The action of T- and CS -syndrome pyrethroids on voltage-sensitive calcium channels in rat brain

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Abstract

Isolated presynaptic nerve terminals (synaptosomes) prepared from rat brain were used to evaluate the action of a classic T-syndrome (cismethrin) and CS-syndrome (deltamethrin) pyrethroid on voltage-sensitive calcium channels by measuring calcium influx and neurotransmitter release with multiple fluorescent assays. Both cismethrin and deltamethrin stimulated calcium influx in a stereospecific manner; however, they did so by different mechanisms. Neurotransmitter released occurred only with synaptosomes treated with deltamethrin. This release was stereospecific, stimulated by depolarization, unaltered by tetrodotoxin, but blocked by ω-conotoxin MVIIC. ^ Electrophysiological experiments with Ca_V 2.2 expressed in *Xenopus* oocytes validated the interaction of deltamethrin with this N-type calcium channel. Thus, cismethrin and deltamethrin elicit different actions at presynaptic nerve terminals. The modification of Ca_V 2.2 voltage-sensitive calcium channels by deltamethrin is consistent with enhanced neurotransmitter release, a physiological response that has been observed during acute neurotoxicity of CS syndrome pyrethroids. ^ Rat brain synaptosomes were also used to evaluate the action of 11 pyrethroids (bifenthrin, bioallethrin, cismethrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, esfenvalerate, fenpropathrin, permethrin, and tefluthrin) by measuring calcium uptake, membrane depolarization, and neurotransmitter release as before. Our results indicate that only a subset of the commercially available pyrethroids act as voltage-sensitive calcium channels agonists (permethrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, and esfenvalerate). Pyrethroids that significantly enhanced calcium influx were also more potent in releasing neurotransmitter. Increased glutamate release appears to be due to an agonistic action of these compounds on Ca_V 2.1 and Ca_V 2.2 voltage-sensitive calcium channels, most associated with neurotransmitter release. ^ Biochemical and electrophysiological experiments provide functional evidence for a distinct mechanism of action for some of the pyrethroids on voltage-sensitive calcium channels at the presynaptic nerve terminal that results in enhanced neurotransmitter release, a response that is consistent with the observed symptomology of CS-syndrome pyrethroids. Such results will allow a more complete understanding of the molecular and cellular nature of pyrethroid-induced neurotoxicity and expand our knowledge of the structure-activity relationships of pyrethroids in regards to the voltage-sensitive calcium channel. ^

Subject Area

Molecular biology|Cellular biology|Toxicology

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