# Taking a shot at neuropathic pain

For all the millions of analgesic pills taken worldwide to relieve everything from toothache to sore joints, there are still few options to tackle the pain from damaged nerves. Two decades ago, neuropathic pain was regarded as a mystery, but progress has been swift and today's journals are awash with data on cellular changes triggered by an injured or diseased nervous system. The challenge, however, is to pick which of these myriad changes are essential to neuropathic pain and worth pursuing as drug targets. With this in mind, researchers and clinicians gathered at a Novartis Foundation symposium (Sept 30–Oct 2, Tsukuba, Japan) where the latest ideas were held up to scrutiny.

Pain is meant to be unpleasant because it operates as a defence mechanism. Yet for those who suffer neuropathic pain—an estimated 8 million people in the USA and 0·5 million in the UK—a normal body function turns into a crippling disease. Diabetes, alcoholism, HIV, cancer, sciatica, herpes zoster (shingles), and trauma can all trigger painful neuropathies.

Although a single hypothesis is unlikely to explain all neuropathic pain, a common thread is emerging. "Neural plasticity is becoming the most important key word in understanding pain", said Takao Kumazawa (Aichi Medical University, Japan). Changes in the peripheral nerves, the dorsal root ganglion (DRG), and spinal cord all play a part, and increasingly, cortical mechanisms are thought to be involved.

A lot of the blame could be attributed to hyperexcitable neurons. Injure a sensory axon, and the neuron starts firing spontaneously—a phenomenon known as ectopic discharge. These DRG neurons also become more responsive, and are more likely to fire in response to weak stimuli. The abnormal expression of sodium channels seems to drive this hyperexcitability. Tricyclic antidepressants and anticonvulsant drugs—commonly used in the clinic to treat neuropathic pain—target sodium channel activity. "What these drugs have in common is that they turn off the ectopic firing of injured sensory neurons", says Marshall Devor (The Hebrew University of Jerusalem, Israel). "Unfortunately, the available drugs are not terribly effective at tolerable doses."

In the quest for newer, more effective drugs, sodium channel blockers have become the flavour of the day. But as Jianren Mao (Harvard Medical School, Boston, USA) cautions: "Sodium channels are important for physiological nerve conduction. We cannot help our patients if the drugs also disrupt normal neurological functions." The question is, which of the dozen different sodium channels subtypes are worth targeting?

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*Pain pathways in the spinal cord*

"It is only recently that we have begun to learn which are particularly important in neuropathic pain", admits Jin Mo Chung (University of Texas, USA), a pioneer in the subject. Chung has studied a rat model in which spinal-nerve ligation gives rise to well-characterised neuropathic pain behaviours. The sodium channels on damaged and ectopically firing DRG neurons are sensitive to tetrodotoxin, specifically the $Na_v1.3$ and the $Na_x$ subtypes. Chung believes these may be the subtypes to exploit when trying to stop neuropathic pain generation.

To compound the problems of hyperexcitable sensory nerves, there are changes in the spinal cord and at the cortical level. "Pain is so important it takes your whole brain to deal with it", argues Min Zhuo (University of Toronto, Canada). "There are changes in the cortex which make responses to pain even bigger."

According to Zhuo, the main change in the brain after nerve injury or amputation is an enhanced synaptic transmission by glutamate—an excitatory neurotransmitter. Zhuo has singled out the anterior cingulate cortex (ACC) where expression of NMDA receptors is cranked up in response to different chronic pain states. What's more, Zhuo has observed that in mice whose adenylyl cyclases (AC1 and AC8)—normally operating downstream of the NMDA receptors—have been knocked out, there is a profound reduction in pain behaviour. These results, says Zhuo, confirm that the blocking of glutamate receptors is a likely pharmacological approach to the treatment of neuropathic pain.

But what are the chances of turning the system back to normal once pain has become established? "Neuropathic pain often does not resolve with time. For patients, the outlook is bleak", says Steve McMahon (King's College London, UK). His quest is to find compounds that stimulate nerve regeneration to find a cure. McMahon has approached the problem knowing that, in neuropathic states, the cocktail of trophic factors and cytokines produced by the damaged nerves is substantially different to normal—hundreds of genes are upregulated or downregulated.

In a striking set of experiments, McMahon has recently managed to alleviate pain in some animals by reversing these changes in gene expression using glial-cell-derived neurotrophic factors (GDNFs) and artemin. The implications of these findings for future therapies are huge. "We now know that GDNFs can reverse ectopic activity, and change sodium channel expression in neuropathic pain models", says an upbeat McMahon.

Mechanism-based medicine takes time to develop, and the delays in the translation from basic research to clinical practice can seem enormous. "The good news is that the intense focus of academia and the pharmaceutical industry on the problem of neuropathic pain suggests that new drugs directed at novel targets should be available in the future", says John Wood (University College London, UK). "The wait will unquestionably be worthwhile."

**Lisa Melton**