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News

Solving the pain puzzle

David Adam pieces together the recent gains in our understanding of pain.

David Adam

The ancient Greeks believed that pain was an emotion, not a true physical sensation. Hit your thumb with a hammer and you do feel pretty emotional, but scientists now know that pain begins as a biochemical response to injury, extreme heat or some other trauma. So the pain of a broken thumb should be easier to fix than the agony of a broken heart.

In recent years, researchers have identified several chemical signal molecules that seem to activate pain-sensing nerves called 'nociceptors', used to inform the brain quickly that their part of the body is in some kind of trouble. Others have even identified the receptors that bind these chemical signals and trigger the pain message.

Targeting these receptors with drugs could turn off pain. But it is difficult to assess the possible benefits and side effects that this may bring, because most research so far has only been carried out in test tubes.

Hot stuff

Genetic engineering techniques are now allowing the effects of these pain signals -- and what happens when they are prevented from getting through -- to be investigated in animals. This is taking researchers closer to understanding how we feel pain, and maybe to stopping it.

Perhaps the most famous pain-triggering molecule identified so far is capsaicin, which gives hot chili peppers their powerful kick. Three years ago, a team of pharmacologists based at the University of California, San Francisco, led by David Julius, found the receptor protein that binds capsaicin and sets off its familiar burning sensation[1]. Using nerve cells and chili extracts they could see how the receptor effectively opened a gate to admit pain.

Capsaicin triggers pain in exactly the same way that high temperature does; hence lukewarm, spicy food can still feel burning hot. Interestingly, the team's research concurred with what many Mexican cooks have long insisted: that the heat difference between chili peppers can be measured in so-called 'Scoville units'. Hot habañero peppers activate the receptors as much as pure capsaicin; extracts ranking further down the Scoville scale had a measurably lower effect.

There were suggestions at the time that new painkillers could be designed to stop capsaicin and its protein receptor, called VR1, binding in blistering-hot union. But cells in culture do not feel and react to pain so the overall effects such drugs may have were uncertain.

It's a knockout

Earlier this year, genetic engineering allowed Julius and his team to take a closer look at what happens in whole animals when VR1 cannot function: by building a mouse that doesn't have the VR1 receptors at all[2].

Such gene 'knockout' mice have been widely used to study everything from human ear development to aggressive behaviour. Researchers effectively leaf through the animal's genetic instruction book (its DNA) until they find the relevant page -- in this case, how to express VR1. Then they rip the page out by disabling the gene, before building the mouse from the truncated instructions. The target gene -- and its protein product -- are missing, but everything else remains intact.

Encouragingly, the mutant mice happily drank water laced with capsaicin (used in police pepper sprays and even as grizzly bear deterrent) that the normal mice turned their snouts up at. The mice missing VR1 could also better tolerate painful heat.

But pain was not cut off completely. Heat applied to tails and paws eventually became too much even for the mice with a taste for fiery salsa. This is a crucial point, says pain researcher John Wood at University College London, UK, because it shows that more than one chemical process is involved in pain.

"The idea that just one pain channel or receptor could be the target for a drug is a little naïve," Wood says. "The situation is far more complicated than that." Pharmaceutical companies have been searching for over a decade for pain-relievers based on the capsaicin pathway with little apparent success, he adds.

But targeting capsaicin receptors does show promise for the treatment of inflammatory pain like burns, he says. Sunburnt skin becomes hypersensitive to even mild increases in temperature because the pain neurons overreact. Capsaicin can reduce this sensitivity, raising the threshold temperature that burnt skin must reach before it feels sore[3].

Another look at ATP

Wood's team has been studying another key molecule in the pain pathway: ATP (adenosine triphosphate) -- better known as the energy

packets unwrapped by the body to generate heat, flex muscles and do just about everything else requiring power. ATP was first identified as a possible pain-triggering molecule some time ago because it is released from damaged cells, but the recent focus on capsaicin has seen the idea fall from favour.

Now Wood's team and other researchers at the pharmaceutical company Roche Bioscience in the USA have investigated just how much ATP affects pain signalling using more knockout mice. Both groups announce their findings this week in Nature[4,5].

This receptor is called '$P2X_3$', and the results appear pretty conclusive. Mice with sore paws usually lick them. But mice missing $P2X_3$ licked painful paws less frequently than those with an intact genome. This suggests that the pain message is not getting through as successfully.

Like VR1, the $P2X_3$ receptor is an ion channel -- it spans cell membranes and allows only certain types of ions to pass through. The $P2X_3$ receptor opens its doors when it meets ATP -- causing the nerve cell to fire and the mice to feel pain. Remove the $P2X_3$ access doors and ATP floats around outside, with no way of triggering pain.

Again, some researchers have suggested that drugs targeting $P2X_3$ could dull pain. But the new results warn that the situation is not so straightforward: mice missing $P2X_3$ also urinate less frequently, for example, probably because a full bladder releases ATP as its 'empty me' signal.

And knockout mice missing $P2X_3$ could not enjoy a hot, relaxing bath, for example, because they cannot detect mild skin warming. But surprisingly and more seriously, the team also found that blocking ATP signals seems to aggravate pain caused by skin inflammation.

Now what?

"These results clearly show the importance of ATP and the $P2X_3$ receptors in sensing certain types of pain," says pain researcher Sean Cook of Oregon Health Sciences University, Portland, USA. "But many pieces of the puzzle are still missing." Absent clues include how different types of tissue damage trigger ATP release and how long the chemical messenger survives in the body.

"It's quite disappointing in some ways as we were all hoping for some kind of huge breakthrough," Wood admits. The subtlety of the interactions between different pain pathways, he says, make it difficult to block pain completely.

He believes that one possible solution could be crossing the different types of genetic knockout mice -- to allow more than one pathway to be investigated at one time. Such attempts seem some way off, however. "Knockout mice are a tremendous pain to make," Wood explains.

References

1. Caterina, M.J. et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* **389**, 816 - 824 1997. | Article | PubMed | ISI | ChemPort |
2. Caterina, M.J. et al. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science* **288**, 306 - 313 2000. | Article | PubMed | ISI | ChemPort |
3. Davis, J.B. et al. Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. *Nature* **405**, 183 - 187 2000. | Article | PubMed | ISI | ChemPort |
4. Cockayne, D.A. et al. Urinary bladder hyporeflexia and reduced pain-related behaviour in P2X3-deficient mice. *Nature* **407**, 1011 - 1015 2000. | Article | PubMed | ISI | ChemPort |
5. Souslova, V. et al. Warm-coding deficits and aberrant inflammatory pain in mice lacking P2X3 receptors. *Nature* **407**, 1015 - 1017 2000. | Article | PubMed | ISI | ChemPort |