Editors' view

Human models of hyperalgesia and pain (chilli pepper with your acid indigestion, Sir?)

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'It is easier to find men who will volunteer to die, than to find those who are willing to endure pain with patience' (*attributed to Julius Caesar*)

Nociception vs. pain

The perception of harmful stimuli (termed *nociception* from Sherrington's terms 'nociceptive' and 'nociceptor') is closely related to, but distinct from, the sensation of pain. Polymodal nociceptors (PMNs) are peripheral sensory neurons that respond to noxious (i.e. potentially tissue-damaging) stimuli. They are mainly non-myelinated C fibres whose endings respond to intense thermal, mechanical and chemical stimuli (and hence are 'polymodal'). PMN fibres terminate in the dorsal horn of the spinal cord, forming synaptic connections¹ with transmission neurons running to the thalamus. Chemical stimuli acting on PMNs include bradykinin, protons, ATP and vanilloids (e.g. capsaicin, the component of chilli peppers responsible for their fiery flavour). PMNs are sensitized by prostaglandins, which explains the analgesic effect of anti-inflammatory drugs, particularly in the presence of inflammation. The transient receptor potential vanilloid receptor 1 (TRPV1) receptor responds to noxious heat as well as capsaicin-like agonists.

Pain (distinct from nociception) includes a strong emotional component; its intensity depends critically on several additional factors in conjunction with the noxious stimulus itself, notably the context in which tissue injury occurs (e.g. football pitch vs. dentist's chair), its chronicity and any associated inflammation. All of these strongly influence the threshold at which a potentially harmful

stimulus is perceived as painful. Reduction in this threshold defines the state of *hyperalgesia* (enhanced pain from even a mildly noxious stimulus), familiar to anyone who has suffered a sprained ankle or a scald, and which results from a combination of sensitization of peripheral nociceptive nerve terminals and facilitation of central pain pathways.

Peripheral sensitization is due to mediators such as bradykinin and prostaglandins, while the central component reflects facilitation of synaptic transmission in the central pain pathways [1]. Central facilitation displays the phenomenon of 'wind-up' (synaptic potentials steadily increase in amplitude with each stimulus) and is prevented by antagonists of NMDA, and of substance P and by inhibitors of nitric oxide synthesis, although none of these antagonists or inhibitors has as yet led to new and therapeutically useful analgesic drugs. Substance P and calcitonin gene-related peptide (CGRP), released from the central connections of C-fibres in the dorsal horn of the spinal cord, are also released peripherally (as a consequence of an axon reflex), causing neurogenic inflammation, which amplifies and sustains the activation of nociceptive afferent fibres. Nerve growth factor (NGF), a cytokine-like mediator produced by inflamed tissue, acts on a kinase-linked receptor known as TrkA located on PMNs, and increased production of NGF may cause hyperalgesia [2].

Many analgesics, particularly opioids, disproportionately reduce the distress associated with pain compared with their effect on awareness of the noxious stimulus *per se*, and this is not explained by nonspecific sedative effects. The activity of opioid analgesics in animal models such as the mouse 'tail-flick' (a flick of the tail in response to heat), which mainly assess antinociceptive activity, is poorly correlated with clinical efficacy [1]. Can tests in humans do better? Symptoms of pain in diseases such as myocardial infarction, arthritis or pancreatitis are dramatically

¹Sherrington also introduced the term 'synapse'.

alleviated by analgesic drugs, and demonstration of efficacy in such situations is the 'proof of the pudding' ultimately required by licensing authorities. Such phase 3 studies must be performed against an active comparator such as morphine and are not made easier by co-morbidities. 'Silent' (i.e. asymptomatic) myocardial infarction is not uncommon in patients with diabetes mellitus (a potent risk factor for atheromatous disease), possibly because of associated neuropathy, exemplifying such problems. Deciding which drug to test in which disease at what dose and with what regimen is all-important for clinical and commercial success: phase 3 studies are extremely expensive, and there is seldom much chance for a second bite of the cherry, unlike in basic pharmacology, and no commercial reward for a negative answer (however scientifically reliable) to the 'wrong' question!

Human models of pain and hyperalgesia

Early phase human studies of analgesic drugs contribute critically to such decision making, but have problems of their own. Healthy people are not usually in pain, so to take advantage of the fact that human subjects can communicate more subtly and precisely than other mammals, one must subject them to some controlled form of hurt. This sort of experiment raises ethical problems (the research is not 'therapeutic', in the sense that the subject could benefit directly, and pain or discomfort are inevitable), but with suitably informed consent research ethics committees have, wisely, supported such studies, with reasonable economic compensation for the volunteers. Historically, subjective responses using a visual analogue scale to quantify responses to applications of drugs and putative mediators, separately and in combination, to the base of a blister raised on the forearm and then de-roofed under sterile conditions [3] has taken us far beyond what was possible using animal models in defining mechanisms of nociception.

Such acute experiments do not, however, address the relative effectiveness of analgesic drugs in chronic conditions, in which wind-up and neurogenic inflammation are in play. Human models of hyperalgesia and their use in assessing analgesic actions of opioids have previously been reviewed in the *Journal* [4], and in the current issue the same Danish group describes an interesting experiment in healthy volunteers (who did not, fortunately, share the attitude quoted above of Caesar's legionaries), using a model of hyperalgesia produced by perfusing the oesophagus with acid and capsaicin [5]. The protocol compared oral morphine 30 mg, oxycodone 15 mg and placebo in a three-way crossover. After sensitization of the pain system, oxycodone had a greater effect than morphine on skin, muscle and oesophageal pain stimulation. The authors argue that the relatively high dose of mor-

phine ensured that differences in bioavailability or other kinetic factors did not favour oxycodone, and that oxycodone differs qualitatively from morphine in its analgesic effect following induction of hyperalgesia. This conclusion might have been even more convincing if it had been possible to study the effects of the same doses of morphine, oxycodone and placebo after dummy oesophageal perfusion (ideally in the same subjects) and to have shown that morphine was more effective than oxycodone, in other words direct evidence that the hyperalgesia-inducing intervention had changed the relative potencies of the two opioids. This would have been even more demanding for the volunteers, and the authors are suitably cautious in their interpretation, wisely so, especially in view of the long and sometimes controversial history of oxycodone as an analgesic.

Oxycodone

Oxycodone was synthesized in 1916 by Freund & Speyer in Frankfurt from thebaine (derived from opium and first used clinically by Falk only 1 year later. Drug development was faster during the first world war!). It was developed as one of several new semi-synthetic opioids in an attempt to improve on morphine, diacetylmorphine and codeine (<http://en.wikipedia.org/wiki/Oxycodone>). Bayer had recently discontinued diacetylmorphine ('heroin') because of drug abuse, and it was hoped that oxycodone would retain the analgesic efficacy of potent opioids but cause less dependence. It does differ in its acute effects from other potent opioids, partly at least because of its pharmacokinetics, and is preferred to morphine by many patients and prescribers such that in 2007 worldwide consumption of oxycodone (52 tons) exceeded that of morphine (39 tons) as reported by the International Narcotic Control Board Report of 2008 (http://www.incb.org/pdf/annual-report/2008/en/AR_08_English.pdf). One brand achieved sales in the USA that exceeded \$2.5 billion in 2008, but oxycodone (particularly its extended release formulation) has been widely abused and causes withdrawal symptoms if discontinued abruptly. There is evidence from animal studies that, unlike morphine, it binds preferentially to κ -opioid receptors [6] possibly acting as a κ_{2b} -opioid partial agonist [7], but this is disputed [8] and it also binds to μ -opioid receptors (<http://en.wikipedia.org/wiki/Oxycodone>). The differential roles of active metabolites of both morphine (morphine-3-glucuronide, M3G, and morphine-6-glucuronide, M6G) and oxycodone (oxymorphone), differences in the non-neuronal effects of glial-activation between oxycodone and morphine and the important role of opioid-induced hyperalgesia also contribute to differences in clinical effects between these two opioids. It is tempting to attribute the superior efficacy of 15 mg oxycodone vs. 30 mg morphine [5] to induction of hyperalgesia and perhaps to increased expression of

κ -opioid receptors in response to oesophageal acid/capsaicin in the experiments described by Olesen and her colleagues. If so, this could point the way to analgesic strategies more precisely targeted at specific kinds of painful disorder with precisely assigned individual phenotyping. Further experimental work will be needed to decide whether this is indeed the case, reminding us that translational medicine often remains a protracted business.

Competing interests

There are no competing interests to declare.

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