

## a pain soothed

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Pain is part of an animal's life. It is there to tell us that something is wrong, and needs to be attended to. There is moral pain. And physical pain, the more definable of the two, which serves two purposes. The first, to warn us of tissue damage and, more often than not, its localisation. The second, to understand where danger lies, so as to avoid it in the future. Unless, of course, it has been lethal. Ever since Life emerged, Nature has been using pain as a means of communication. Though perhaps violent, it is usually very conclusive, which is why many animals have developed toxins they inject into potential predators to ward them off. Among these toxins are the well-known venom cocktails snakes, scorpions and spiders are able to conjure up. In answer to this, a few animals have developed mechanisms to ease the pain – or even suppress it altogether. This is the case of one species of mouse – the Southern grasshopper mouse from the Texan desert – who feels next to no pain when stung by the bark scorpion. As a consequence, the mouse is able to ignore the sting and eat the scorpion. Recent studies have demonstrated that this extraordinary ability is due to changes in the structure of a given type of pore: sodium channel protein type 10 subunit alpha, or Nav1.8.



Feel no pain, by Kim Roberti

Courtesy of the artist

Reducing the effects of pain sounds very attractive. Which it is, if the origin of the pain is known and you wish to alleviate it. However, if an animal is insensitive to pain, or has a pain threshold which is high, it may not be aware of damage made to a part of its body. In this respect, there is the very rare infliction found in humans, known as congenital indifference to pain (CIP)<sup>1</sup>. A well-known case is that of a

young Pakistani street performer who was able to run knives through his arms or walk on red hot coal, without ever feeling pain. His body, however, suffered since he frequently ended up visiting the hospital for repair. And he died at the very early age of fourteen<sup>1</sup>.

So, if the Southern grasshopper mouse – *Onychomys torridus* – has developed resistance to bark scorpion venom, it must be for a very good reason. And, the reason is: food. This specific mouse lives in the deserts of North America and Mexico, a part of the world where the usual diet – fruit and grains – of a rodent is difficult to come by. So, instead of finding another place to live, the grasshopper mouse developed a system so that its means of sustenance became the animal it shares the desert with, i.e. the bark scorpion, or *Centruroides sculpturatus*. This process must have taken a very long time from an evolutionary point of view but the outcome is surprising. The grasshopper mouse takes hardly any notice of the scorpion's multiple stings, and even begins to feast on it by beginning with the stinger and the bulb which contains the venom.

Why does this particular mouse feel nothing in response to the scorpion's venom? In animals, pain is transmitted from its origin to the spinal cord and the brain, via sensory neurons known

as nociceptors. In nociceptors, the pain signal is relayed via transmembrane channels that are scattered along their length. In mammals, acute pain is transmitted to the central nervous system by way of two specific voltage-gated sodium channels: Nav1.7 and Nav1.8. The former initiates the pain signal, while the latter makes sure it is propagated. In the case of the grasshopper mouse, pain is actually triggered off quite normally, while Nav1.8 – instead of propagating the pain signal – stops it from going any further. As a result, the mouse does feel a little sting, of little consequence, however, because Nav1.8 checks it and the scorpion's venom ends up acting, in effect, as an analgesic.

On the molecular level, what is happening? Nav1.8 is a transmembrane protein made up of four domains, each of which has six transmembrane segments. It is the second domain which interacts with the scorpion's venom, itself composed of multiple small peptides. When comparing the sodium channel's amino-acid sequence of the grasshopper mouse and the common mouse, *Mus musculus*, the scientists discovered that there were a number of mutations in the second domain – the peptide-binding domain. More specifically, there is one important amino-acid

change where glutamine is replaced by glutamic acid. This amino-acid swap hinders the transmission of the pain signal, though it is not yet known exactly how. Could it be that a venom peptide simply blocks the channel pore so that transmission is arrested? Or do venom peptides bind to the inner side of the pore, producing the same effect?

What is remarkable here is that time has thought up a strategy, not to modify the target channel of venom peptides – Nav1.7 – but to make changes to a secondary channel, Nav1.8. Moreover, scorpion peptides typically activate channels and hence the current whereas, in the case of the grasshopper mouse, the current is checked, and the peptides act as painkillers. *C. sculpturatus* and *O. torridus* provide a first-class model for understanding how pain is transmitted, and for designing novel drugs in the treatment of pain. What is more, Nav1.8 has more sequence diversity in mammals, making it a far better target for drug design than Nav1.7, which is highly conserved with other sodium channels in the brain and the body. There is no doubt that pain will continue to divert many a scientist, as it continues to be the silent guide of animal instinct.

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#### Cross-references to UniProt

Sodium channel protein type 10 subunit alpha, *Onychomys torridus* (Southern grasshopper mouse) : P0DMA5

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