Subverting the biological actions of Conus peptides to modulate physiological responses

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The peptides from various *Conus* venoms have been grouped by Olivera (1997) into cabals, whose members have synergistic actions even though members of a single cabal may have different targets. For example, members of the motor cabal may inhibit muscle contraction and induce flaccid paralysis by blocking either neuromuscular transmission, or by targeting muscle sodium channels to block the generation of muscle action potentials. On the other hand, different members of the lightning strike cabal appear to induce excitotoxic shock, with rapid-onset rigid paralysis, by inhibition of sodium channel inactivation and by block of voltage-gated potassium channels. Actions of *Conus* peptides, studied in species other than the natural prey, have revealed cases of unexpected and specific targeting which open possibilities for pharmacological modulation of a variety of processes. Examples include certain μ-conotoxins, nominally considered to be members of the motor cabal, which inhibit particular neuronal sodium channel isoforms more strongly than their canonical target from skeletal muscle. Thus, in a mouse model, μ-conotoxin KIIIA has performed more effectively as an analgesic than lidocaine (Zhang *et al.*, 2007). Conkunitzin-S1, a member of the Kunitz inhibitor family of peptides, blocks certain voltage-gated potassium channels (Bayrhuber *et al.*, 2005) and thereby has the potential to enhance electrical bursting activity. The molecular correlates and physiological consequences of these surprising and striking actions are becoming evident.

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