(Zostrix)

Capsaicin is an alkaloid derived from the chilli pepper, which has been known in Europe since the time of Columbus in the fifteenth century. 150 years ago, Turnbull ([i]) recognised that tincture of capsicum was helpful in treating chilblains and toothache. Capsaicin is the active ingredient in peppers, which causes the burning sensation when you eat them.

In 1997, Caterina et al ([ii]) described the capsaicin receptor as a heat-activated ion channel, only found in neurons that process pain.

This receptor was later cloned by David Julius and Jon Levine of the University of California, San Francisco (UCSF).

It is termed vanilloid receptor subtype 1(VR1). This receptor is implicated in both the treatment of chronic pain and urinary incontinence.

Companies such as Neurogen have identified a number of compounds, which act on this receptor as antagonists and from this they hope to develop therapeutic substances.

The initial response to capsaicin is increased pain: an exaggerated sensitivity, which triggers a process that sensitises the pain response and causes it to react even to non-painful stimuli.

This process is also triggered by inflammation or tissue injury and one of the substances that mediate it is Nerve Growth Factor (NGF) , which Mendell and Shu have found boosts the

activity of the capsaicin receptor. ([iii])

However, repeated applications deactivate the capsaicin receptor: overstimulating the receptor may destroy the sensory nerve endings.

Repeated administration of Capsaicin is known deplete peripheral neuropeptides ([iv] [v]), notably Substance P, which is known to be essential in pain transmission and is involved in inflammatory conditions such as arthritis. It is therefore most useful for pain of peripheral origin, such as postherpetic neuralgia or diabetic neuropathy.

An easy way to picture this process is to think of what happens when you first eat spicy food: there is a lot of burning in the mouth.

However, if you become accustomed to eating curries or chili, you are able to eat food that you would previously found caused intolerable burning.

It is important to note that after a single exposure to capsaicin, the burning occurs rapidly and wears off slowly.

Repeated exposure before the burning has dissipated may lead to sensitisation: more intense pain. ([vi])

However, if the exposure is repeated after the burning has stopped, desensitisation occurs: reduction in pain. ([vii])

It seems that capsaicin raises the pain threshold and this can be further raised by gradually increasing the concentration in a series of repeated applications.([viii])

Watson et al looked at capsaicin to treat postherpetic neuralgia ([ix]) and post-mastectomy pain ([x]) and found that a cream containing 0.025% can be an effective analgesic.

However, these were small studies and McQuay ([xi]) suggests that it remains to be established whether capsaicin is beneficial in these two conditions.

In 1994, Zhang et al ([xii]) conducted a meta-analysis of the efficacy of topical capsaicin. They found that of 4 trials involving patients with diabetic neuropathy, using 0.075% cream, 4 times a day for 4-8 weeks, 2 showed significant benefit.

However, the number-needed-to-treat (NNT: how many patients need to be treated for 1 to be successful) is 4.2 compared with 2 trials of oral anticonvulsant therapy which showed NNT of 2.5 (low NNT= more effective). One of 3 trials in osteoarthritis found significant benefit.

They reported one trial of treatment of postherpetic neuralgia using 0.075% 3-4 times a day for 6 weeks, which found a significant benefit.

More recently in 1999, Sindrup and Jensen (xxi/ [xiii]) cited a NNT of 5.9 for capsaicin in treating diabetic neuropathy, 5.3 for peripheral neuralgia and 3.5 for peripheral nerve injury, based on placebo-controlled studies, which showed more than 50% pain relief. (cf. tricyclic antidepressants: 2.4, 2.3 and 2.5 respectively; Gabapentin 3.7 for Diabetic neuropathy and 3.2 for postherpetic neuralgia).

The Capsaicin Study Group ([xiv]) conducted an 8 week trial of 0.075% capsaicin cream to treat diabetic neuropathy.

They found that this was an effective treatment and that the most common adverse effect was burning sensation, which was reported by 63% of the patients.

Researchers ([xv]) have studied the effect of much stronger, 5-10% solutions of capsaicin. (note: in the States sports shops sell 1% capsaicin solution as a grizzly bear repellent!!)

They found that 9 out of 10 patients with intractable chronic pain (HIV, diabetic neuropathy, postherpetic neuralgia) experienced significant and lasting relief. (6-8 months)

Seven out of 10 had more than 50% relief, all 10 had some relief.

In this study, patients were given regional anaesthesia prior to application of the capsaicin, and morphine to treat the burning which tended to last up to 5 days after application (note: morphine reduced the burning from capsaicin but did not help the presenting neuropathic pain).

The degree to which the regional anaesthesia may have affected the outcome is unclear.

Recent literature on treatment of postherpetic neuralgia ([xvi] [xvii]) suggests that capsaicin is a useful part of the clinical armamentarium for this condition.

However, Paice et al ([xviii]) found it ineffective against HIV-related neuropathic pain.

Capsaicin may also be helpful in orofacial pain ([xix]): trigeminal neuralgia, atypical facial neuralgia and Burning Mouth Syndrome.

Berger et al ([xx]) described an extemporaneous formulation of cayenne pepper candy used to treat mouth pain secondary to chemotherapy or radiotherapy; they varied the amount of cayenne pepper, which allowed them to escalate the concentration as the patients' tolerance developed.

Patients who became desensitised to low concentrations tolerated exposure to higher concentrations more easily.

All patients had some relief from mucositis pain and 2 out of 11 had complete resolution of symptoms with continued use (4-6 candies over 2-4 days). 2 patients stopped using the candy due to adverse effects.

USING CAPSAICIN: it is available in 0.025-0.075% strength cream/gel OTC. Generally speaking, an adequate trial of capsaicin requires 4 applications a day for 4 weeks.

The burning sensation may be relieved by local anaesthetic gel (lidocaine 0.5%) McCleane ([xi]
) has tried glyceryl trinitrate (GTN) added to the cream and found that this reduces the burning and may also enhance the analgesic effect.

"Capsaicin usually burns when first applied. It sometimes takes more than a day or two for the effect to kick in, which is when the burning sensation stops. So spending a little more time building up a tolerance to the burning sensation might be one way to make the discomfort a bit more bearable....

It takes something with true detergent action to get this stuff off your skin -- a mild baby

shampoo or dish liquid is your best bet -- and a wipe-down with rubbing alcohol won't hurt either.

But if you can tolerate it on your skin for at least 15 minutes (so say the package inserts) you will get the benefit even if you have to wash it off later." Source: Anonymous. ([xxii])

Adverse effects: as mentioned: burning after each application for up to 5 days after first application.

An abstract in Science/Health ([xxiii]) mentions that loss of substance P may lead to urinary retention and may have adverse effects on the peripheral nervous system.

However, this was referring to ingestion of capsaicin orally (and presumably refers to the potential effects on healthy individuals: those with peripheral neuropathy already have damaged peripheral nervous system anyway).

A search of the medical literature does not find significant problems due to topical capsaicin, but it must be noted that long-term studies have yet to be done. A recent paper ([xxiv]) does discuss the effects of oral capsaicin on reflux, gastric emptying and dyspepsia (indigestion).

It concludes that capsaicin taken orally (5mg in gelatin capsules) "enhances noxious postprandial heartburn, presumably by direct effects on sensory neurons."

CAPSAICIN IN COMBINATION:

McCleane has recently published (June 2000 [xxv]) results of a study of topical application of doxepin hydrochloride, capsaicin and a combination of both and found that they produce analgesia in chronic neuropathic pain.

He used 3.3% doxepin hydrochloride, 0.025% capsaicin and a combination of 3. 3% doxepin and 0.025% capsaicin.

The results showed "Overall pain was significantly reduced by doxepin, capsaicin and doxepin/capsaicin to a similar extent.

The analgesia with doxepin/capsaicin was of more rapid onset. Capsaicin significantly reduced sensitivity and shooting pain.

Burning pain was increased by doxepin and by capsaicin and to a lesser extent by doxepin/capsaicin."

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