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Honokiol Modulates $GABA_A$ Receptors Subunit Specifically

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Honokiol, a neolignan compound isolated from *Magnolia* species has been suggested to interact with $GABA_A$ receptors. Evidence comes from honokiol-induced enhanced [^{3}H]muscimol binding [1] and anxiolytic action in behavioural studies [2]. The molecular mechanism and possible subunit-specific effects of honokiol on $GABA_A$ receptors are currently unknown. In the present study we investigated the action of honokiol on $GABA_A$ receptors of 7 different subunit compositions ($\alpha_1\beta_2\gamma_{2s}$, $\alpha_1\beta_2$, $\alpha_1\beta_1$, $\alpha_1\beta_3$, $\alpha_2\beta_2$, $\alpha_3\beta_2$ and $\alpha_5\beta_2$) that were expressed in *Xenopus* oocytes. The modulation of chloride currents (I_{GABA}) was studied with two-microelectrode voltage-clamp technique by means of a fast perfusion system [3]. Honokiol dose-dependently and subunit-specifically enhanced I_{GABA} with EC_{50} values ranging from 23 ($\alpha_5\beta_2$) to 60 µM ($\alpha_1\beta_3$). The strongest I_{GABA} potentiation was observed for receptors containing α_3 subunits (e.g. 2410% for $\alpha_3\beta_2$). 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_{GABA} through $\alpha_1\beta_1$ receptors (260%) was substantially smaller than for $\alpha_1\beta_2$ receptors (1034%) or $\alpha_1\beta_3$ receptors (878%). I_{GABA} potentiation was reduced by a mutation known to inhibit loreclezole action $\alpha_1\beta_2$-N265S (410%) and enhanced for $\alpha_1\beta_1$-S290N (966%) receptors. I_{GABA} 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 $GABA_A$ receptors. Our data indicate a possible interaction with the loreclezole binding determinants.

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