New compound fires up pain research

Helen Dell, BMN News

A newly identified compound that blocks a pain receptor will provide a useful tool in the study of how humans sense painful noxious stimuli, such as heat, acid and chilli, according to UK researchers.

Feeling hot, hot, hot

The fiery pain of chilli is sensed when its pungent component, capsaicin, activates the vanilloid receptor-1, also called TRPV1. But, while a glass of water will probably soothe the burn of too much chilli, other pain sensations mediated by the receptor are less easily dealt with.

TRPV1 also responds to heat and acid, and is thought to be involved in several conditions that involve a pain component, or aberrant sensory processing – migraine and irritable bowel syndrome, for example.

The receptor is potentially an important target for pain, says Andrew Randall, Professor of Neurophysiology at GlaxoSmithKline at Harlow in Essex, UK (http://www.gsk.com) – and one that a lot of pharmaceutical companies are investigating.

'It is very highly expressed in nociceptive neurons – pain-sensing neurons,' he said. 'And expression there is modulated by pain-sensing states that are potentially related to disease.'

High throughput screening

Therefore, Randall and his colleagues developed a high-throughput screen to search for molecules that inhibited the activation of the receptor. They used cells that expressed TRPV1, and loaded them up with a fluorescent molecule that responds to calcium ion concentration. Activating the receptor with capsaicin increases the intracellular

concentration of calcium, measured as fluorescence, and the researchers tested for molecules that blocked this effect.

They detected a compound – SB366791 – that inhibited the activation of TRPV1 in a concentration-dependent manner. In addition, unlike other currently available antagonists, this compound blocked activation of the receptor by acid or heat. It is also selective, with little or no affect on a large panel of other receptor molecules, including other ion channels.

'It is a much more selective antagonist of this channel, with less off-target effects than the molecules that are classically used as [TRPV1] antagonists,' said Randall. 'We think it's a very useful tool for studying the biology [of TRPV1].'

Michael Caterina, Assistant Professor of Biological Chemistry at Johns Hopkins University School of Medicine in Baltimore (http://www.jhu.edu), and one of the team that originally cloned the TRPV1 receptor, agrees. 'Any new pharmacological tool to study vanilloid receptors in the laboratory is a very valuable thing,' he said. 'The characterization [of SB366791] has a detail that exceeds what has been done for certain other molecules.'

Of rat and man

But what makes the study stand out is that the researchers have demonstrated that the compound works for both human and rat TRPV1, he says. 'For humans, this has potential therapeutic implications, but the fact that it is also effective in rat offers the opportunity to take this back into the basic science laboratory and ask some more-detailed questions about what it's doing.'

However, Caterina has a few reservations about the paper. 'They don't present any *in vivo* data, so we don't know whether this will translate into the whole animal,' he noted. 'And although they test this compound against one closely related member of the vanilloid receptor family, TRPV4, there is a curious absence of data on whether this compound can block the activity of several other closely related molecules, TRPV2, 3, 5 and 6.'

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