibition and 5-HT<sub>3</sub> receptor antagonism by MCI-225 enhance the central noradrenergic and cholinergic function, and in turn, MCI-225 may affect attention, learning and memory.

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