

## LEADING ARTICLE

## Capsaicin and menthol in the treatment of itch and pain: recently cloned receptors provide the key

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Topical capsaicin is reported to be an effective treatment for idiopathic intractable pruritis ani. While both capsaicin and menthol application produce a transient perianal burning sensation, only capsaicin relieves itching. Classical observations on functional desensitisation of nociceptors by capsaicin may explain the beneficial effects but the recent discovery of a range of receptors which respond to capsaicin, menthol, and temperature, and their expression in subsets of sensory nerve fibres, provides an exciting prospect towards advancing our understanding and treatment of sensory dysfunction.

(about 10–15 minutes), only capsaicin relieved the itching, generally on the first day of treatment. These observations invite consideration of both the mechanisms of action of capsaicin and menthol, and the underlying cause of this idiopathic condition. Why do capsaicin and menthol both produce burning, when capsaicin normally evokes a burning sensation and menthol a cold sensation? Why does capsaicin but not menthol have a beneficial effect? Why is there an effect on itch? Why do some patients find capsaicin intolerable and others fail to respond? Why is it necessary to repeat capsaicin application for continued benefit? This article pieces together available data in an attempt to answer these fascinating questions, and proposes a possible cause for this idiopathic condition. The recent discovery of a range of receptors which respond to capsaicin, menthol, and temperature, and their expression in subsets of sensory nerve fibres, provides an exciting prospect to advance our understanding and treatment of sensory dysfunction.

## SUMMARY

Topical capsaicin is reported to be an effective treatment for idiopathic intractable pruritis ani. While both capsaicin and menthol application produced a transient perianal burning sensation only capsaicin relieved the itching. While classical observations on functional desensitisation of nociceptors by capsaicin may explain the beneficial effects, other features and the underlying cause require consideration of recently discovered receptors and their regulators. It is proposed that in these patients there is a phenotypic change in polymodal sensory fibres which normally express the capsaicin/heat receptor (VR1/TRPV1) but which now also express the menthol/cool receptor (TRPM8); in support, VR1 positive sensory fibres in rodents do not normally express TRPM8 but these are coexpressed and functional in nerve growth factor (NGF) rich conditions in vitro. Pruritis ani may thus be a persistent hypersensitivity state triggered by inflammatory products, as NGF is known to be increased by inflammation. While it is argued whether itch is produced by ligands activating specific “itch fibres” and/or very localised repetitive stimuli to polymodal fibres which do not generate sufficient surround inhibition in the spinal cord, the beneficial effects of capsaicin indicate that the fibres mediating pathological itch must express the capsaicin receptor VR1.

## BACKGROUND

In this issue of *Gut*, Lysy and colleagues<sup>1</sup> report that an appropriate dose of capsaicin applied topically is an effective treatment for idiopathic intractable pruritis ani [see page 1323]. While both capsaicin and menthol application (the menthol was applied as placebo) produced a perianal burning sensation for a similar duration

## USE OF TOPICAL CAPSAICIN

The use of topical and intravesical capsaicin, with varying efficacy and tolerability, has previously been reported in a number of chronic itch, pain, and hypersensitivity states.<sup>2–3</sup> They include neuropathic, inflammatory, and idiopathic clinical conditions, such as painful diabetic neuropathy, post herpetic neuralgia, itch associated with allergy or uraemia, cluster headache, arthritis pain, and urinary bladder hypersensitivity or hyperreflexia.<sup>4–6</sup> The mechanisms discussed here are pertinent in general terms to these conditions.

Capsaicin is the pungent agent in chilli peppers. The classical view is that capsaicin application at first activates a subset of polymodal nociceptor fibres that express its receptor, increasing membrane permeability to cations; this leads to release of neuropeptides such as substance P from nerve terminals and burning pain.<sup>2</sup> However, prolonged or repeated application of capsaicin leads to two types of desensitisation: one “pharmacological”, where there is progressive decline in response to capsaicin, and the other “functional desensitisation”, with reduction or loss to other stimuli also.<sup>2</sup> The latter is observed following application of higher concentrations of capsaicin and is thought to be the basis of clinical efficacy. High doses of capsaicin are known to

**Abbreviations:** NGF, nerve growth factor; VR1, vanilloid receptor 1.

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**Table 1** Range of temperature sensing receptors

Ion channel	Activating temperature	Activators
VRL-1 (TRPV2)	-53° C	Noxious heat
VR1 (TRPV1)	-43° C (lower temperatures on sensitisation)	Noxious heat, capsaicin, pH <5.9
TRPV3/TRPV4 (VRL-2)	30-40° C	Warm
CMR1/TRPM8	-25° C	Cold menthol
ANKTM1	<17° C	Noxious cold

produce nerve terminal degeneration via mechanisms that include calcium entry into the terminal and activation of calcium sensitive proteases.<sup>2</sup> It has now been established that topical skin application in therapeutic doses (capsaicin 0.075%) produces profound loss of intraepidermal fibres within 24 hours,<sup>7</sup> and that the efficacy of intravesical application of capsaicin or its potent analogue RTX (resiniferatoxin) in bladder hyperreflexia is related to a decrease in suburothelial sensory nerve fibres expressing the capsaicin receptor (our observations with Professor CJ Fowler).

“Topical skin application in therapeutic doses (capsaicin 0.075%) produces profound loss of intraepidermal fibres within 24 hours”

Degenerated nerve terminals may lose contact with cells that secrete NGF (predominantly the basal keratinocytes in skin and basal urothelial cells in bladder)<sup>8</sup>; NGF taken up by nerve terminals and transported retrogradely to the sensory cell body normally regulates its expression of the capsaicin receptor (VR1), substance P, and other key molecules required for nociception.<sup>2</sup> Dysfunction of NGF uptake by terminals or its retrograde axonal transport, without degeneration, may have similar consequences. Nerve terminals can regenerate and reinnervate NGF rich targets if capsaicin application is discontinued,<sup>7-9</sup> requiring repeated application for efficacy.

### CLASSICAL EXPLANATIONS

These classical observations may explain some of the findings in the paper by Lysy and colleagues.<sup>1</sup> Topical capsaicin appears to activate nociceptors to produce a burning sensation and then seems to produce functional desensitisation in the majority of patients; repeated application appears necessary at a well tolerated dose. In some patients the initial burning is not well tolerated even at this low dose, either because of an excessive increase in VR1 receptor expression/sensitisation (as in inflammatory bowel disease),<sup>10</sup> increased numbers of VR1 positive sensory fibres (as in idiopathic rectal hypersensitivity),<sup>11</sup> or for psychological reasons; in others, non-responders, this concentration (0.006%) may be too low to produce functional desensitisation. It would have been helpful to have some indication of the effect of this dose of capsaicin (and menthol) applied to the same region in a control group. Skin biopsies would be necessary in future studies to establish any structural changes contributing to the beneficial functional effect—for example, loss of intraepidermal or subepidermal fibres, as is the case in bladder hyperreflexia. However, in order to address the other questions raised above, some recent discoveries need to be considered, and the pathophysiology of itch.

### NOVEL RECEPTOR MECHANISMS

The capsaicin or vanilloid receptor VR1 was first cloned in 1997<sup>12</sup> (this is also called TRPV1 according to a new nomenclature, see tables 1 and 2). VR1 mRNA was initially reported to be restricted to small diameter nociceptor sensory neurones but more recently has been reported in brain and

**Table 2** Vanilloid receptor nomenclature

VR1	TRPV1
VRL-1	TRPV2
VRL-2	TRPV4
VRL-3	TRPV3
ECAC1	TRPV5
ECAC2	TRPV6

VR1, vanilloid receptor 1; VRL-1, vanilloid receptor-like 1; ECAC, epithelial Ca<sup>2+</sup> channel (Ca<sup>2+</sup> selective vanilloid-like receptor); TRP, transient receptor potential; V, vanilloid.

peripheral blood mononuclear cells. Capsaicin, heat, protons, alcohol, and the endogenous agonists anandamide, eicosanoids, and leukotriene B have been shown to have an effect on the capsaicin receptor. Four other proteins have been discovered that respond to different ranges of temperature (table 1)<sup>13-15</sup> but only VR1 is activated by vanilloids such as capsaicin. One of these other receptors, TRPM8, can be activated by cool temperatures, and by the cooling agent menthol. Thus it might be argued that in patients with pruritis ani, menthol paradoxically produces burning by activating the same polymodal fibres that express VR1, and which may be sensitised; however, unlike capsaicin, menthol does not produce desensitisation or nerve terminal damage, hence its lack of beneficial effect.

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This explanation is at first glance refuted by the findings (in rodents) that the subset of sensory fibres which express VR1 do not normally coexpress TRPM8, and while sensory fibres that express the cold receptor ANKTM1 (so named because it contains ankyrin and transmembrane domains) do coexpress VR1, they are not responsive to menthol.<sup>13-15</sup> One explanation could be that humans are different to rodents, and normally coexpress VR1 and TRPM8 (eating a mint does not help and may worsen the burning sensation produced by eating a chilli). An alternative explanation, which may even point the way to the underlying causation of the sensory symptoms, is the finding that large numbers of rodent sensory neurones in culture respond to both capsaicin and menthol, attributed to the high NGF levels used *in vitro*<sup>15</sup>—as NGF levels are known to be increased by inflammation, this could lead to coexpression of menthol receptors in polymodal fibres normally expressing capsaicin receptors alone, accounting for the same sensation (burning) for a similar duration in these patients. While speculative, this also implies that a change in sensory neurone phenotype in these patients results from an increase in NGF, currently or in the past (that is, a persistent hypersensitivity state, see Chan and colleagues<sup>11</sup>). It is unlikely that the

similar initial effect of capsaicin and menthol in these patients reflects a parallel increase in sensitivity or numbers of completely different subsets of TRPM8 and VR1 positive fibres but this cannot be excluded. It would be interesting to know if there is differential expression of histamine receptors in these fibre subtypes in normal and pathological conditions.

### EFFECT ON ITCH

Why the effect on capsaicin on itch? Some authors argue, on the basis of microneurography studies in human volunteers, that itch is mediated by a distinct subset of C fibres which respond to histamine but not mechanical stimuli—that is, are different from polymodal or C fibres which respond to mechanical stimuli and heat (CMH fibres) and respond only poorly to histamine.<sup>16</sup> These “itch fibres” have reported conduction velocities half those of CMH fibres (0.5 m/s), and receptive fields that are three times greater. Others argue that itch results from a particular pattern of stimulation of nociceptors—some very localised repetitive stimuli do not generate sufficient surround inhibition in the spinal cord, such as pricking the lips to produce itch, whereas scratching generates central inhibition to suppress the itch.<sup>4</sup> Failure of these central inhibitory mechanisms is also invoked to explain the itch in some subjects who have lesions restricted to the central nervous system.<sup>4</sup> Topical application of capsaicin in normal human skin may produce some itch and pricking prior to burning. In rodent skin, C mechanoreceptors have good histamine sensitivity.<sup>17</sup>

“The effect of capsaicin suggests that fibres mediating itch in patients with pruritis ani must express VR1”

The different mechanisms proposed for itch may not be mutually exclusive but the effect of capsaicin suggests that fibres mediating itch in patients with pruritis ani must express VR1. Specific “itch fibres” could express VR1 and become functionally desensitised to different stimuli, such as histamine, by capsaicin. VR1 is expressed by the majority of unmyelinated fibres, both those that respond to NGF and express substance P and those that respond to another trophic factor GDNF (glial derived neurotrophic factor) and do not express substance P. The association of spontaneous itch, burning pain induced by capsaicin, and menthol, and the beneficial effect of capsaicin, suggests that the underlying process probably does involve polymodal fibres in these patients, even if the effect of capsaicin is related only to “itch fibres” which express VR1. Cooling and menthol ameliorated experimental itch in one volunteer study<sup>18</sup> although this could be a central effect; menthol was reported not to have an effect in another study.<sup>19</sup> Presumably, the reason why these patients complained of spontaneous itch and not spontaneous burning pain is related to a particular agent in their skin which activates “itch fibres”

and/or produces a distinct pattern of fibre activation in polymodal fibres, interpreted as itch; one study failed to find different discharge patterns for itch and burning stimuli using microneurography in human volunteers<sup>20</sup> but the situation may be different in pathophysiological states. Further studies correlating sensory thresholds with tissue markers of subsets of nerve fibres and their activators may reveal the distinct “signature” of pathophysiological itch—we now have the molecular tools to unravel this fascinating conundrum.

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