Killer snails ease the pain

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The ocean depths have yielded up another useful resource for drug discovery, this time a painkiller with an added, and apparently unique, benefit: accelerated tissue repair in damaged nerves. Scientists in Australia have extracted an interesting polypeptide from the venom of a marine snail, and dubbed it ACV1 [1]. They expect that the new therapy will soon enter human trials; one day it could offer the millions who suffer chronic pain a more attractive alternative to the derivatives of opium.

The need for better pain therapy

Chronic pain, resulting from cancer, AIDS, arthritis or injury, afflicts almost 60% of people in the developed world at some time in their lives, according to Bruce Livett, Deputy Head of Biochemistry and Molecular Biology at the University of Melbourne (http://www.biochemistry.unimelb.edu.au) and an expert on the cone shell, the marine snail from whose venom his team extracted the new drug (Fig. 1).

Many physicians are loathe to prescribe the 'gold standard' of opioid drugs, morphine, for chronic pain. Despite its effectiveness, it is notoriously problematic: besides its potential for addiction, it can cause several minor side effects, notably constipation and respiratory depression. 'The global market for drugs to treat this form of pain is in excess of US$1 billion and the medical profession is crying out for alternative drug treatments,' according to Livett.

Analgesic drug comes out of its shell

Cone shells, fish-eating molluscs from the genus *Conus,* are found in reef systems around the world; the specimens used in this Melbourne study were from the Great Barrier Reef off Australia's East coast. They use a highly toxic venom to paralyze their prey, and have been known to attack humans, sometimes fatally. In recent years, some of these venoms have been found to contain therapeutically useful peptides. These include the conotoxins, and one such peptide has reached the final stages of human trials as an analgesic [2]. Unfortunately, they tend to have side effects, including raised blood pressure in some patients. At a recent conference, Livett provided details of animal studies that showed the new conotoxin, ACV1, to be more powerful and long-lasting in its effects than either morphine or the earlier conotoxins [1].

Figure 1. *Conus textile*, an example of a cone shell. These marine snails, which have long been prized for their beautiful shells, now hold a fresh allure as sources of a new analgesic extracted from their deadly venom. Photograph courtesy of David Paul, Zoology Department, Melbourne University.

After a pain stimulus or tissue injury, pain sensations reach the CNS through interactions of receptors on peripheral sensory neurons and their associated pain peptides. ACV1 is a short peptide that can block such receptors and thus attenuate the sensation of pain. The proposed site of inhibition is the neuronal nicotinic acetylcholine receptor on the first-order neurons (unmyelinated primary afferent sensory nerves) in the neuronal pathway involved in pain transmission, explains Zeinab Khalil, Deputy Director of the University of Melbourne's National Ageing Research Institute and one of Livett's collaborators.

Because ACV1 blocks a different class of receptor than earlier, more problematic drugs, it is unlikely to cause the same side effects in humans. Indeed, during *in vivo* experiments lasting up to 12 weeks in rats, the team found no adverse behavioural or motor effects. ACV1 has the further advantage of being smaller and therefore cheaper and easier to synthesize than the larger conotoxin drugs. Also, it can be injected into muscle or fat, rather than into the spinal column, as the other conotoxin drugs require.

Faster, better, cheaper

Further tests on rats have shown that the drug also accelerates tissue repair in damaged nerves. The researchers propose that this might be related to its prolonged analgesic effect. 'A faster repair process means a reduction in pain,' Khalil explained. 'We are still investigating the mechanisms underlying the ability of the compound to accelerate recovery. But what we see is amazing.'

Eight weeks after injury to the peripheral nervous system, animals that received only vehicle as a treatment had just 47% functional activity in their injured neurons, compared with an 83% functional activity among animals that received ACV1 treatment for only one week. (The comparison is with age-matched control animals with intact nerves.)

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Joel Hochman, Executive Director of the National Foundation for the Treatment of Pain (http://www.paincare.org), has a physician's perspective of what effect such a drug might have on what he calls 'the shameful blight' of the current undertreatment of pain. 'It holds the promise of providing a means of blocking pain peripherally, with no impact on cognitive function,' he said. 'Such a medication would eliminate 'opiophobia' and should make every physician willing to treat pain.'

After taking out a full patent on the drug [3], Livett and his team are seeking a commercial partner to take the compound into human trials and develop it into a therapeutic option for sufferers of chronic pain. Given that the acceleration of recovery in injured nerves is a unique property not previously documented for other analgesics, and given that the experiments have been repeated several times, Khalil commented, 'We are extremely confident.'

References

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2 McIntosh, J.M. and Jones, R.M. (2001) Cone venom-from accidental stings to deliberate injection. *Toxicon* 39, 1447–1451

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Edible vaccines against human papilloma virus

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Mice can develop an immune response against human papilloma virus (HPV), the cause of cervical cancer, if they eat potatoes containing a vaccine directed against the disease. A research team has created it for those to whom the vaccine matters urgently – women in developing countries, where 80% of deaths from cervical cancer occur.

'The beauty of an oral vaccine is that you don't need a needle,' said Robert Rose, Assistant Professor of Medicine, Microbiology and Immunology at the University of Rochester Medical Center (http://www.rochester.edu), who presented the findings. 'In most cases you don't even need a doctor.'

HPV

Human papilloma virus is one of the most common sexually transmitted diseases, and the cause of virtually all cases of cervical cancer. Not all types of HPV cause pre-cancerous changes, but certain strains of the virus incorporate themselves into cell nuclei and cause the cell to divide abnormally. Screening can detect cervical cancer, and vaccines are in development, but at present, preventive measures such as safe sex and limiting the numbers of sexual partners are the only sure ways to avoid infection.

The prospect of delivering vaccines by transgenic fruits or vegetables in developing countries is a 'very attractive' way to prevent cancer in large numbers of women at low cost, commented Martin Bachmann, Executive Vice President and Chief Scientific Officer at Cytos Biotechnology (http://www.cytos.com), because powerful diagnostic tools are largely missing in these areas. Introducing novel vaccines to developing countries is a major problem, he observed, largely because of the cost and distribution problems. 'Since raw potatoes may not be particularly delicious to eat, it remains to be seen whether this particular choice of vegetable turns out to be optimal,' he added. 'On the other hand, who would not want to prevent his sexual diseases with a beer and chips?'

VLP technology

The researchers in Rochester began studying HPV in the 1980s, but the latest developments are a collaboration between scientists at Rochester and others at Cornell University (http://www.cornell.edu) and Tulane University Health Sciences Center (http://www.tulane.edu/hsc.cfm). Rose presented the latest results at the recent fifth annual *Conference on Vaccine Research* in Baltimore, MD, USA [1].

In the early 1990s, the Rochester team isolated the gene sequence of the HPV protein envelope [2], and created virus-like particles (VLPs) that are non-infectious but resemble viral particles. Immunization with VLPs, they found, could induce potentially protective immunity against infection [3]. Oral vaccinations in mice induced serum IgA and IgG antibodies against VLP that efficiently neutralized HPV (type 11) virions *in vitro* [4,5].

In 1997, the group began a VLP vaccination study in human volunteers [6]. The subjects tolerated the vaccine well,

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