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Development of a novel cognitive enhancer, T-588, and its effect on the central nervous system

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Alzheimer's disease is believed to be associated with the loss of cholinergic activity in the cortex and hippocampus. In addition, it has been reported that the monoaminergic systems which also controls brain functions are disturbed in Alzheimer's patients. Based on these neurochemical background, a number of cholinesterase inhibitors including tacrine and its analogues and some monoamine oxidase inhibitors such as L-deprenyl and monoamine reuptake inhibitors have been developed for the treatment of dementia, but all of the known drugs are not truly effective.

We thought that a drug that activates only one neurotransmitter system is not effective enough for the treatment of the symptoms associated with Alzheimer's disease and vascular dementia, and we conceived that an agent enhancing both central cholinergic and monoaminergic functions would be useful for the treatment of dementia

In our initial investigation directed to developing a potent cognitive enhancer, we focused on finding a prototype compound by structural modifications of acetylcholine. First, we selected compounds which cause both anti-amnestic and anti-hypoxic activities in mice. Among them, we selected T-136, as our prototype compound. Next, we synthesized a series of bicyclic aryl analogues of T-136. We finally selected T-588, titled compound and compared the pharmacological properties of T-588 with those of tacrine, used in the treatment of Alzheimer's disease in the U.S.A and with indeloxazine and bifemelane, used as cerebral improvers in Japan. T-588's potency to ameliorate CO2-induced amnesia is 10-fold as great as tacrine, and 300-fold as great as the prototype compound, T-136, but indeloxazine and bifemelane are inactive. The anti-hypoxic activity of T-588 is almost comparable to indeloxazine. The acute toxicity of T588 in mice is less toxic than tacrine. Another notable feature of T-588 is a good serum-to-brain penetration in spite of its low lipophilicity in rats.

We investigated the effect of T-588 on experimental cerebral anoxia, scopolamine-induced EEG changes, and memory impairment. T-588 showed a significant and dose-dependent prolongation of the survival time in normobaric hypoxia, KCN-induced anoxia and decapitation-induced gasping at doses of 30 - 100 mg/kg, p.o.. In order to investigate the mechanisms for the anti-anoxic action of T-588, we tested the effect of scopolamine on the protective action of T-588. Scopolamine at a dose of 1 mg/kg did not affect the survival time in all of the models. The anti-hypoxic effect of T-588 was completely inhibited by pretreatment with scopolamine, while the anti-anoxic effect was partially inhibited. On the other hand, the effect on the gasping duration was not affected

by scopolamine. These results suggest that the activation of the central nervous cholinergic system is involved as one of the mechanisms for the anti-anoxic action of T-588. Intravenous injection of scopolamine at a dose of 0.05 mg/kg increased the appearance rate of delta and theta waves, and decreased that of beta waves in rabbits. T-588 improved these scopolamine-induced EEG changes at a dose of 0.1 mg/kg, i.v. 15 min before scopolamine injection, and tacrine also ameliorated the scopolamine-induced EEG changes at 1 mg/kg, i.v..

Next, we examined the effects of T-588 on memory impairment in passive avoidance response in rodents, active avoidance response in cerebral embolized rats and spatial navigation task in ischemic rats. T-588 proved beneficial effects on scopolamine-, C02-, and BF lesion-induced memory impairments in the passive avoidance test at 0.1 - 10 mg/kg, p.o. and tacrine also improved the impairment at 1 - 10 mg/kg, p.o.. The cerebral embolization was produced by injecting the microspheres (mean size: 48 μm) in 20% dextran into the left internal carotid artery. Necroses were observed in several regions of rat brain taken 8 weeks after cerebral embolization, and enlargement of the lateral ventricle indicating atrophy of the hippocampus was also observed. The levels of acetylcholine and monoamines obtained at 1 and 8 weeks after the cerebral embolization significantly decreased. The cerebral embolization caused marked impairment of acquisition in active avoidance response. T-588 significantly ameliorated learning impairment in the embolized rats to the level of sham control at doses of 3 and 10 mg/kg, p.o., but tacrine had no effect at doses 0.3 - 3 mg/kg, p.o.. T-588 also significantly improved the spatial memory impairment in ischemic rats to the level of sham control at a dose of 3 mg/kg, p.o.. It is quite startling that repeated administration of T-588 at chronic phase ameliorated the memory and learning impairment in the embolized rats and ischemic rats.

Although the mechanism for T-588 is not clear, actions confirmed are as followings: 1) T-588 facilitates releases of acetylcholine and monoamines. 2) T-588 stimulates phosphoinositide (PI) hydrolysis and cAMP formation. 3) T-588 potentiates NGF-dependent morphological differentiation of PC 12 cells.

To summarize;

1. We have discovered a highly potent cognitive enhancing agent, T-588, by a structural modification of our own prototype compound.
2. T-588 is characterized by potent amnesia-reversal activity, protective activity against hypoxia, and low acute toxicity.
3. These results suggest the usefulness of T-588 in clinical treatment of memory impairment resulting from Alzheimer's disease or cerebral disorders.