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Commentary

Antiallodynic effects of a confused α -conotoxin: Vc1.1 relieves neuropathic pain via off target actions on GABA_B receptors and N-type channels

Venoms from predatory marine organisms such as fish-hunting cone snails are a rich source of bioactive compounds that bind to, and regulate a wide range of voltage- and ligand-gated ion channels. These snails use a cocktail of peptide toxins to rapidly stun and ultimately kill their prey. The individual toxins contained within the venom selectively target specific ion channel subfamilies [3]. For example, μ -conotoxins and ω -conotoxins, respectively, block voltage gated sodium and calcium channels, whereas the α -conotoxins are typically thought of as antagonists of nicotinic acetylcholine receptors [5]. Of course, the primary purpose of cone snail venom is to kill fish. However, because there is sufficient conservation in ion channel sequences among fish and mammals, many types of cone snail toxins also potently interact with human ion channel proteins [3]. On one hand, this poses a danger to humans coming into contact with various *conus* species, but on the other hand, the selectivity and potency of individual peptide toxins can potentially be harnessed for therapeutic purposes. A prime example is the clinical use of ω -conotoxin MVIIA, a potent inhibitor of N-type calcium channels that can be delivered intrathecally to mediate analgesia in patients with severe pain [1]. A number of biotechnology companies and academic research laboratories are actively seeking other conotoxin molecules for use as therapeutics in humans [3]. This includes Vc1.1, an α -conotoxin from *Conus victoriae* that is currently in phase II clinical trials for neuropathic pain.

Callaghan and colleagues recently reported a Vc1.1 mediated inhibition of N-type calcium channels in rat sensory neurons [2]. These authors showed that this inhibition was dependent on a Vc1.1 action on GABA_B receptors, rather than on its canonical target (i.e., the nicotinic receptor). While this is in itself unusual, what is even more perplexing is that when activated by Vc1.1, GABA_B receptors appear to signal by a novel and still undefined pathway to the N-type channel protein. But irrespective of the precise mode of action, the fact that N-type channels are inhibited by Vc1.1 suggested the possibility that its therapeutic actions are also mediated via N-types, rather than an effect on nicotinic receptors. In this issue of Pain, Kimlis and colleagues [4] examine the mechanism of Vc1.1 mediated analgesia in rats, along with that of two related α -conotoxins AulB (*Conus aulicus*) and MII (*Conus magus*). The authors first characterized the effect of the three toxins on recombinant acetylcholine receptors expressed in *Xenopus* oocytes, and found that only Vc1.1 significantly inhibited $\alpha 9\alpha 10$ receptors. The authors then demonstrated that Vc1.1 and AulB, but not MII, triggered a GABA_B receptor-mediated inhibition of native N-type currents in dorsal root ganglion neurons. The distinct target selectivities of the three toxins thus provided the authors with a unique tool kit to probe for the involvement of nicotinic and

GABA_B receptors in the afferent pain pathway. For this purpose, Kimlis and colleagues examined the effects of the three toxins on mechanical allodynia in a peripheral nerve ligation model. When injected intramuscularly, all three toxins produced an increase in mechanical paw withdrawal threshold with Vc1.1 being the most potent inhibitor, followed by AulB and MII, and the effects of Vc1.1 were blocked by a GABA_B receptor antagonist. Collectively, these data show that the antiallodynic actions of all three α -conotoxins are not mediated by $\alpha 9\alpha 10$ receptors and that $\alpha 9\alpha 10$ receptors are not significantly involved in the transmission of peripheral pain signals. Furthermore, the data provide compelling evidence that molecules such as Vc1.1 mediate their therapeutic actions via GABA_B receptor induced inhibition of N-type calcium channels.

It is well established that inhibiting N-type calcium channels is a suitable objective for the development of analgesics, either directly, or indirectly via the activation of G protein coupled receptors [1]. The new findings with Vc1.1 fit with the latter notion, despite the fact that the Vc1.1 induced effect appears to involve a novel, and as yet not fully characterized mechanism of coupling between the receptor and the channel. The observation that MII also produced antiallodynic effects even though it did not act on either N-type channels or $\alpha 9\alpha 10$ receptors suggests that inhibition of other types of nicotinic receptors such as $\alpha 3\beta 2$ [5] may help to alleviate mechanical allodynia. If so, then it may well be possible that inhibition of both GABA_B and nicotinic receptors could synergistically mediate analgesia. Future studies involving co-administration of compounds such as Vc1.1 and MII, or the identification of novel α -conotoxins with a combined action on both receptor types may be useful in testing such a possibility.

Conflicts of interest

The author has no conflicts of interest in relation to this commentary.

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