Ginkgolide A, Ginkgolide B and Bilobalide are antagonists of insect GABA receptors

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Ginkgo biloba is one of the most widely used herbal medicines across the world. Extracts from the Ginkgo biloba leaf include the terpene trilactones ginkgolide A (GA), ginkgolide B (GB) and bilobalide (BB). These compounds are non-competitive antagonists of the GABA_A and glycine receptors (Huang et al. 2004) (Hawthorne et al. 2006), and are structurally related to picrotoxin (PTX), also a non-competitive antagonist of these receptors. These compounds are thought to bind in the channel of these receptors. The aim of this study was to assess the properties of these compounds on an insect GABA receptor and to determine the role of the 2’ and 6’ channel-lining (M2) residues.

The insect GABA receptor subunit RDL (Accession number P25132) was cloned into pGEMHE. Xenopus oocytes were injected with 5ng cRNA and the effects of GA, GB, BB and PTX on GABA currents were recorded 24 h later using two-electrode voltage clamping. Channel-lining mutants A2’S and T6’V were created using site-directed mutagenesis (Quikchange, Stratagene) and their effect on antagonist potency was assessed.

GA, GB and BB had similar inhibitory potency to PTX (Table 1). Both T6’V and A2’S mutant receptors decreased antagonist sensitivity: pIC_{50} values for T6’V were 4.3±0.8, 3.5±0.4, ≤3 and 2.6±0.6 for GA, GB, BB and PTX respectively; pIC_{50} values for A2’S were 5.6±0.1, 5.0±1.2, 4.7±1.4 and 3.6±0.1 for GA, GB, BB and PTX respectively.

GA, GB and BB are antagonists of RDL receptors with similar IC_{50} values to PTX. Channel-lining mutants A2’S and T6’V reduced antagonist sensitivity with the T6’V mutant having a stronger effect than the A2’S mutant. We conclude that GA, GB and BB block the channel of the RDL insect GABA receptor.
