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Meeting abstract

Effects of the coumarin scopoletin on learning and memory, on release of acetylcholine from brain synaptosomes and on long-term potentiation in hippocampus

Ariane Hornick[1], Andreas Lieb[1], Nguyen P Vo[1], Judith Rollinger[2], Hermann Stuppner[2] and Helmut Prast*[1]

Address: [1]Department of Pharmacology and Toxicology, Institute of Pharmacy, Leopold-Franzens-University of Innsbruck, 6020 Innsbruck, Austria and [2]Department of Pharmacognosy, Institute of Pharmacy, Leopold-Franzens-University of Innsbruck, 6020 Innsbruck, Austria

Email: Helmut Prast* - helmut.prast@uibk.ac.at

* Corresponding author

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Background

Among the chemical class of coumarins several substances have been described to be effective as cognition enhancers. We have recently characterized the coumarin scopoletin as a compound which fits a pharmacophore model of AChE inhibitors and enhances the release of ACh in rat brain [1]. Now, a comprehensive study was carried out in order to investigate the effects of scopoletin on learning and memory, on release of ACh from synaptosomes and on hippocampal long-term potentiation (LTP) in order to uncover the mechanism of action.

Materials and methods

Learning and memory: The effect of scopoletin on learning and memory was tested on normal and scopolamine-amnestic mice with the T-maze alternation and the object recognition test. *Release of ACh from synaptosomes of rat brain frontal cortex:* Synaptosomes were incubated with [^{3}H]choline and the release of the formed [^{3}H]ACh from superfused synaptosomes placed on filters was determined. The effect of scopoletin, galantamine and mecamylamine on ACh release was investigated. *Neural transmission and neuroplasticity in hippocampus:* Basal field EPSPs (fEPSPs) and LTP-amplified fEPSPs were evoked in the CA1 subfield of slices of rat hippocampus by stimulation of the Schaffer collateral projection and the effects of scopoletin, nicotine and mecamylamine on basal fEPSPs and on LTP were studied.

Results

Scopoletin (20 μg; i.c.v.) abolished the scopolamine-induced impairment on alternation in the T-maze and on object recognition, while it was ineffective in normal mice. Scopoletin enhanced the 15 mM K^+-induced release of ACh from synaptosomes, showing a bell-shaped dose-effect curve (maximum effective concentration: 4 μM), similar to that of galantamine (maximum effective concentration: 1 μM). The effect of both compounds was blocked by the nAChR antagonist mecamylamine, showing the involvement of nAChRs. In superfused slices from rat hippocampus, scopoletin (4 μM) did not influence basal fEPSPs but it amplified the LTP-induced increase of the fEPSPs. The effect of scopoletin on neuronal plasticity was abolished by mecamylamine. These properties of scopoletin were also found for the positive control compound nicotine.

Conclusion

The effects of scopoletin on the performance of mice in the learning tasks and on hippocampal LTP suggest that this compound exerts cognition-enhancing properties. The inhibition of LTP amplification and of presynaptic synaptosomal ACh release by mecamylamine point to the

involvement of nAChRs. Though previous studies found AChE inhibitory (IC_{50}: 168 μM) and weak MAO inhibitory activity, the predominant mechanism of action might be the nicotinic agonist property.

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References
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