Honokiol Modulates GABA<sub>A</sub> Receptors Subunit Specifically

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Honokiol, a neolignan compound isolated from <i>Magnolia</i> species has been suggested to interact with GABA<sub>A</sub> receptors. Evidence comes from honokiol-induced enhanced [<sup>3</sup>H]muscimol binding [1] and anxiolytic action in behavioural studies [2]. The molecular mechanism and possible subunit-specific effects of honokiol on GABA<sub>A</sub> receptors are currently unknown. In the present study we investigated the action of honokiol on GABA<sub>A</sub> receptors of 7 different subunit compositions (α<sub>1</sub>β<sub>2</sub>γ<sub>2</sub>s, α<sub>1</sub>β<sub>2</sub>, α<sub>1</sub>β<sub>1</sub>, α<sub>1</sub>β<sub>3</sub>, α<sub>2</sub>β<sub>2</sub>, α<sub>3</sub>β<sub>2</sub> and α<sub>5</sub>β<sub>2</sub>) that were expressed in <i>Xenopus</i> oocytes. The modulation of chloride currents (I<sub>GABA</sub>) was studied with two-microelectrode voltage-clamp technique by means of a fast perfusion system [3]. Honokiol dose-dependently and subunit-specifically enhanced I<sub>GABA</sub> with EC<sub>50</sub> values ranging from 23 (α<sub>5</sub>β<sub>2</sub>) to 60 µM (α<sub>1</sub>β<sub>3</sub>). The strongest I<sub>GABA</sub> potentiation was observed for receptors containing α<sub>3</sub> subunits (e.g. 2410% for α<sub>1</sub>β<sub>2</sub>γ<sub>2</sub>s). The action of honokiol (at GABA concentrations eliciting 5–10% of the maximal response) on receptors containing different α subunits is shown below.

Potentiation of I<sub>GABA</sub> through α<sub>1</sub>β<sub>1</sub> receptors (260%) was substantially smaller than for α<sub>1</sub>β<sub>2</sub> receptors (1034%) or α<sub>1</sub>β<sub>3</sub> receptors (878%). I<sub>GABA</sub> potentiation was reduced by a mutation known to inhibit loreclezole action α<sub>1</sub>β<sub>2</sub>-N265S (410%) and enhanced for α<sub>1</sub>β<sub>1</sub>-S290N (966%) receptors. I<sub>GABA</sub> modulation by diazepam was additive and honokiol action was not blocked by flumazenil (1 µM) indicating that this compound does not interact with the benzodiazepine-binding site. In summary, honokiol was identified as a highly efficient and subunit specific modulator of GABA<sub>A</sub> receptors. Our data indicate a possible interaction with the loreclezole binding determinants.

