Natural Selection and Pain Meet at a Sodium Channel

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lated into German for this reason. This may be considered a variation of, or possibly an addition to, the Weberian theory on the religious origin of modern capitalism. The German sociologist Max Weber argued that the teaching of hard work and frugality, and especially the view that economic success in life was a sign of being chosen for a next life, spurred entrepreneurship. Perhaps it was not the religious teaching and moral values of Protestantism that created an economic growth impetus, but rather the latter's emphasis on the accumulation of human capital, of men and women (*4*).

The Malthusian revolution plus the increased participation of women in agriculture and reduction in fertility—coupled, in parts of Europe, with a new emphasis on the accumulation of human capital and possibly some religious fervor—would constitute the perfect catalyst for the birth of capitalism and the rapid social and economic growth that followed. It was the complex interaction of a plague, cultural values, accumulation of human capital, and development of new technologies that created the spark that ignited the modern economic system.

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EVOLUTION

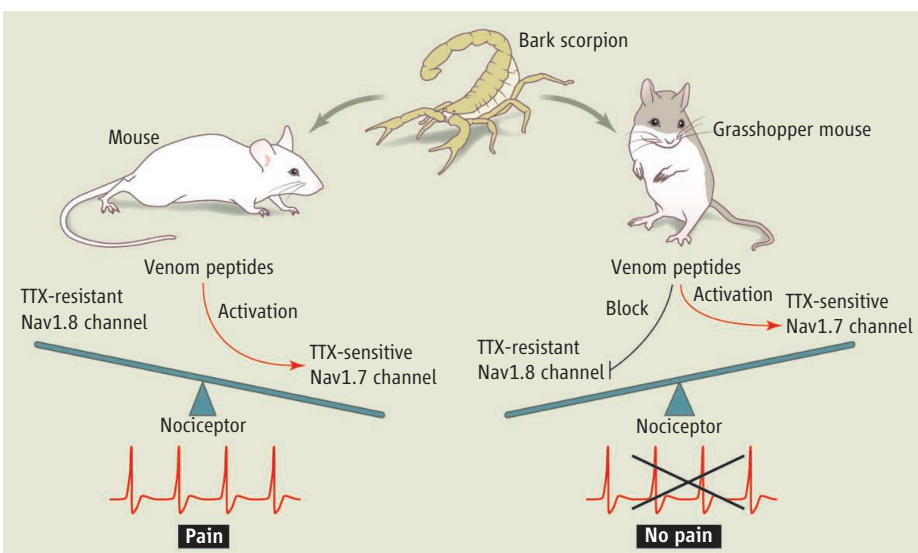
Natural Selection and Pain Meet at a Sodium Channel

Grasshopper mice can feed on toxic bark scorpions because they have evolved resistance to the pain normally caused by the toxin in the scorpion sting.

Gary R. Lewin

In the animal kingdom, extreme conditions drive adaptive change to enable species to live in and exploit challenging environments. Nociceptors—sensory fibers activated by noxious stimuli to signal pain—enable animals to detect and avoid potentially harmful stimuli, presumably because such stimuli lead to the experience of pain. Variation in pain sensitivity has not traditionally been considered as a trait that is selected for, or against, in the race to adapt to new environments. On page 441 of this issue, Rowe *et al*. show that evolutionary change in a voltage-gated sodium channel (Nav) drives resistance to painful neurotoxins that enables grasshopper mice (*Onychomys torridus*) in the Arizona desert to prey on an otherwise inaccessible food source, namely bark scorpions (*Centruroides sculpturatus*) (*1*).

Nociceptors detect a wide range of harmful stimuli, such as mechanical insult, chemicals, acid, or extreme temperature. Yet the nociceptive systems that detect such hazards are remarkably conserved throughout the animal kingdom (*2*). Nociceptors relay damage signals in the form of action potential trains that travel long distances from skin to spinal cord. Mammalian nociceptors are equipped with a mix of voltage-gated sodium channels that sustain action potential firing. Two critical members of this mix are the tetrodotoxin (TTX)–resistant Nav1.8 and TTX-sensitive Nav1.7 channels (TTX is a pufferfish toxin that potently blocks sodium channels). Both channels are selectively expressed in nociceptors, and gene knockout studies in mice or their mutation in humans are associated with reduced pain or sometimes a complete absence of pain (*3*).



Pain and gain. The bark scorpion toxin activates Nav1.7 channels in grasshopper mice and lab mice. But in grasshopper mice, the toxin potently inhibits the Nav1.8 channel in the same sensory neurons, tipping the balance to inhibit action potential firing in nociceptors. This evolutionary adaptation allows grasshopper mice to feed on bark scorpions with impunity. In contrast, the lab mouse Nav1.8 channel is not blocked by the toxin and the scorpion sting excites nociceptors, causing intense pain.

Rowe *et al*. began by observing that the venom of the bark scorpion, native to the Arizona desert, causes intense behavior indicative of pain in lab mice, probably by activating the Nav1.7 channel. However, grasshopper mice living in the Arizona desert regularly kill and consume bark scorpions, without any apparent discomfort from multiple stings experienced during prey capture. Recordings from freshly isolated sensory neurons from grasshopper mice and lab mice revealed that the isolated bark scorpion venom strongly activates lab mouse sensory neurons, but strongly inhibited action potential firing in grasshopper mouse sensory neurons.

The authors used pharmacological isolation of the TTX-resistant Nav1.8 current in isolated sensory neurons to show that the

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scorpion toxin potently inhibited the TTX-resistant Nav1.8 channel current in grasshopper mice neurons, but had no effect on this current in lab mouse sensory neurons (see the figure). They then cloned the Nav1.8 ion channel of the grasshopper mouse to identify the amino acids responsible for the channel block produced by the scorpion venom. A series of elegant domain switching and site-directed mutagenesis studies identified variations in critical residues in domain II, a region adjacent to the pore, that convert Nav1.8 into a venom-sensitive channel. Just switching the sequence order of an acidic glutamic acid (E) and a hydrophilic glutamine (Q) separated by two conserved residues was sufficient to render grasshopper mouse Nav1.8 insensitive to the venom, just like the lab mouse channel.

Animals in the order Rodentia make up more than 40% of all mammalian species and inhabit a vast number of often extreme habitats worldwide. The role of acidic residues in the grasshopper mouse Nav1.8 channel is reminiscent of the way in which another rodent species has coopted charged residues in the Nav1.7 channel to increase inhibition by acid. The subterranean naked mole rat (*Heterocephalus glaber*), indigenous to the dry high plateaus of east Africa, is in no danger from scorpions, but is confronted with high ambient CO_2 in its crowded underground habitat. High CO_2 is painful, probably because it is converted to acid in exposed tissues. However, acid does not seem to bother naked mole rats, because its Nav1.7 is potently inhibited by acid to block nociceptor firing. Evolution has driven changes in the naked mole rat Nav1.7 channel sequence so that two of three charged residues are altered near the pore to potently increase channel inhibition by protons (*4*).

It is striking that both the Nav1.7 and 1.8 channels, which are critical for the propagation of pain information along nociceptor axons to the central nervous system, have undergone strong selective changes in different animals. These changes probably promoted by the extremity of the niches to which the animals have adapted. Scorpion toxins activate nociceptors and produce pain by dramatically slowing the inactivation of sodium channels like Nav1.7. It remains to be shown whether the grasshopper mouse Nav1.7 channel is just as potently activated by components of bark scorpion venom as the same channel is in lab mice. Other factors might contribute to the grasshopper mouse's insensitivity to scorpion venom; for example, Rowe *et al.* found that larger depolarizing impulses were needed to evoke action potentials in sensory neurons from grasshopper mice relative to those from lab mice.

Pharmaceutical companies have a great interest in developing new analgesic drugs that do what the bark scorpion toxin does in grasshopper mice: prevent pain. Evolution has over millions of years achieved an analgesic strategy tailored to one rodent species. The challenge will be to identify channel sequence variants that have allowed different species to adapt to their unique environments. Gene technology offers the possibility to reverse engineer such variants into lab rodents. Drug designers could well be able to take advantage of the millions of years of natural selection to find new approaches to tackle important drug targets like sodium channels.

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CHEMISTRY

Expanding the Scope of Fluorine Tags for PET Imaging

A fast fluorination method can allow a wider range of drug molecules to be imaged in the body with positron emission tomography (PET).

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Millions of patients undergo PET (positron emission tomography) imaging every year, but there is a critical unmet need for new PET imaging probes capable of diagnosing and monitoring a multitude of diseases. One of the most versatile radionuclides for PET imaging is ^{18}F, but rapid chemical synthesis of any probe based on ^{18}F is essential because its physical half-life is only 110 min. Huiban *et al.* (*1*) recently reported an improved method for labeling trifluoromethylarenes (Ar-CF_3) with ^{18}F that could greatly facilitate the development and adoption of new PET probes and allow the site of action of existing drugs to be identified.

The only PET probe that has achieved widespread clinical application in the United States thus far is 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG; see the figure, panels A and B), which images cancer metabolism by pinpointing areas of high glucose usage (*2*, *3*). Because cancer cells generally burn extra glucose as fuel, FDG-PET provides clinicians with a diagram of cancer cell activity within the body. This method is now the standard of care in oncology for diagnosis, staging, and monitoring therapy. With the recent development of scanners that combine PET with computed tomography (CT), clinicians can now compare three-dimensional anatomical CT images with biochemical maps of fuel consumption in cancer tissue. For the past two decades, FDG has been the only ^{18}F drug approved by the U.S. Food and Drug Administration (FDA) for PET imaging.

Because PET-CT scans can reveal vital information about the anatomical structure within the body and its regional glucose consumption during the same examination, this method has the potential for understanding many other pathophysiological processes. In 2012, the FDA approved a second PET drug, Amyvid (florbetapir f18) (see the figure, panels A and C) (*4*), for detecting β-amyloid plaques, clumps of proteins that form around neurons in the brain and contribute to the development of Alzheimer's disease (AD). Amyvid is now being used for patient selec-

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