Glycine at the third position of TM3 determines the action of fluralaner on insect and rat GABA receptor

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Abstract

BACKGROUND AND PURPOSE Fluralaner is a novel isoxazoline insecticide with broad insect spectrum, and mainly acts on the insect GABA receptor with unique binding action, but its molecular interaction with insect GABA receptor has not been deeply identified on molecular level according to its selectivity between target (insect) and non-target (mammal) organisms. EXPERIMENTAL APPOACH The potential binding residues (I258T and L275I in TM1; V288I, M298N, G303N and A304S in TM2; G3'M/S, A327S, G336N, M338I and A339F in TM3; M473V and I477D in TM4) were predicted by SYBYL-X 2.1 software, and verified respectively by the site-directed mutagenesis and two-electrode voltage clamp (TEVC) technique. KEY RESULTS In the 11 predicted amino acids, the G3'M has the strongest ability to reduce the sensitivity of recombinant rice stem borer RDL homomeric channel to fluralaner. Compared with the wild-type (WT)-RDL, the G3'M mutation almost completely abolish the binding of fluralaner and avermectin, but not fipronil on recombinant homomeric channel of RDL from several orders of insects in vitro. In addition, the M3'G on rat Mus musculus β2 improved the sensitivity of recombinant heteromeric Mmα1β2-M3'G channel to fluralaner. Our results demonstrated that the glycine at the third position of TM3 determines the action of fluralaner and should be the binding site of fluralaner with RDL. CONCLUSION AND IMPLICATIONS These results would contribute to understanding the molecular interaction of fluralaner with RDL homomeric channel and may be used to guide future modification of isoxazolines to achieve highly selective control of pests with minimal effects on non-targeted organisms.

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