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Review

Modulation of insect Ca_V channels by peptidic spider toxins

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Abstract

Insects have a much smaller repertoire of voltage-gated calcium (Ca_V) channels than vertebrates. *Drosophila melanogaster* harbors only a single ortholog of each of the vertebrate Ca_V1, Ca_V2, and Ca_V3 subtypes, although its basal inventory is expanded by alternative splicing and editing of Ca_V channel transcripts. Nevertheless, there appears to be little functional plasticity within this limited panel of insect Ca_V channels, since severe loss-of-function mutations in genes encoding the pore-forming α_1 subunits in *Drosophila* are embryonic lethal. Since the primary role of spider venom is to paralyze or kill insect prey, it is not surprising that most, if not all, spider venoms contain peptides that potently modify the activity of these functionally critical insect Ca_V channels. Unfortunately, it has proven difficult to determine the precise ion channel subtypes recognized by these peptide toxins since insect Ca_V channels have significantly different pharmacology to their vertebrate counterparts, and cloned insect Ca_V channels are not available for electrophysiological studies. However, biochemical and genetic studies indicate that some of these spider toxins might ultimately become the defining pharmacology for certain subtypes of insect Ca_V channels. This review focuses on peptidic spider toxins that specifically target insect Ca_V channels. In addition to providing novel molecular tools for ion channel characterization, some of these toxins are being used as leads to develop new methods for controlling insect pests.

Keywords: Ca_V channel; Spider toxin; Peptide toxin; Insect control; Insecticide; PLTX-II, Atracotoxin; Agatoxin

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1. Introduction

The range of eukaryotic organisms that produce toxins for prey capture, defense, or competitor deterrence is astonishingly diverse and includes arthropods, molluscs, cnidarians, plants, and numerous vertebrates such as snakes, frogs, lizards, and the platypus. Despite this phylogenetic diversity, the venoms of spiders, scorpions, and cone snails have received disproportionate attention in recent years due to the remarkable extent and diversity of gene-encoded peptide toxins that are expressed in their venom glands (Goudet et al., 2002; Lewis and Garcia, 2003; Escoubas and Rash, 2004; Tedford et al., 2004b; Terlau and Olivera, 2004; Sollod et al., 2005). These toxins evolved primarily for the purpose of rapidly paralyzing or killing envenomated prey, and therefore it is not surprising that the vast majority of these peptides target specific subtypes of voltage- or ligand-gated ion channels (Lewis and Garcia, 2003; Sollod et al., 2005).

The pioneering studies of Michael Adams and Baldomero Olivera in the late 1980s and early 1990s (Adams et al., 1993b; Olivera et al., 1994) demonstrated that the molecular specificity of many spider and cone snail toxins makes them ideal tools for pharmacological identification of specific subtypes of vertebrate ion channels. For example, ω-conotoxin GVIA (from the cone snail *Conus geographus*) and ω-agatoxin IVA (from the American funnel-web spider *Agelenopsis aperta*) are commonly used to identify specific subtypes of vertebrate voltage-gated calcium channels, while various α-conotoxins are often the only means of pharmacologically discriminating the myriad subtypes of nicotinic acetylcholine receptors (Janes, 2005). The remarkable molecular specificity of these toxins also makes them potentially useful pharmaceutical agents for modifying the activity of ion channels implicated in human disease. For example, ω-conotoxin MVIIA, marketed under the trade name Prialt®, was recently approved by the FDA for treatment of severe chronic pain (Miljanich, 2004).

Most spiders prey exclusively on insects and other small arthropods, and therefore it is rather surprising that spider venoms have only more recently been examined for their potential to specifically target *insect* ion channels. These studies have revealed that spiders are capable of producing peptide toxins that specifically alter the activity of various subtypes of insect ion channels without having significant effects on the vertebrate orthologs of these channels. In addition to being useful as leads for the development of insecticides with novel modes of action, some of these toxins might prove invaluable for characterizing the biological functions of insect channels. This review focuses on peptidic spider toxins that specifically target insect voltage-gated calcium channels.

2. Molecular characteristics of voltage-gated calcium channels

Voltage-gated calcium (Ca_V) channels form membrane pores that open in response to membrane depolarization to allow the influx of extracellular calcium ions. They mediate a wide range of critical intracellular processes, including muscle contraction, hormone and neurotransmitter release, neurotransmission, and regulation of enzymatic activities and patterns of gene expression (Catterall, 2000). Ca_V channels are divided into two broad superfamilies based on their voltage-dependence of activation: low-voltage-activated (LVA) Ca_V channels are activated by small membrane depolarizations and show rapid voltage-dependent inactivation, whereas high-voltage-activated (HVA) Ca_V channels are only activated by larger depolarizations