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Reverse pharmacology of *sceletium tortuosum*

A "reverse pharmacology" approach was started with an extract of *Sceletium tortuosum*, currently sold as Zembrin® in the USA, Canada, Brazil, Malaysia, and South Africa. It is a proprietary extract of a low-alkaloid cultivated selection of *Sceletium tortuosum*, and is used by healthy people for enhancing mood, decreasing anxiety and stress and improving cognitive function under stressful situations. As test model the hippocampus slice *in vitro* was chosen to compare its effects with four of its alkaloid constituents, namely Mesembrine, Mesembrenone, Mesembrenol and Mesembranol. Measurement of the amplitude of population spikes was performed in the presence of single shock stimulation and theta burst stimulation resulting in long term potentiation (LTP). Rats were treated daily for one week with 5 or 10 mg/kg of Zembrin® before the hippocampus was taken out for *in vitro* analysis. Amplitudes of the population spikes were dose dependently attenuated. Out of four glutamate receptor agonists only Fluorowillardine was completely unable to induce its agonistic action. This points to an AMPA receptor mediated attenuation of hippocampal excitability produced by repetitive dosing of Zembrin®. Superfusing the slices directly with the alkaloids at nanomolar concentrations (3.5 – 35 nM) resulted in a concentration dependent attenuation of population spike amplitudes. However, only Mesembrenol and Mesembranol were able to prevent the action of Fluorowillardine, thus resembling the effect of the whole extract. Comparing now the chemical formula of the alkaloids in terms of a structure activity relationship, the hydroxy group at C6 instead of a carbonyl group in mesembranol seems to be essential for interaction with AMPA dependent transmission. Since attenuation of AMPA mediated transmission has been related to successful adjunctive treatment of epileptic patients, Mesembranol - following the principle and methodology of "reverse pharmacology" - might serve as chemical lead for the development of new drugs for the treatment of epilepsy.

Biography

Wilfried Dimpfel is Honorary Professor at Justus-Liebig-University Giessen, Germany, since 1983. He is Pharmacologist and got his Neurophysiological Education during 1973-1974 as Max Kade stipend (New York) at the NIH Bethesda from Phil Nelson. Together with Hans-Carlos Hofmann, a Physicist and Mathematician, he developed quantitative EEG software for research and practice. He is Consultant and CSO at NeuroCode AG, Wetzlar, Germany. He published more than 150 papers in peer-reviewed journals.

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