

Genes pronounce on persistent pain

The printed journal includes an image merely for illustration

Time to block BH4 synthesis?

US and German scientists report that peripheral neuropathic and inflammatory pain is partly due to increased synthesis of tetrahydrobiopterin (BH4) and that the intensity and persistence of this pain depends on the patient's genetic polymorphisms for GTP cyclohydrolase (GCH1), the rate limiting enzyme in BH4 synthesis (*Nature Med* 2006; published online Oct 22. DOI:10.1038/nm1490). "The involvement of BH4 in pain is something quite new," explains Clifford J Woolf (Massachusetts General Hospital, Boston, Massachusetts), "and our result show that the amount produced is, in part, genetically determined. This could help us control pain more efficiently in many people."

To ascertain which genes might be involved in persistent pain, the researchers screened the activity

of several hundred in the dorsal root ganglia of rats after spared nerve injury—a model of peripheral neuropathic pain. The GCH1 and sepiapterin reductase genes were upregulated, leading to increased BH4 production, which is essential in the production of several neurotransmitters and nitric oxide.

"When we added 2,4-diamino-6-hydroxypyrimidine [DHAP], a weak inhibitor of GCH1, four days after injury, mechanical and cold pain hypersensitivity were reduced after just one hour", explains Woolf. "It also had similar effects in chronic pain tests when first administered after 17 days, and in an inflammatory pain model."

Blocking sepiapterin reductase, which works downstream of GCH1, also reduced BH4 synthesis and had similar analgesic effects. By contrast, when the researchers administered the active enantiomer of BH4 to the experimental animals via a spinal catheter they suffered more intense pain.

"We then asked whether the fact that some people suffer chronic pain well after their injury has healed might be controlled by variations in the gene for GCH1—in essence, whether there are genetic polymorphisms that might invest people with distinct pain phenotypes", explains Woolf.

After genotyping 168 human adults who had undergone surgical

discectomy for disc hernia, the researchers detected a GCH1 haplotype with an allelic frequency of 15.4% that was strongly associated with very low scores for persistent leg pain.

"Patients who had two alleles of this were the least likely to have such pain, heterozygotes were more likely to suffer it, and patients with no copy at all were most likely to suffer it. Similar findings were made for experimental pain sensitivity in healthy volunteers. This variation seems to render the gene less likely to switch on, so less BH4 is produced. A person's genotype could therefore indicate what analgesic interventions will be needed after certain types of surgery."

"Clearly BH4 affects nitric oxide production in the dorsal root ganglia and these studies strongly implicate this process in these pain models", remarked Timothy Brennan (University of Iowa, Iowa City, USA). "Additional BH4-dependent processes in other pain transmission pathways are possibly as important. Although features of pathologic pain were readily and easily modified in these animal models, we anticipate treatment in human disease states to be much more difficult, both in reduction of symptoms and management of treatment related side-effects."

Adrian Burton

Hacking the brain with computer chips

Researchers have artificially manipulated long-term plasticity in the motor cortex of freely behaving monkeys with an electronic implant. Eberhard Fetz and colleagues showed that an artificial connection between the two sites via the implant strengthened weak neural connections between the sites (*Nature* 2006;

published online Oct 22. DOI:10.1038/nature05226).

The findings of these new studies have several implications for neurorehabilitation in those with neurological disorders who have severely impaired neural connections. "It seems conceivable that this technology could be used to strengthen

impaired neural connections between part of the brain, as in cortical stroke, or possibly even between the brain and spinal cord", Fetz (Washington National Primate Research Center, University of Washington, Seattle, WA, USA) told *The Lancet Neurology*.

The researchers implanted an array of electrodes into the brains of two