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Title: In vivo characterization of natural product GABAA modulators and their derivatives

Abstract in Englisch

Valerenic acid (VA) and piperine positively modulate GABAA receptors comprising β2- or β3-subunits. The therapeutic potential of these natural products and their derivatives is largely unknown. The aim of this study was to analyze anxiolytic, sedative, and anticonvulsive effects of VA, piperine and selected derivatives. Effects on anxiety-related behavior of C57BL/6N mice were studied by means of the elevated plus maze (EPM) and the light dark choice test (LDT). Effects on locomotor activity (sedation) were analyzed by means of the open field test.

Effects on seizure threshold were assessed making use of the Pentylenetetrazole (PTZ)-tail vein infusion test. Plasma levels of VA and selected piperine derivatives were estimated at different time points after intraperitoneal administration. Out of the studied VA ester derivatives, the methylester and propylester derivatives induced more pronounced anxiolytic effects with a faster onset than VA. The anticonvulsive effect of the methylester occurred with a faster onset than VA. In contrast, the ethylester of VA induced longer lasting anxiolytic and anticonvulsive effects, occurring with a delayed onset. After intraperitoneal application of VA esters to the animals free VA was detected in plasma, suggesting release of VA.

I conclude, that VA esters may serve as prodrugs of VA. VA amide derivatives (VA-amide, VA-methylamide, and VA-tetrazole) displaying stronger positive modulation of β2/3-containing GABAA receptors over β1-containing receptors compared to VA also induced more pronounced elevation of seizure threshold. In line with this stronger anticonvulsive effect, VA-amide and VA-tetrazole displayed more pronounced anxiolytic effects in the EPM and the LDT than VA. In contrast, unselective compounds were found to be inactive in vivo (e.g. VA-dimethylamide) or induced anticonvulsive effects only at higher doses (VA-ethylamide, VA-diethylamide). From the studied piperine derivatives, SCT-66 and compound 23 induced significantly more pronounced anxiolytic effects than piperine. At higher doses (≥ 30 mg/kg) bodyweight both compounds reduced locomotor activity. In addition, SCT-66 also significantly elevated PTZ-induced seizure threshold. Most notably, SCT-66 did -unlike piperine- not reduce body temperature, suggesting no activation of TRPV1 channels in vivo.

Taken together, the studied VA derivatives may serve as scaffolds for the development of novel anxiolytics and/or anticonvulsants with faster onset, longer duration and/or stronger action compared to VA. Piperine derivatives SCT-66 and compound 23 induce more pronounced anxiolysis in mice than piperine and thus may be an interesting starting point for the development of novel anxiolytics.