Published in final edited form as:

Gut. 2008 July ; 57(7): 882–884. doi:10.1136/gut.2008.149724.

TRPV1: a new target for treatment of visceral pain in IBS?

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Keywords

TRPV1; visceral pain; irritable bowel syndrome; colitis; novel analgesics

Spices and pain: a common world

The taste of food is heightened by seasoning, and food prepared with the right mixture of spices is one of the major human pleasures and as such a matter of huge economic dimension. It is therefore no wonder that the trade in spices has been of vast historical importance and a major driving force in the late medieval contacts between the East and West.¹ The chemicals responsible for the gustatory and olfactory pleasures of spices are secondary metabolites elaborated by plants primarily for their defence.¹ By some strange perversion, many humans have learned to enjoy low doses of these toxic chemicals, and in so doing ensure the success and survival of the plants producing spices.¹

What are the mechanisms whereby we sense spices, and what do they have to do with functional disorders of the gastrointestinal (GI) tract? Even one decade ago, nobody could envision that a large family of closely related ion channels act as molecular sensors for distinct spices, yet also detect other sensory modalities including pain.² The pioneer that triggered this avalanche of discoveries was the “capsaicin receptor”, now termed TRPV1 which stands for “transient receptor potential vanilloid 1” ion channel. Responsible for the piquancy of red pepper (*Capsicum* spp.), the vanilloid capsaicin in its pure form is one of the most painful chemicals we know. It was the Hungarian pharmacologist Nicolas Jancsó who in the middle of the 20th century first recognized that capsaicin acts specifically on nociceptive afferent neurons.³ The exploration of this unique pharmacological profile of capsaicin led, in 1997, to the identification of TRPV1 as the molecular sensor of capsaicin, selectively expressed by unmyelinated and some thinly myelinated primary afferent neurons.⁴ The capsaicin receptor belongs to the superfamily of transient receptor potential (TRP) ion channels, so named after the role these channels play in *Drosophila* phototransduction. By now at least 28 different TRP subunit genes have been identified in

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Competing Interest None to declare.

mammals, comprising 6 families.⁵ Three subunit families, namely the vanilloid TRPs (TRPVs), the melastatin TRPs (TRPMs) and an ankyrin TRP (TRPA1), are relevant to spice sensing (Box 1).² The TRP channel subunits are made of 6 transmembrane domains with a pore between transmembrane domains 5 and 6.⁵

TRPV1, a polymodal nocisensor upregulated in inflammation and hyperalgesia

Analysis of heterologously expressed TRPV1 has shown that functional channels are most likely assembled as homotetramers that have a high permeability for Ca^{2+} . Importantly, TRPV1 behaves as a polymodal nocisensor *par excellence*, being receptive to noxious heat (above 42 °C), acidosis (pH < 6), capsaicin and endovanilloids.^{2,4} Mild acidosis (pH 7 - 6) and other factors associated with inflammation and hyperalgesia (e.g., prostaglandins, bradykinin, adenosine triphosphate, 5-hydroxytryptamine and nerve growth factor) are able to sensitize TRPV1 and enhance the probability of channel gating by heat, protons and capsaicin.^{4,6} As a result, the temperature threshold for TRPV1 activation is lowered so that this cation channel may become active at normal body temperature.⁴

The property of TRPV1 to become sensitized by proalgesic and inflammatory mediators has raised enormous interest in this nocisensor being a novel drug target for the treatment of chronic pain and hyperalgesia. Two further aspects have significantly added to this concept. In the periphery, TRPV1 is predominantly expressed by primary afferent neurons subserving nociception, i.e., sensory neurons with mostly unmyelinated fibres.^{4,6} This is also true for the innervation of the GI tract, in which most TRPV1 has been localized to sensory nerve fibres originating from the dorsal root and nodose ganglia.⁷ In the mouse, TRPV1-positive neurons are more prevalent among spinal afferents supplying the colon than among afferents innervating skin or muscle.⁸ In addition, TRPV1 in nociceptive afferent neurons is upregulated in inflammation, which is true both for rodents with experimental colitis induced by trinitrobenzene sulphonic acid^{9,10} and patients with inflammatory bowel disease.¹¹

TRPV1 in gastrointestinal pain without overt inflammation

Importantly, upregulation of TRPV1 in afferent nerve fibres has been observed in the absence of overt inflammation as is typical of patients with irritable bowel syndrome (IBS). As reported in the present issue of *Gut*, Akbar and colleagues¹² found that TRPV1-immunoreactive nerve fibres in biopsies taken from the rectosigmoid junction of IBS patients were on average 3.5 times more frequent than in control subjects. This increase in TRPV1 expression correlated significantly with the pain severity rated on a visual analogue scale, whereas the other variables measured (substance P, c-kit and CD3 in the biopsies, gender, age, type of intervention for collecting biopsies, type of IBS relative to stool frequency and consistency, anxiety and depression index) were ruled out to be predictors of pain severity.¹²

The observations of Akbar et al.¹² make a case for TRPV1 being involved in abdominal pain associated with IBS and other functional GI disorders. This concept is consistent with

experimental and clinical findings. In rodents, capsaicin excites abdominal afferent neurons and induces behavioural reactions indicative of pain,⁷ much as stimulation of TRPV1 in the stomach or jejunum of humans evokes pain.^{13,14} TRPV1 is not only enhanced in painful IBS¹² but also in idiopathic rectal hypersensitivity and faecal urgency.¹⁵ The correlation of rectosigmoid TRPV1 expression with pain severity in IBS patients¹² is reminiscent of the hypersensitivity to capsaicin that characterizes a proportion of patients with functional dyspepsia (FD).¹⁴ This suggests that TRPV1 function is enhanced in FD, a conjecture that is in line with the beneficial effect of “capsaicin desensitization” by repeated capsaicin administration to FD patients.¹⁶

The implication of TRPV1 in IBS¹² and FD¹⁴ is paralleled by emerging evidence that TRPV1 has a bearing on post-inflammatory colonic hyperalgesia in rodents. For instance, the behavioural pain reaction to intracolonic administration of capsaicin remains enhanced long after resolution of dextrane sodium sulphate-induced colitis.¹⁷ Zymosan-evoked colitis likewise causes hypersensitivity to colorectal distension that persists for at least 7 weeks post-treatment when there is no sign of inflammation left in the colon.¹⁸ This persistent hyperalgesia is blunted in mice deficient in TRPV1.¹⁸ Similar observations were made in adult rats that had been exposed to chemical irritation of the colon with acetic acid as neonates. The intervention in the rat pups causes persistent upregulation of TRPV1 in the dorsal root ganglia and persistent hypersensitivity to colorectal distension in the absence of colonic inflammation.¹⁹

These findings indicate that preceding inflammation provides a trigger to enhance expression and function of TRPV1, a change that does not reverse once inflammation is gone. As Akbar et al.¹² point out, up to a third of patients develops IBS following a spell of infectious gastroenteritis. There is also increasing evidence that IBS patients exhibit signs of immune cell recruitment and activation in the mucosa, attesting to a low-grade inflammatory process. Akbar et al.¹² report that not only neuronal TRPV1, but also substance P-immunoreactive nerve elements, CD3 lymphocytes and mast cells staining for c-kit are more prevalent in biopsies from IBS patients than in control specimens. Mediators released from GI immune and endocrine cells of IBS patients are known to excite afferent nerve fibres²⁰ and to enhance their long-term sensory gain.^{18,21} This inflammation-driven change in the functional phenotype seems to depend on TRPV1, given that the ability of inflammatory mediators to sensitise mechanosensitive afferents in the colon is attenuated in TRPV1 knockout mice.²¹ It remains unclear, however, as to how GI hyperalgesia develops in IBS patients in which there is no history of a preceding infection or inflammation.

TRPV1 blockers for IBS: an approach with high risk and potential

Recognition of TRPV1 as a multimodal nociceptor, its sensitization by inflammatory and proalgesic pathways and its upregulation under conditions of hyperalgesia have made this ion channel an attractive target for novel antinociceptive drugs. TRPV1 function can be counteracted by multiple approaches: desensitizing TRPV1 agonists, TRPV1 blockers and compounds that prevent TRPV1 trafficking to and integration in the cell membrane. How much is invested into the ongoing evaluation of these approaches can be deduced from the

current patent literature which discloses more than 1,000 natural and synthetic compounds as TRPV1 activators or blockers.

The first approach to silence TRPV1 makes use of the long-known property of capsaicin to desensitize afferent neurons to the excitatory action of this spice as well as other noxious stimuli.^{22,23} Due to excess influx of Ca^{2+} and other cations following repeated stimulation of TRPV1, sensory neurons are defunctionalized and depleted of their transmitters for a prolonged period of time. Such an action is the most likely explanation why oral intake of capsaicin-containing capsules for 5 weeks reduces epigastric pain and other complaints of FD patients.¹⁶ Initially, however, “TRPV1 agonist therapy” exacerbates pain, and for this reason TRPV1 agonists that cause rapid desensitization (such as resiniferatoxin) are preferred. Site-specific “TRPV1 agonist therapy” is currently tested for certain indications such post-herpetic neuralgia, irritable bladder and osteoarthritis.²³ In this context one may ask the question whether regular intake of capsaicin through hot food could prevent or “spice out” IBS pain.

Unlike desensitizing TRPV1 agonists, TRPV1 blockers selectively target this nocisensor and prevent its function. It has, for instance, been shown that the ability of trinitrobenzene sulphonic acid to induce colitis, TRPV1 overexpression and hyperalgesia is counteracted by the TRPV1 blocker JYL1421 given either before or after induction of inflammation.⁹ If it can be proved that TRPV1 is causally involved in the pain associated with IBS, TRPV1 blockers would indeed be a novel class of drugs to go for. But will they be efficacious and safe? This question can at present not be answered in an affirmative manner. The point is that TRPV1 is one of many nocisensors that subserve homeostatic functions including protection of the GI mucosa and thermoregulation, interference with which may result in adverse consequences.

TRPV1 is known to be a sensor of heat,^{2,4} a role that is not only relevant to the protection of external surfaces such as skin and mouth but also to the control of body temperature. Gavva et al.²⁴ have shown that TRPV1 blockers representing various chemotypes cause hyperthermia in rats, dogs and monkeys by a peripheral site of action. This suggests that TRPV1 on visceral afferents plays an important role in monitoring core temperature and providing important feedback information for thermoregulation. Another physiological implication of TRPV1 is to protect the GI mucosa.^{7,9,22,25} Thus, disruption of the TRPV1 gene increases the susceptibility to develop colitis in response to dinitrobenzene sulphonic acid.²⁵ Paradoxically, dextrane sulphate sodium-evoked colitis is ameliorated by TRPV1 blockade, but this aberrant finding may be explained by the ability of dextrane sulphate sodium to indirectly activate TRPV1.²⁶

Given the homeostatic roles of TRPV1, the challenge for an effective and safe IBS therapy will be to suppress the pathological contribution of “excess” TRPV1 to pain while preserving its physiological function.^{6,25,26,27} It seems unlikely to achieve this goal with competitive or noncompetitive TRPV1 blockers unless their dosage is precisely titrated. There are, however, alternative approaches worth pursuing. One opportunity could be to develop *uncompetitive* blockers that preferentially bind to the active, open state of the channel and therefore will predominantly silence overactive TRPV1. Another approach that

appears increasingly feasible is interference with the intracellular trafficking of TRPV1 to the cell membrane, which will result in a reduction of TRPV1 channels on the cell surface. This is of functional relevance because TRPV1 overactivity involves enhanced translocation of TRPV1 from the cytosol to the plasma membrane.^{28,29,30} By blocking the trafficking of TRPV1 to the cell surface, for instance by botulinum neurotoxin A,²⁸ it would be possible to prevent the function of newly synthesized TRPV1 while leaving channels already integrated in the cell membrane operational.

In summary, TRPV1 is an IBS drug target with high potential, if its upregulation in this disorder reflects a causal implication rather than just a marker of enhanced sensitivity and functionality of afferent neurons or enhanced arborization of their fibres in the periphery. At the same time, it is a drug target with high risk, because the therapeutic approach needs to differentiate between the physiological and pathological implications of this nociceptor. In addition, the question comes up as to whether neutralization of TRPV1 overactivity alone is sufficient to silence IBS pain, given that sensory neurons express several tens of TRP subunits and other potential nociceptors. Variety is the spice of life, and redundancy the safeguard to enjoy it.

Acknowledgements

Work in the author's laboratory is supported by FWF - The Austrian Science Funds and the Zukunftsfonds Steiermark.

Abbreviations used in this paper

FD	functional dyspepsia
GI	gastrointestinal
IBS	irritable bowel syndrome
TRP	transient receptor potential
TRPV1	transient receptor potential vanilloid 1

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Box 1

TRP (transient receptor potential) ion channels subserve different pain modalities and spice sensations. The box shows a selection of spice agonists that activate 4 different members of the TRP channel family: the vanilloid TRP channels TRPV1 and TRPV3, the melastatin TRP channel TRPM8 and the ankyrin TRP channel TRPA1.

TRP channels for pain and spices

Ion channel	Pain modality	Spice agonists
TRPV1	Heat Acidosis	Capsaicin (red pepper) Gingerol (ginger) Piperine (black pepper) Zingerone (ginger)
TRPV3	None (warmth)	Carvacrol (oregano) Eugenol (clove) Thymol (thyme) Vanillin (vanilla)
TRPM8	Cold	Menthol (mint)
TRPA1	Irritant pain	Allicin (garlic) Allyl isothiocyanate (mustard, horseradish, wasabi) Carvacrol (oregano) Cinnamaldehyde (cinnamon) Diallyl disulfide (garlic) Gingerol (ginger)