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paths of discomfort

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We are all bound to become prey, predator or competitor one day. Whichever way you look at it. That is why, over time, all living beings have acquired their very own palette of defence mechanisms. Roses grow thorns. Bacteria fire toxins. Panthers run fast, chameleons blend into the environment and humans hurl a few well-chosen words. The whole point of developing such mechanisms is to shun the threat of some sort of insult, or worse: death. Bees sting, dogs bite, ivy poisons, your opponent humiliates you. Everything that has to do with defence frequently involves hurt or physical pain. Why? Because it is the best way to say: "go away, and don't come back". Cone snails have developed one of the most varied and plentiful venomous cocktails that are known, which have been extensively studied. Recently, researchers discovered that one component of such a cocktail makes humans itch. This is an intriguing discovery since itching is – so scientists believe – not far removed from pain. The component is a particular conotoxin, a venom peptide coined conorfamide.

Still Life (ca. 1640), by Balthasar van der Ast

Source: Museum Boijmans (NL)

Cone snails, or cone shells, are predatory sea snails typically found in warm and tropical seas around the planet, in particular in the Western Indo-Pacific region. There are hundreds of different kinds of cone snails – anything between 600 and 800, with new species described every year – each of which is predatory. Their prey? Small fish, other molluscs or marine worms. Cone snails come in all shapes and sizes, sometimes reaching over 20cm in length, and with protective shells that frequently sport colourful patterns attractive to the human eye, and hence a nice souvenir to pick up and take back home. Each species of cone snail is, however, venomous and several can even be fatal to humans, in particular the larger tropical cone snails that prey on fish and whose habitats are in warm, shallow waters.

There are hundreds of different species of cone snails and, between them, thousands of different conotoxins or venom peptides. Much in the way soldiers load their guns with ammunition, each cone snail has its own batch of venom peptides – which may amount to hundreds of compounds – ready to use in the face of adversity. Unlike a gun's ammunition, however, conotoxins have no effect on the cone snail that produces its venom, but they will affect a variety of physiological functions in the organism they are assaulting – functions as vital as the cardiovascular, reproductive and sensory systems, or feeding and respiration – by targeting diverse and specific pathways.

To date, two different kinds of conotoxins have been characterized: those that modulate voltage-gated ion channels, and those that modulate ligand-gated ion channels. Conorfamides are a major component of the Australian *Conus victoria* venom, for instance, and belong to what is known as the RFamide neuropeptide family. RFamide neuropeptides are characterized by a C-terminal sequence that ends with an RF-amide motif, i.e. an Arginine residue (R) followed by a Phenylanaline (F) residue and NH_2 added post-translationally – hence the name cono-RF-amides, or conorfamides. Conotoxins are short peptides, varying between 10 and 35 amino acids, and conorfamides are among the shortest of all, measuring barely 12 amino acids in length. How do conorfamides work? In all likelihood, they interfere with ligand-gated ion channels, probably by binding to a G-protein coupled receptor in the peripheral neurons of their prey. This would affect ion

exchange across neuronal membranes and, consequently, downstream pathways involved in the prey's cardiovascular system or respiration for example.

Scientists are able to claim this, not because they have managed to dismantle and observe the molecular process in cone snails but because conorfamides happen to create a surprising side effect in tetrapods, i.e. itches. Itches are either histamine-dependent or they are not. In mice, and humanized transgenic mice, conorfamides bind to Mas-related G-protein coupled receptors (MRGPRs) – itch receptors – on neuronal membranes located at the point of envenomation or irritation, such as skin for instance. The "sting" message – or "itch" message in this case – is then relayed by way of the opening and shutting of ion channels, from the peripheral nervous system to the brain that will then sense the itch, and send off a message to give it a scratch. It is not difficult to see that the itch/scratch system seems to echo the sting/pain system, and no one is quite sure if itches and pain follow the same route, or indeed parallel routes.

What is an itch, you may ask. Why do we suddenly feel an itch, and does it have any biological meaning? The German physician Samuel Hafenreffer (1587-1660) was the first to describe scientifically the unpleasant sensation, as he called it, and he named it: pruritus. Itches only occur on our skin, or in our throats, nowhere else in our bodies, which is no doubt fortunate. Like pain, an itch tells you where something is happening so you'll give it a scratch. Unlike pain however, it is not clear what the exact message is. An itch could be the doings of a spider crawling up your arm, a mosquito sting, inflammation, dry skin, wool rubbing against your skin or even a psychiatric disorder or simply shyness. By scratching, you whip away whichever creature or whatever fabric is bothering you. By doing this – say some scientists – you replace the sensation of itch by pain, by digging your nails into your skin. Certainly an itch is a means of communication, our bodies saying: "have a look here".

There has been great interest in cone snail venom in the past years because they provide a valuable source of bioactive peptides that have mammalian targets: they are small and fast-acting, and their targets are usually specific, to the exclusion of another, which should mean that there are no side effects. Conotoxins already provide the basis for pain killers to replace addictive opioid drugs against severe pain, which currently represent one of the deadliest drug crises in American history. Scientists are also looking into the characteristic itching caused by an anti-malaria drug known as chloroquine and the design of an anti-itch drug inspired by a conorfamide, which would inhibit MRGPRs and hence the itch sensation. Indeed, many conorfamides show prospects for being potent drugs and not only where pain or itches are involved but also in the treatment of other serious and common afflictions such as Alzheimer's disease, Parkinson's disease, depression and epilepsy.

Cross-references to UniProt

Conorfamide-Vc1, *Conus victoriae* (Queen Victoria cone): P0DOZ7
Conorfamide-Tx2, *Conus textile* (Cloth-of-gold cone): P0DM27

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