SEA ANEMONE TOXINS: INSECTICIDES AND PAINKILLERS OF THE FUTURE?

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Nature has provided sea anemones with cells called, nematocysts, that contain a venom for defensive and offensive purposes. In such venom, numerous bioactive molecules (toxins) can be found. Since these molecules appear to be extremely potent and selective, the use of these toxins for purposes like pharmaceuticals (read: the development of new generations of drugs, like antibiotics, analgesics, ...), or agricultural compounds (read: novel generation of pesticides that are environmental friendly without resistance known) has triggered a strong interest.

Sea anemones pray on crustaceae (like shrimps, lobsters, ...), but can also be attacked by them. So no wonder that nature has designed and equipped sea anemones with toxins that target crustaceae. Very interestingly, since crustaceae are evolutionary linked to insects, it was found that the same toxins from sea anemones also are effective against insects. So even when a sea anemone will never encounter an insect during his life, nature has engineered beautiful insecticides in the sea, and we can exploit these molecules to be applied/used in a different habitat/environment.

The target in insects is the voltage-gated sodium (Na) channel, not surprisingly, since this target is also the one used by the oldest generation of insecticides like DDT.

As such, the toxins found in the venom of sea anemones provide a unique resource for future development of new generation(s) of insecticides, with the advantage that no resistance against these toxins exists and moreover that they are environmentally friendly which is a clear plus point as compared to DDT and related molecules.

In this study, particular attention was paid to APETx3, a novel peptide isolated from the sea anemone *Anthopleura elegantissima*, being a naturally occurring mutant from APETx1, only differing by a Thr to Pro substitution at position 3. APETx1 is believed to be a selective modulator of human *ether-á-go-go* related gene (h*ERG*) potassium channels with a *K*d of 34nM. We have subjected APETx1, 2, and 3 to an electrophysiological screening on a wide range of 24 ion channels expressed in *Xenopus laevis* oocytes:10 cloned voltage-gated sodium channels (NaV1.2–NaV1.8, the insect channels DmNaV1, BgNaV1–1a, and the arachnid channel VdNaV1) and 14 cloned voltage-gated potassium channels (KV1.1–KV1.6, KV2.1, KV3.1, KV4.2, KV4.3, KV7.2, KV7.4, hERG, and the insect channel *Shaker* IR). Surprisingly, the Thr3Pro substitution results in a complete abolishment of APETx3 modulation on h*ERG* channels and provides this toxin the ability to become a potent (EC50 276nM) modulator of voltage-gated sodium channels (NaVs) because it slows down the inactivation of mammalian and insect NaV channels. Our study also shows that the homologous toxins APETx1 and APETx2 display promiscuous properties since they are also capable of recognizing NaV channels with IC50 values of 31nM and 114nM, respectively, causing an inhibition of the sodium conductance without affecting the inactivation. The inhibitory effects observed on particular isoforms of NaV channels predicts these toxins to be a novel class of analgesics.