Could the heat of certain spices solve some of medicine's biggest problems? **Moheb Costandi** tackles a burning question

Catching fire

IT STARTS out as a pleasant tingle, before growing into a burning sensation that feels like your whole mouth is ablaze. You sweat, you cry, and your nose streams. You gasp for water, but it feels like nothing can douse the flames. Once the pain has subsided, however, you suspect you'll seek out an even more extreme fix the next time around.

Anyone who enjoys a curry knows this feeling – and chefs have been using the sensation of chillies and other peppers to spice up their culinary experiments for centuries. But it is only in the last decade or so that scientists have begun to understand how we taste piquant foods. Now they have found the mechanism that not only explains the heat of chillies and wasabi, but also the soothing cooling of flavours like menthol.

The implications of this discovery extend far beyond cuisine. The same mechanisms build the body's internal thermometer, and some animals even use them to see in the dark. Understand these pathways, and the humble chilli may open new avenues of research for conditions as diverse as chronic pain, obesity and cancer.

SPENCER WILSON

The story begins in earnest in 1997, with David Julius at the University of California, San Francisco. Although people had long speculated about the source of the chilli's fire, his team was the first to discover how its key component, capsaicin, sets our mouth aflame. Most of our sensory perception depends on specific "channels" on the surface of certain cells, each responding to a different kind of stimulation. When the channel is activated, its pores open up, allowing electrical charge in the form of ions – charged particles – to flow in. These ion channels are often found on nerves, where this influx of ions triggers an electrical impulse.

There were many candidates for the channel that responds to capsaicin, but with some nifty genetics work, Julius was able to pin it down. It is called TRPV1. Crucially, he then showed that the channel also responds to uncomfortably hot temperatures – about 43 °C or higher – that would be enough to damage tissue. This neatly explains why chillies feel like they are burning the mouth.

Other TRP (pronounced "trip") channels had previously been implicated in different kinds of sensory perception, but this was the first to represent our internal thermometer (see diagram, page 47). It didn't take long for other, related protein channels to emerge that explain our sensitivity to other temperatures and food ingredients. In 2002, for instance, Julius discovered the TRPM8 channel, which is activated by relatively cool temperatures, between about 10 and 30 °C. This channel is also triggered by menthol, giving it that cooling sensation.

Just chillin'

Having identified the TRPM8 channel, Julius and his colleagues went on to create a strain of genetically engineered mice that carried two defective copies of the gene that normally codes for its protein. They then tested the animals' sensitivity to cold by placing them in a box containing two chambers, each with a different ambient temperature, and compared their behaviour with that of their normal littermates.

The normal mice showed a strong preference for the chamber kept at 30 °C, but the genetically engineered animals happily stayed in the colder chamber for long periods of time, preferring the warmer one only when the temperature dropped to below 15 °C. They were also far less able than their littermates to distinguish between cool and warm surfaces.

The researchers are now filling in the other gaps in our understanding of the body's ›

thermostat. As they do so, it is becoming clear that in some animals these mechanisms have evolved in surprising ways. For instance, in pit vipers and vampire bats, a super-sensitive variant of the TRPA1 channel, which responds to temperatures of around 10 °C, has been co-opted for infrared-based thermal imaging.

A new understanding of the senses was only half the cause for excitement, however, as it soon emerged that these channels' responsibilities are wide-ranging, potentially implicating them in a range of disorders. Of particular interest is the fact that they are found on nerves that respond to painful stimuli – and that they can act as a kind of switch that amplifies or damps down the nerve's sensitivity. When that mechanism backfires, thanks to certain mutations, even the slightest changes in temperature can produce devastating pain (see "Worse than childbirth", below). But the flip side is that these channels open promising avenues of research for new kinds of analgesics that could potentially use the pathway as an entry point.

Initially, most research focused on TRPV1 – the first channel that Julius discovered. Unfortunately, finding ways to alter pain perception through this route was much more difficult than it first seemed, since the potential drugs were quickly found to have unwanted and potentially dangerous side effects. Because TRPV1 is involved in detecting hot temperatures, anything that blocked its function made people less sensitive to painful heat. That meant they were more prone to injury, by scalding themselves in a hot shower for instance. And, due to its involvement in regulating the core body temperature, drugs that block the channel can cause a dangerously high fever. "Every major pharmaceutical company piled in," says pain researcher John Wood at University College London, "and something like $60 billion was spent trying to make drugs based on TRPV1. We made hundreds and characterised them really carefully, but none were any good."

Such problems have discouraged many researchers, but there may be a way around them if we better understand the way the channels react to their immediate environment. In 2013, Peter McNaughton, then at the University of Cambridge, and his colleagues found a protein that modulates TRPV1 function during inflammation. The protein, called AKAP79, seems to shift the cell's molecules into specific formations. "It localises some of the components of signalling pathways to the right regions inside the cell, so that they're ready to go when the pathway is switched on," says Joan Btesh, also at Cambridge, who led the work. The result is that when this protein is present in excess, the TRPV1 channel has a lower threshold for generating nervous impulses. That means that normally innocuous temperatures feel painful – a serious problem in chronic pain conditions, including fibromyalgia, migraine and certain injuries.

Drooling at the dentist

Luckily, there may be a way to reverse the effect. McNaughton and Btesh's team has found a chemical that stops the AKAP79 protein from binding to the TRPV1 protein channel, reducing the pain associated with the inflammation. And, crucially, it works without reducing sensitivity to heat. "By blocking the interaction between the two proteins, we're reducing the number of TRPV1 channels that are available to respond to stimuli, and preventing the modification of channels that are already in the cell membrane," says Btesh. So far, experiments with mice have been positive.

Others are looking at ways to apply these drugs in small regions of the body, for better local anaesthetics. At the moment, an unpleasant effect of having a local anaesthetic at the dentist is that the drugs knock out all your nerve cells, including those involved in moving the muscles, leaving your face temporarily paralysed. One solution is to use the capsaicin in chilli, or related molecules, as a kind of key to preferentially unlock pain nerves: by temporarily opening the heat channel, it creates an entry for an analgesic to then work its way into the cell. Since the nerves involved in moving muscles don't have the same receptor, they would be left unaffected, so the recipient is not turned into a drooling mess.

Given the many thermal channels on nerve cells, there may also be many other targets. For example, it's well known that cooling has analgesic effects in some painful conditions, such as osteoarthritis, and that it has a soothing effect in inflammation. This is likely to involve TRPM8, but other TRP channels probably play a role, too, which could complicate the picture. And since too much activity in these pathways could also induce an unpleasant hypersensitivity to cold, it could be tricky to find a drug that achieves a comfortable medium.

CULTURA RM/JOSEPH GIACOMIN/GETTY

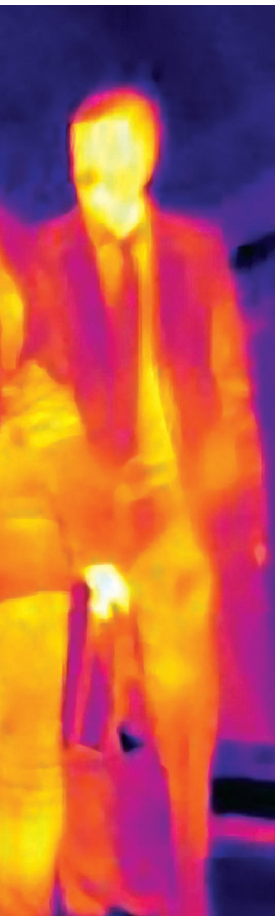
WORSE THAN CHILDBIRTH

Extreme heat or cold can cause pain for all of us – but for some people even small shifts in temperature can be agony. In 2010, John Wood at University College London and his colleagues identified a condition called familial episodic pain syndrome in a Colombian family who had been reporting symptoms of severe pain.

"When these people get cold or tired, they have excruciating chest pain which knocks them out," Wood says. "They come out of it, exhausted, after about 2 hours. The women say that the pain they feel is worse than childbirth."

After Wood's team sequenced the genomes of the family members, they identified a mutation in the TRPA1 gene that seemed to lie behind the family's condition. This gene coded for a cell-surface receptor protein, or channel, that had previously been found to respond to very cold temperatures. Rather than deactivating TRPA1, the mutation identified by Wood and his colleagues sensitises the channel, so that the TRPA1 protein becomes active when it should be resting.

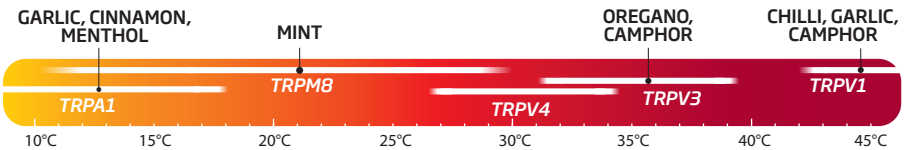
Wood adds that this pain syndrome is probably unique to the Colombian family in which the mutation was identified. So while this research provides useful insight about the involvement of TRP channels in pain states, it is unlikely that drug companies will spend any money to develop a way of relieving this family's acute discomfort.



Our bodies' heat sensors do a whole lot more besides

The thermostat within

Our internal thermometer is made from a series of *TRP* proteins each of which reacts to a different temperature range. They can also be activated by food ingredients to induce a burning or cooling sensation



In the meantime, other researchers are looking at the possibility of using these channels to fight fat. One idea could be to use the channels to fiddle with the body's thermostat to control energy expenditure so that it burns those excess pounds. Clearly, it is something that would need to be done with care – besides the dangers seen in the pain relief studies, the benefits can be unpredictable too. For instance, you might think that knocking out the heat sensing mechanism would have the same response as a cold temperature, triggering automatic mechanisms to burn more heat to compensate. Yet the animal studies have been conflicting: although in some studies, mice lacking the TRPV1 receptor have been shown to lose weight, in others they gain it.

There are hints that gently stimulating TRPV1 receptors could be the answer instead. For instance, activation of the TRPV1 channel seems to suppress the production of adipocytes – cells that are specialised to store energy as fat. Other studies have suggested that stimulating the channel can cause the body to burn fat it has already built up. And since it is involved in taste, it may contribute to the feeling of being full after eating a meal, which prevents us from overeating.

Although the exact reason for this response is still under discussion, human trials so far have been promising. Subjects asked to take a regular dose of capsaicin every day, for instance, showed a modest increase in the calories they burn – enough for a steady weight loss over the course of months.

Perhaps most surprising is the discovery that these channels might also be involved in tumour growth. TRPM8, which allows us to taste mint, is known to be present at abnormally high levels in prostate cancer, for example. The more severe the cancer, the higher the levels of this protein in the cancerous cells. Animal research suggests that here, the channel may have been co-opted in a cellular signalling pathway that sets off cell division. Since these channels are also found in the epithelial cells that line blood vessels, they might also contribute to the spread of cancer by promoting the formation of blood vessels that feed tumours.

Targeting the TRPM8 pathway may therefore provide a way to control growth of cancer. In one experiment, chemicals that inhibit TRPM8 activity were shown to reduce the proliferation of prostate cancer cells growing in a Petri dish. Such experiments could eventually lead to drugs that prevent the spread of the disease. Indeed, one clinical trial is already under way.

These prospects are a world away from Julius's first work on the fiery mystery of chilli. What once seemed like a curiosity for curry lovers now looks set to carve out its own corner in healthcare.

For the time being, we can at least say one thing with certainty: in the field of medicine, few areas of research are as hot right now. ■

Moheb Costandi is a journalist based in London. His book *50 Human Brain Ideas You Really Need to Know* was published by Quercus last year

THEY CALL HIM THE ICEMAN...

...And for good reason. Wim Hof, a 59-year-old Dutchman, has a remarkable ability to withstand extremely cold temperatures for long periods of time. This ability has garnered him no less than 20 world records. In 2009, Hof reached the summit of Mount Kilimanjaro in two days, wearing nothing but a pair of shorts. Later in the same year, he ran a full marathon above the Arctic circle in Finland, in temperatures of about -20 °C – again, wearing only shorts. And in 2011, he broke his own world record for ice endurance, by staying immersed in freezing water for just under 2 hours.

Hof puts this down to an ability to take conscious control over his bodily functions. "It's mind over matter," he says. "I've learned through breathing exercises to take control of my nervous, cardiovascular and immune systems. It makes me able to stay in the cold for longer, and to endure a lot of pain."

Hof's claims are backed by scientific evidence. A 2012 case study by researchers from Radboud University in Nijmegen, the Netherlands, showed that his meditation technique appears to produce a controlled stress response, reducing the unpleasant feelings that normally come with freezing weather.

Genetics is likely to play a role, too, with one particular gene that may produce individual differences in sensitivity to cold. The gene encodes a receptor protein, or channel, called TRPM8, which is normally found in a subset of pain-sensing nerve fibres. Certain TRPM8 variants might make people more or less sensitive to painfully cold temperatures, and there may even be mutations that make people completely insensitive to them.

"I'm not aware of any mutations that have been identified in the human TRPM8 gene," says physiologist David Julius at the University of California, San Francisco, "but someone like Hof sounds like a good candidate for DNA sequencing."