NEWS & VIEWS

Foot and mouth — an argument for analgesics.

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NEUROSCIENCE

A local route to pain relief

Edwin W. McCleskey

Local anaesthetics stop pain, but block all other sensations too. In rats, one molecular delivery vehicle makes an unusual local anaesthetic specific for pain — provided a little spice is added to the mix first.

Medicine has no shortage of great anaesthetics: they have been making surgery tolerable by eliminating consciousness, or by blocking complete nerve systems, for 160 years. But what we do need more of are good analgesics: drugs that suppress pain without affecting any other sensation. On page 607 of this issue, Binshtok and his colleagues — based at the Massachusetts General Hospital in Boston, where surgical anaesthesia was first demonstrated in 1846 — report a new approach to analgesia[1]. They have found a way to deliver a local anaesthetic so that it blocks pain sensing alone.

To those in the know, an anaesthetic seems the last place to look for an analgesic effect. When you are numbed for the dentist's drill, the anaesthetic used blocks all the voltage-gated sodium channels in a nerve. These are proteins that conduct action potentials in nerve axons by timing, with submillisecond precision, the flow of current in the form of sodium ions across cell membranes. Blocking all sodium channels blocks all sensation; it blocks movement if the affected nerve includes motor axons, or the responses of internal organs if a controlling 'autonomic' nerve is exposed. Recently, however, certain sodium channels have been identified as being present only in pain-sensing neurons[2]. Drug companies have thus begun to comb their libraries of uncommercialized local anaesthetics for a 'magic bullet' drug that affects pain alone.

Binshtok *et al.*[1] follow a different path. They study the TRPV1 ion channel, which is opened up by capsaicin — the chemical that makes chilli peppers spicy and creates the burning sensation when they are rubbed on skin — or by temperatures that rise above 42 °C, the skin temperature that we consider unpleasantly warm. The temperature-dependent gating of TRPV1 and its specific expression profile, as demonstrated in a series of animal and human studies[3], show that it is a molecular sensor for noxious heat that is expressed only on small nociceptors. Nociceptors are sensory neurons that translate noxious stimuli into action potentials and conduct these electrical signals from the site of stimulation to the spinal cord. Small nociceptors conduct slowly (at about 1 m s^{-1}), and TRPV1-positive neurons therefore mediate slowly developing, persistent pain — anything from the half-minute of smarting after stubbing a toe to the never-ending discomfort of an arthritic joint.

Crucial to the story is that, although the pore of the TRPV1 channel rejects negatively charged anions, it promiscuously allows most positively charged inorganic cations to pass — and even organic cations as large as some local anaesthetics. In most cases, this is irrelevant: local anaesthetics are generally weak acids that occur in both a positively charged (protonated) form and an uncharged, 'free-base' form. As free bases, local anaesthetics readily permeate lipid cell membranes without the need to pass through the pores of an open ion channel. This is why they shut down sodium channels in all neurons; indeed, the potency of an anaesthetic rises in proportion to its lipid solubility.

Once an anaesthetic has passed through the membrane, it blocks the sodium channel from within by docking in a wide hydrophobic vestibule just to the inner side of the sodium selectivity filter, the narrowest part of the channel's pore[4]. This inner vestibule, whose existence was first deduced in potassium channels[5] and has now been seen in their crystal structure[6], is common to all voltage-gated ion channels and is the binding site for many different drugs used against various voltage-gated channels[7].

But there is one particular anaesthetic, known as QX-314, that cannot infiltrate lipid membranes under its own steam: it has a permanent positive charge, making it lipid-insoluble. As a result, it fails to block sodium

NATURE|Vol 449|4 October 2007

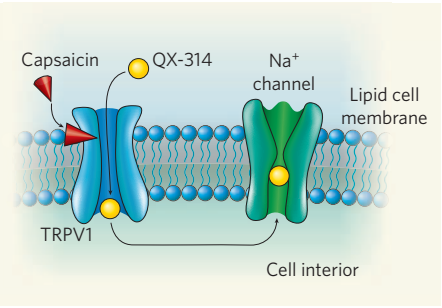

Figure 1 | A spicy solution. QX-314, a charged local anaesthetic, cannot pass through a lipid cell membrane. Instead, it gains access to the cell's interior through TRPV1, an ion channel that is opened by capsaicin, the 'hot' component in chilli peppers. Once inside, QX-314 can bind to the inner vestibule of sodium (Na^+) channels, the site for local anaesthetic action. This transmembrane access route for QX-314 exists only on nociceptors, pain-sensing neurons on which TRPV1 is expressed. Thus, as Binshtok *et al.*[1] show, administering a mix of QX-314 and capsaicin acts as an analgesic, shutting off pain sensation without affecting any other nerve responses.

channels when applied outside cells, although it succeeds when injected into them. Once inside, QX-314 binds within the hydrophobic vestibule just like any other anaesthetic. In fact, kinetic features of QX-314's blocking mechanism — dependence on the direction of current flow and on membrane voltage — were the initial evidence for the vestibule binding site of anaesthetics in general.

What if QX-314 could be delivered to the insides of cells through the large, cation-selective pores of the TRPV1 channel? By exploiting the fact that TRPV1 resides only on nociceptors, this might inhibit pain without other side effects. And Binshtok *et al.*[1] found that, although neither capsaicin nor QX-314 alone could shut off the sodium channel or action potentials, applied simultaneously to nociceptors they could do just that (Fig. 1). When injected into the foot or perfused onto a nerve of a rat, the mixture inhibited the animal's sensitivity to noxious thermal and mechanical stimuli without causing paralysis. This analgesia lasted about 2 hours.

The significance of this discovery might go beyond just the blockade of sodium channels. First, the same sort of strategy might prove useful for delivering other drugs to other voltage-gated channels. Second, local anaesthetics are more than simple ion-channel blockers. At low concentrations, they exhibit a clinically important selectivity, known as 'use-dependent inhibition', by binding with greater affinity to inactivated sodium channels than to those poised to open[8]. Low concentrations of anaesthetic thus selectively inhibit sodium channels in cells that are frequently firing action potentials, because those channels cycle more frequently through the inactivated state.

Such selective targeting of hyperactive cells explains why the local anaesthetic lidocaine, when perfused into the entire body at very low concentrations, suppresses certain cardiac arrhythmias without affecting nerves. Pathological pain — pain that is persistent but not caused by an existing injury — is another example of hyperactivity, this time in nociceptors. Nerve blocking by local anaesthetics is sometimes used to treat pathological pain because relief from the pain persists long after the initial numbness wears off; this might be because low, residual levels of local anaesthetic selectively inhibit nociceptors that are too active[9]. If Binshtok and colleagues[1] are right, the humble local anaesthetic may thus prove to have four mechanisms for specificity: through infusion onto a particular nerve for its most basic application; through use-dependence, as a remedy for electrical hyperactivity; through the targeting of distinct subtypes of sodium channel to alter the activity of distinct cells that express them; and now through the TRPV1 channel, a nociceptive drug-delivery vehicle that yields an analgesic effect.

But before we get carried away, the TRPV1 trick must first be shown to work in humans. In addition, the ideal cocktail of capsaicin and TRPV1 modulators must be found, in order to avoid any damage that capsaicin would cause at excessive levels. It will be useful, too, to optimize the use-dependence and TRPV1-permeability of QX-314. This drug, which was until now just an exotic reagent used by ion-channel biologists, will be the focus of a new effort in the search for better analgesics. ■

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ATOMIC PHYSICS

Cold meeting at a junction

Charles A. Sackett

The Josephson effect is a macroscopic manifestation of quantum mechanics usually seen in superconductors. Observation of this effect in a gas of ultracold atoms demonstrates the underlying unity of solid and gaseous systems.

On page 579 of this issue[1], Levy *et al.* report the observation of the Josephson effect in a cold atomic gas. Brian Josephson discovered the original version of this effect in 1962, when he was a young graduate student at the University of Cambridge[2], and it earned him a share of the 1973 Nobel Prize in Physics.

Josephson considered what happens when two superconducting plates are placed next to each other with an insulating layer between them. In a world determined by classical physics, this makes a simple capacitor that stores up static electric charges. But quantum mechanics warns us that it is hard to pin a particle down in any one place. Because of this, if the Josephson junction is formed with a sufficiently thin insulator, electrons from one plate can tunnel through the barrier to the other plate, resulting in a flow of current.

For plates made of normally conducting metal, this tunnelling is haphazard, and the effect is equivalent to that of a resistor shorting the capacitor. But in a superconductor, where current can flow without resistance, the quantum state of the electrons is highly correlated, and the tunnelling becomes coherent. Josephson's breakthrough was to realize that this meant interference could be observed, because the tunnelling wavefunction from one electrode combines with that from the other in a way that depends on their relative phase. This interference gives rise to two main effects. First, a steady current can flow through the junction even when no voltage is applied. Second, when a steady voltage is applied, an oscillating current results. These are known respectively as the d.c. and a.c. Josephson effects. They are at the heart of many important technologies, particularly in the measurement of electric and magnetic fields.

Levy *et al.*[1] do not use superconductors, but start with a gas of rubidium atoms in the form of a Bose–Einstein condensate. Condensates are a kind of superfluid, in which the atoms share a quantum wavefunction just as electrons do in a superconductor. The atoms are at a temperature just a few billionths of a degree above absolute zero, and are held in vacuum using a magnetic trap (a box to keep them from drifting away). Levy *et al.* divided this trap in two by sending a tightly focused laser beam through its centre. The beam formed a barrier for the atoms that was analogous to the insulating layer in the original Josephson effect; it was similarly narrow enough that atoms on one side had a non-zero probability of tunnelling through to the other.

Following a suggestion made by Giovanazzi