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Effects of kava on benzodiazepine and GABA receptor binding

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Kava is an intoxicating, but non-alcoholic beverage produced from the pepper plant, *Piper methysticum* Forst. and widely consumed in the South Pacific islands. This substance is now being used, and abused, by some Australian aboriginal communities. The active ingredients of kava are the α-pyrones which consist of a family of lipid soluble compounds with a variety of psychoactive properties. These compounds include kawain (KAW), dihydrokawain (DHK), methysticin (METH), dihydromethysticin (DHM), dehydromethysticin (DeHM), yangonin (YANG), tetrahydroyangonin (THY) and desmethoxyyangonin (DMY). The first four compounds are regarded as responsible for most of the pharmacological effects including muscle relaxation, anticonvulsant activity, hypnosedative activity and analgesia (Keller and Klohs, 1963). Such actions are suggestive of the benzodiazepine class of drugs and thus we have studied the effects of several of the kava-pyrones on binding to benzodiazepine and to GABA receptors.

Eight of the pyrones (dissolved in DMSO) were tested for their ability to compete with [^{3}H]-diazepam binding to rat forebrain membranes *in vitro*. Several of the compounds had weak activity viz. DeHM (IC50 of 46 μM), YANG (IC50 of 49 μM) although the most pharmacologically active pyrones (KAW, DHK, METH, DHM) gave less than 40% displacement at 200 μM. However, pharmacokinetic studies (Keledjian et al., 1988) have shown that such high concentrations may be achieved in the CNS after administration of behaviourally active doses of the kava pyrones. Thus we investigated benzodiazepine binding in more detail. *Ex vivo* studies in mice after i.p. injection of active doses of kava compounds did not detect any significant effects on [^{3}H]-diazepam binding to crude forebrain homogenates, whereas diazepam, used as a positive control, gave the expected complete displacement. Kava resin was investigated also in binding studies in *in vivo* binding studies mice. Animals were dosed i.p. with 150 mg/kg resin then 5 or 50 min were injected i.v. with 2 μCi/20 g body wt of the benzodiazepine antagonist, [^{3}H]-Ro15-1788, and sacrificed 10 min later. Kava resin did not cause significant inhibition of binding in forebrain tissue whereas clonazapam gave complete inhibition of specific binding.

The effects of DHK, DHM, YANG and THY (100 μM and 1 mM) were tested on the binding of [^{3}H]-GABA and [^{3}H]-(-)-baclofen to $GABA_A$ and $GABA_B$ sites (respectively) in washed forebrain and cerebellar synaptosomal membranes. None of compounds had any significant effect on binding to the cerebellar membranes. THY and DHM produced only slight (< 25%) albeit statistically significant inhibition of GABA binding in forebrain membranes. However there was no significant inhibition of $GABA_A$ binding in membranes after treatment with triton detergent (which removes lipid components and increases specific binding) by any of these compounds or by METH.

This suggests that the minimal effects seen in the binding studies may be due to some interaction of the compounds with lipid components of the membranes near the receptor complex rather than any direct receptor interaction.

References

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