

EUROBRAIN

The perception of pain and temperature

THE PERCEPTION OF PAIN AND TEMPERATURE

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THE USEFULNESS OF PAIN

When the body is subjected to injury from without or within, it must be informed of this as quickly as possible so as to mount a rapid reaction. The main function of acute pain is therefore to warn the body of such attacks. The nociceptors, the nerve terminals dedicated to this preventive role, are distributed throughout the body (skin, muscles and joints, viscera) with the exception of the brain itself, which is protected by layers of extremely sensitive tissue, the meninges.

Nociception can be considered as a sense in the same way as vision or olfaction, but, in contrast to these, it brings into play a wide spectrum of transduction mechanisms, mechanisms that transform a physical or chemical stimulus into an electrical signal, so as to relay the information from the external world to the brain. Nociceptors have the special characteristic

of being sensitive to several types of stimuli, such as intense pressure, chemical agents and temperatures harmful to the body. In addition, nociceptor activity and, consequently, pain sensations must not be consciously perceived except in the case of attack, so the body must be able to distinguish dangerous stimuli from harmless ones, such as a caress or the heat of the sun's rays.

THE DIFFERENT TYPES OF NOCICEPTOR

In the same way that the spectrum of noxious stimuli that we can perceive is wide, different types of nociceptor are found, depending on where they are located (viscera, or skin, muscles and joints) and the type of noxious stimuli that excite them. For the skin in particular, the sensory fibres responsible for nociception are subdivided into categories on the basis of their diameter and the thickness of



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The perception of pain

their myelin layer, two critical parameters directly related to the speed of conduction of electrical signals. Nociceptors are the free terminals of weakly myelinated or non-myelinated small diameter sensory fibres, which can be subdivided into A δ and C fibres, the latter having a smaller diameter and slower conduction speed (less than 2 m/s). A δ fibres are somewhat faster (up to 30 m/s) and carry the sharp sensation of pain caused by an acute noxious stimulus while C fibres report slow, dull persisting pain. Thus, pain-related information travels relatively slowly to the brain compared to information from other touch neurones that travels at speeds up to 100 m/s. In addition, as with all sensory fibres, the information from nociceptors is not sent directly to the brain, but progresses by successive steps, passing through a first relay at the level of the spinal cord, then through a second at the level of the thalamus, a sort of redistribution and analysis centre for sensory fibres, before finally reaching various areas of cerebral cortex where the pain is consciously interpreted by the body.

WHY WOUNDING AMPLIFIES PAIN

When the body is damaged, e.g., by wounding, the properties of the nociceptors are modified. The zone of inflammation becomes hypersensitive, and stimuli that are harmless under normal conditions are perceived as a painful attack, a phenomenon known as hyperalgesia. This explains why the simple application of a warm compress to a patient's wound can give rise to acute pain. The activation threshold for nociceptors becomes lower than normal because it is modulated by chemical substances released by the injured cells. Furthermore, the response of the spinal cord neurones increases,

which explains the local hypersensitivity of the body.

One of the scientific perspectives currently of interest in medicine is to understand the molecular mechanisms responsible for nociceptor activity. The hope is that, one day, we will be able to manipulate these mechanisms to relieve the pain caused by tissue injury. The fact that nociceptors are polymodal, i.e. activated by stimuli of different types, constitutes a crucial problem that limits current palliative care. For instance, local anaesthetics effectively block all sensory receptor types but completely blocking peripheral sensory information would leave the body at the mercy of potential dangers, rather than providing relief. Consequently, current research is aimed at determining whether it is possible to dissociate the molecular mechanisms that activate nociceptors after a burn from those brought into play by intense pressure or by a harmful chemical substance, in order to block them in a more selective way.

FROM HOT PEPPERS TO THERMORECEPTORS

A first decisive step in research on thermo-nociceptors was taken by David Julius and his team in 1997. Intrigued by the burning sensation experienced after eating a chilli pepper-containing dish, these researchers asked whether *capsaicin*, the molecule responsible for the chemical attack perceived by the nociceptors, was able to activate the same type of membrane receptor as a hot stimulus. They identified the type of receptor to which capsaicin binds, the *vanilloid receptor (VR1)*, then verified that it was also activated by high temperatures***. This receptor is part of a larger family of ion channels, the *transient receptor*

and temperature

THE THERMAL GRILL ILLUSION

In 1896, the Danish physiologist, T. Thunberg, demonstrated a curious tactile illusion related to thermoception, namely, that when the palm of the hand comes into contact with a grid formed from alternate warm and cool bars, we experience a strange sensation of burning. However, if we touch a similar grill in which all the bars are at the same cool or warm temperature as before, no pain is felt. It is only recently that researchers have been able to explain this phenomenon. They were guided to the solution by the fact that the body has difficulty in distinguishing a very hot stimulus from a stimulus lower than 15°C, both being perceived as burning. This means that the same nociceptive fibres are activated by a stimulus that is either too hot or too cold. The pain felt when the bimodal grill comes into contact with the hand indicates that these nociceptors are again activated, but, this time, by temperatures not harmful to the body. In fact, three types of cells are activated: thermoreceptors activated by the warm bars, thermoreceptors activated by the cool bars and nociceptors, which cause the pain. All this information is integrated at the level of the spinal cord before being relayed to the brain. It would therefore seem that, when we touch a grill at a uniform temperature that presents no danger to the body, only one type of thermoreceptor is activated and this inhibits or masks the activity of the nociceptors at the level of the spinal cord. However, when we touch objects that are simultaneously warm and cool, both types of thermoreceptors are activated, which is interpreted by the spinal cord neurons as bad news. As a consequence, the activity of the nociceptors is no longer inhibited and becomes perceptible as an illusion of burning.

potential (TRP) family and was renamed as TRPV1. The transduction mechanism activated by capsaicin is thus the same as that brought into play when we burn ourselves: TRPV1-associated membrane channels open and allow the entry of a current which depolarises the neuron, resulting in the generation of an electrical signal which propagates to the brain. The TRPV1 therefore function as a sort of

***To prove this, they knocked out the gene coding for VR1 to produce mice that did not express VR1, then verified that these mice were not sensitive to a high temperature. However, they found that the mice were still sensitive to temperatures above 50°C, suggesting that another type of receptor activates nociceptors sensitive to very high temperatures.

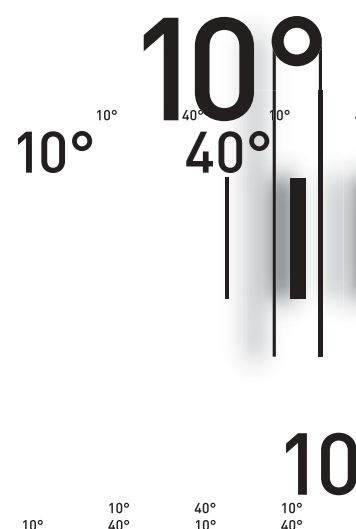
molecular thermometer, since they activate the nociceptor when the temperature of the stimulus exceeds 43°C.

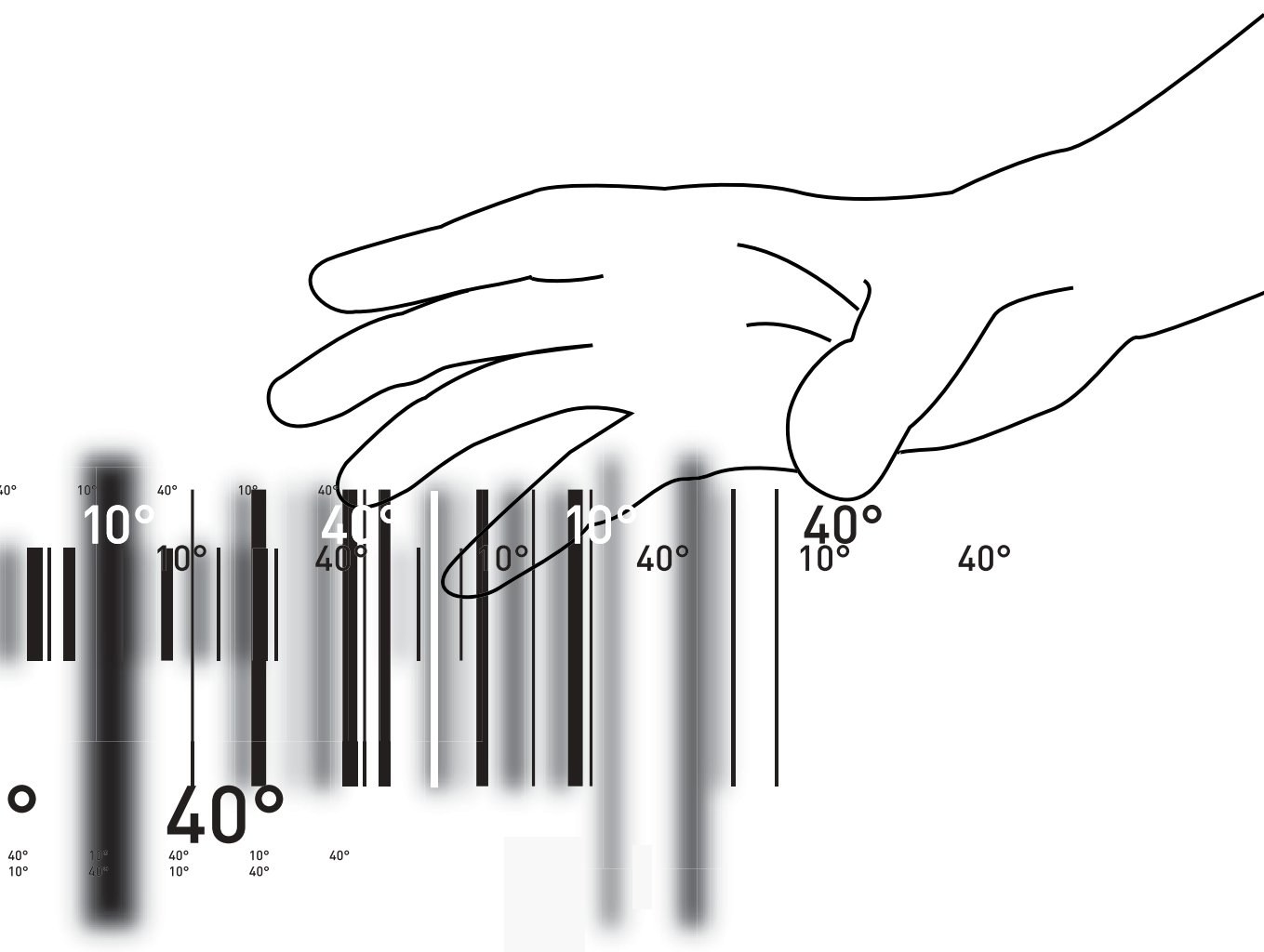
TRPV1-bearing nociceptors account for more than half of the population of nociceptors and are sensitive to capsaicin and moderately hot stimuli. Their activity increases as the temperature increases. However, when the temperature exceeds 52°C, an additional type of membrane receptor is mobilised. In contrast with TRPV1 described above, they react only to a high temperature and not to capsaicin. Scientists initially called them the *vanilloid receptor-like (VRL-1)* channel. The structure of the latter is very similar to that of the TRPV1 and they belong to the same

channel family, the main difference being that they are not activated by capsaicin, and it is now named the TRPV2 channel.

THE COOLING SENSATION OF MENTHOL

These conclusive results obtained with chillies encouraged the researchers to adapt their method to identify cold-specific receptors. The feeling of coolness produced by a menthol sweet is familiar to everyone, and, in 2002, Julius and his team were able to demonstrate that the receptors activated by menthol were the same as those activated by a temperature of 15°C, hence they named this receptor the *cold- and menthol-sensitive receptor (CMR1)*. Because this receptor belongs





also to the family of TRP channels, it was later called TRPM8 receptor. A temperature of 15°C is the approximate limit of the pain threshold; however, it should be noted that this limit is clearly more subjective than the pain threshold for a hot stimulus, since everyone describes a shower at a temperature higher than 47°C as very hot, but a non-negligible proportion of individuals feel no pain on entering a lake at a temperature of 15°C. Speaking physiologically, this difference is explained by the fact that all VR1-bearing cells are activated when the temperature exceeds 43°C, whereas the activation threshold for TRPM8-bearing cells is clearly more diffuse, being between 8°C and 30°C. The

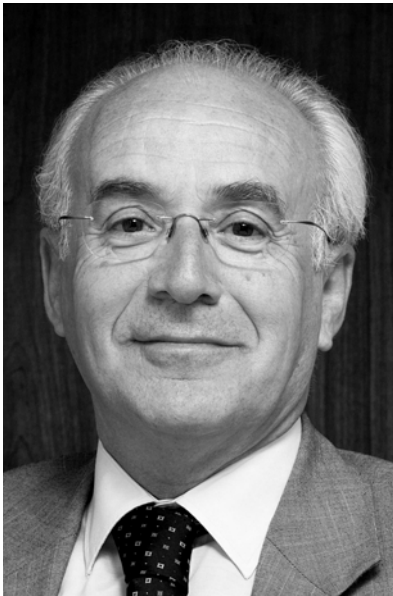
problem that immediately arises is that it becomes difficult to distinguish, among these fibres, between thermoreceptors, that react to moderately low temperatures that are harmless, and nociceptors, which must protect the body from harmful low temperatures. It should be noted that only a small proportion of A δ and C fibres bear TRPM8, whereas many of these fibres are activated when the temperature falls below zero. This indicates that there may be another transduction mechanism for extreme cold. Recently, a new receptor channel named ANKTM1, which apparently responds only to low temperatures in the noxious range, has been described in nociceptor neurones. The impression of

burning ourselves when we touch a cold object, such as ice cubes just taken out of a freezer, may be due to activation of this channel by extreme cold in nociceptor neurones.

HOW DO WE DISTINGUISH BETWEEN INNOCUOUS AND NOXIOUS COLD?

Almost half of TRPM8-bearing thermal receptor neurons also bear TRPV1. This surprising discovery tells us that a considerable number of thermal receptors are activated by both cold and heat.

It has been known for a long time that activation of nociceptors by whatever stimulus type (capsaicin, heat, cold) will produce a sensation of pain. Likewise,



Carlos Belmonte

excitation of innocuous cold receptors will evoke a cooling sensation irrespective of the stimulus that excite them. The question currently preoccupying researchers is the following: if nociceptor and thermal sensitive fibres are activated by both a hot and a cold stimulus, why does the body feel pain in one case and not in the other? The answer probably lies in the variable degree of activation of the different types of neurons: when we touch a very hot object, the discharge frequency of nociceptor fibres is higher than when they are activated by noxious cold and, besides, many innocuous cold-sensitive fibres are silenced. This pattern of activity is interpreted by the brain as pain. When small temperature changes occur, only innocuous cold fibres are activated and we experience a sensation of cooling. In fact, fever evokes cold sensations, probably because it stimulates TRPV1 receptors present in cold fibres. Another emerging lead, reinforced by the thermal grill illusion (see the box), is based on the integration, at the level of the spinal cord, of signals coming from different types of sensory fibres. For example, fibres sensitive to innocuous cold would be able to inhibit the action of nociceptors when we touch a cool object. A clinical observation confirms this view: when the A δ fibres are lesioned, only the type C polymodal nociceptors (bearing both types of receptor) are able to relay the information and the patient feels an intense burning sensation when a cool compress is placed on his skin.

THE SITUATION BECOMES MORE COMPLEX

Although the discovery of TRPM8 made it possible to identify a category of cold-sensitive sensory neurons, the fact that the activation threshold for these receptors is not set at a precise temperature

indicated that the cold transducing mechanism was more complex than the simple activation of a particular receptor. In 2002, the team of Belmonte and Viana, with their co-workers at Alicante, showed that the response of cold receptors brought into play a constellation of ion channels, the expression, density and activation of which are specific to cold thermoceptors. To do this, they established cultures of mouse primary sensory neurons, then picked out neurons sensitive to a lowering of temperature by studying the intracellular calcium spatio-temporal profile, since it is known that, when neurons fire nerve impulses, calcium-permeable ion channels open and the intracellular calcium concentration increases. Viana and Belmonte verified that neurons responding to cold were menthol-sensitive and found that almost half of them also responded to capsaicin. They also noted that it was possible to categorise the cold neurons into two groups according to the intensity of cold to which they were subjected. Each of these two categories has a wide activation temperature spectrum.

Once the fibres of interest had been identified, the researchers used an electrophysiological technique that allowed them to study the signal produced by these neurons when the temperature dropped. Two types of pattern were demonstrated. Neurons sensitive to moderately low temperatures, rapidly depolarised, emitting a burst of action potentials. Some of them had an oscillating membrane potential and generated repeated trains of action potentials. It should be noted that the frequency of these discharge trains was closely correlated with the intensity and rapidity of the temperature drop. The next step consisted of comparing these responses with those of cold-insensitive neurons, then to identify the various

specific ion channels that allow cold-sensitive neurons to behave differently from the others.

A resting cell is permeable to potassium, i.e., the potassium channels present on the membrane are open and the ions are free to move, in accordance with certain physico-chemical constraints, from the interior to the exterior and vice versa. Viana and Belmonte showed that cold-sensitive neurons respond to cold by closing some of their potassium channels, which depolarises the cell and causes it to rapidly generate an electrical signal. This depolarisation possibly adds to that caused by the opening of TRPM8 by cold. However, a priori, all sensory fibres have these potassium channels and should therefore respond to cold. Belmonte and Viana discovered that cold-insensitive neurons have, in addition to the normal potassium channels, another type of channel called IK_D , which is membrane potential-dependent and is scarcely present in cold-sensitive neurons. These IK_D channels tend to counteract the depolarising effect of cold, thus acting as a brake against the effects of cooling. To confirm this mechanism, Belmonte and Viana had the subtle idea of blocking the IK_D channels and thus preventing the associated potassium current from maintaining the membrane potential at the resting level during cooling. As expected, neurons that were initially cold-insensitive became cold-sensitive. This shows that the cold transducing mechanism emerges from the expression, or rather the non-expression, of ion channels on the membrane of neurons that are affected by cold. Viana and Belmonte went further by formulating the hypothesis that the temperature linked to the activation threshold of the cell could be modulated by the density of these two types of membrane channel.

However, much remains to be clarified about these complex mechanisms. The next step will consist of determining the relative role of the TRPM8, ANKTM1 and the non-specific potassium channels in establishing the thermal sensitivity of sensory neurons detecting innocuous and noxious temperature reductions.

By **Mélanie Aeschlimann, PhD**
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