Research Article

Medicinal Chemistry of the Vanilloid (Capsaicin) TRPV1 Receptor: Current Knowledge and Future Perspectives

Laxmikant Gharat,1 and Arpad Szallas2,3*

1Department of Chemistry, Glenmark Pharmaceuticals, Navi Mumbai, India
2Department of Pathology, Monmouth Medical Center, Long Branch, NJ
3Department of Pathology, Drexel University College of Medicine, Philadelphia, PA

ABSTRACT In peripheral sensory neurons, the vanilloid receptor TRPV1 (transient receptor potential vanilloid subfamily, member 1) functions as a molecular integrator of painful stimuli, including those mediated by capsaicin, acid, and heat. Antagonist blockade of TRPV1 activation is under investigation by several pharmaceutical companies in an effort to identify novel agents for pain management. TRPV1 is also expressed, albeit at lower levels, in the brain and in non-neuronal tissues, where its function(s) remains elusive. The contribution of TRPV1 receptor activity to physiological reflexes and disease states is complex and is only beginning to be understood. Consequently, the resultant effects of TRPV1 antagonists on the body may be unforeseen. Indeed, clinical trials with a number of TRPV1 antagonists were recently terminated due to their marked hypothermic activity. In this review article, the medicinal chemistry of TRPV1 antagonists is discussed inasmuch as it relates to the efficacy, safety, tolerability and potential side effects of these compounds. In addition, the available information on the current status of the clinical trials with TRPV1 antagonists is summarized. Drug Dev Res 68:1-21, 2008. ©2008 Wiley-Liss, Inc.

INTRODUCTION AND HISTORICAL PERSPECTIVE Capsaicin (0.01%) is a potent irritant and the ingredient responsible for the pungency of hot chili peppers eaten on a daily basis by an estimated one quarter of the world population. According to new fossil evidence, the cultivation of chili peppers in the Americas has a 6,000-year history [Perry and Flannery, 2007; Perry et al., 2007], with the rest of the World being rapidly conquered after Columbus introduced hot pepper to the Spanish royal court [Naj, 1992]. Connoisseurs of hot, spicy food know the predominant pharmacological actions of capsaicin from personal experience: it induces profuse perspiration (known as gustatory sweating) as well as a hot, burning sensation that dissipates upon repeated challenge [Buck and Burks, 1986; Szallas and Blumberg, 1999; Malmberg and Bley, 2005]. Capsaicin is not only a spice, however, but an extremely versatile agent whose biological uses, covered by more than 900 patents, ranges from culinary applications, including to improve flavor and inhibit bacterial growth, through pain killers to chemical weapons and repellents [Buck and Burks, 1986; Szallas and Blumberg, 1999; Malmberg and Bley, 2005]. The latter group encompasses such diverse applications as pepper spray [Forrester and Stanley, 2003], capsaicin-flavored bird seed to repel squirrels [Roahl, 1996] and self-protectant lotions to keep away sharks. Apparently, there is little new under the sun: Native Americans burnt pepper plants as a chemical

*Correspondence to: Arpad Szallas, MD, Department of Pathology, Monmouth Medical Center, 300 Second Avenue, Long Branch, NJ 07740. E-mail: aszallas@sbhcs.com

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weapon to fight the Conquistadors; they also used chilli concoctions to relieve pain [Naj, 1992]. It is, however, still a mystery why the same pungency that repels squirrels or sharks is perceived as pleasurable by many human beings.

Capsaicin is unique among the naturally occurring irritants in that it initiates the desensitization process, which is followed by a lasting refractory state, traditionally referred to as desensitization, in which the previously excited neuron is refractory to various unrelated stimuli [Buck and Burks, 1986; Szolcsányi, 1989; Szallasi and Blumberg, 1999; Malmberg and Bley, 2005]. Desensitization to capsaicin has a clear therapeutic potential. In fact, as reviewed recently, capsaicin-containing creams have been in clinical use for decades for indications, including diabetic neuropathy [Knotkova et al., 2007].

The concept of a specific capsaicin receptor was first postulated based on the distinct structure—activity relations shown by synthetic capsaicin analogues in their irritant activity [Szolcsányi and Jancsó-Gábor, 1975]. Biochemical proof for the existence of this receptor was furnished by the specific binding of resiniferatoxin (RTX), an ultrapotent capsaicin analogue isolated from the latex of the cactus-like plant, *Euphorbia resinifera* [Szallasi and Blumberg, 1990]. Since capsaicin and RTX share a (homo)vanillyl moiety essential for bioactivity but differ dramatically in the remainder of the molecules, their common membrane recognition sites were termed the vanilloid receptor, VR1 [Szallasi and Blumberg, 1999]. Based on ion uptake and patch-clamp studies, it was postulated that the vanilloid receptor VR1 was a nonselective cation channel with limited selectivity for calcium [Wood et al., 1988]. Indeed, Julius and colleagues [Caterina et al., 1997] employed capsaicin-evoked Ca^{2+} uptake in a rat dorsal root ganglion (DRG) expression system to clone this receptor in 1997.

The past decade has witnessed unprecedented advances in the vanilloid field. The vanilloid VR1 receptor turned out to be the founding member of a now populous receptor family, the TRP (transient release potential) receptors, and, accordingly, was renamed as TRPV1 (transient release potential vanilloid subfamily 1) [Montell et al., 2002]. TRPV1 is no longer an orphan receptor anymore. In fact, activators
of TRPV1 include noxious heat [Caterina et al., 1997] and pungent natural products (e.g., plant products as exemplified by capsaicin [Caterina et al., 1997], jellyfish [Cuypers et al., 2006], and spider toxins [Siemens et al., 2006] through low pH [Tominaga et al., 1998; Jordt et al., 2000] and agents in various “inflammatory soups” [Hwang et al., 2000; Chuang et al., 2001] to anandamide [Zygmunt et al., 1999] and other putative “endovanilloids” (endogenous TRPV1 ligands) [Di Marzo et al., 2002]. In other words, TRPV1 can be thought of as a molecular integrator of diverse noxious and pro-inflammatory stimuli rather than as a specific capsaicin (vanilloid) receptor [Tominaga et al., 1998; Caterina and Julius, 2001]. This observation provides a mechanistic explanation for the characteristic “hot” sensation evoked by capsaicin.

Other related channels (as of today, a total of seven) also turned out to be heat-sensitive, hot, or cold. These receptors, often referred to as “thermoTRPs,” cover a wide temperature range with excitations falling between noxious cold (10°C, TRPA1) and noxious heat (55°C, TRPV2) and show significant overlap of the temperature range in which they are activated [Ferrell et al., 2003; Dhaka et al., 2006].

Although all “thermoTRPs” represent attractive targets for drug development [Krause et al., 2005; Cortright et al., 2007], with the number of small-molecule antagonists already in clinical trials, TRPV1 is clearly in the most advanced stage [Szallasi et al., 2007]. These trials are exciting in that they represent the litmus test for the feasibility of a new pharmacological approach in pain relief, that is, the therapeutic blockade by an antagonist of a peripheral receptor where pain is generated [Szallasi et al., 2007]. If TRPV1 antagonists succeed in clinical practice, it will give further impetus to drug development efforts targeting other TRPV receptors. However, should TRPV1 antagonists prove to live up to the excitement, it could also discourage these efforts. The goal of this review is to provide a comprehensive overview of the medicinal chemistry of TRPV1 ligands, both agonist and antagonists, with emphasis on the latter. We seek an answer to the question raised by Hicks [2006] in a recent editorial in Gastroenterology and Motility: is TRPV1 still hot or it is temperature cool down? But in order to do so, first we have to briefly review the tissue distribution, function, and molecular pharmacology of TRPV1.

TISSUE DISTRIBUTION AND FUNCTION OF TRPV1 IN HEALTH AND DISEASE

TRPV1s can be divided into three major tissue compartments: (1) capsaicin-sensitive sensory neurons in the peripheral nervous system (PNS) [Szallasi, 1996]; (2) neurons in the central nervous system (CNS) [Szallasi and Di Marzo, 2000; Steenland et al., 2006]; and (3) non-neuronal tissues [Gunthorpe and Szallasi, 2007]. The biological function of TRPV1 in the PNS is now well established and is reviewed further below. Despite extensive research, it is still unclear what biological roles TRPV1 may play in the CNS and non-neuronal cells.

TRPV is highly expressed in primary sensory neurons [Caterina et al., 1997; Gao et al., 1999; Sanchez et al., 2001]. Indeed, capsaicin was often referred to as “selective sensory neurotoxin,” and capsaicin sensitivity was widely accepted as a “functional signature” of these cells [Szolcsányi, 1984; 2004]. Generally speaking, capsaicin-sensitive neurons are bipolar neurons with either unmyelinated (C-fibers) or thin myelinated axons (Aδ fibers) and cell bodies in sensory (dorsal root ganglion [DRG], and trigeminal ganglia [Buck and Burks, 1986; Holzer, 1988]. The dorsal ganglion also has a capsaicin-sensitive component; these fibers travel with the vagus nerve and are believed to play a pivotal role in visceral discomfort and pain [Wang et al., 2005]. The peripheral endings of capsaicin-sensitive neurons are sites of release for various pro-inflammatory neuropeptides, the most prominent examples of which are substance P (SP) and calcitonin gene-related peptide (CGRP) [Buck and Burks, 1986; Holzer, 1988]. Of note, spinal terminals also contain endogenous analgesic peptides like galanin [Skofitsch and Jacobowitz, 1985; Crawley et al., 2002]. Spinal galanin levels are upregulated following RTX treatment [Szallasi, 1996] and this effect was suggested to contribute to the cellular mechanism of RTX-evoked desensitization [Xu et al., 1997].

Sensory neuropeptides released from capsaicin-sensitive neurons have been implicated in a wide array of physiological responses and disease states. For instance, sustained release of CGRP plays a role in the physiological regulation of microvascular blood flow [Tum and Brain, 2004]. By contrast, deranged CGRP release was postulated to contribute to the pathomechanism of both migraine [Geppetti et al., 2005; Bonomi et al., 2007] and hypertension [Marquez-Rodas et al., 2006]. In a rat model of hypertension, there is now good evidence that CGRP release is evoked by endovanilloids, and in particular methanandamide, acting on TRPV1 [Wang et al., 2007]. Slow SP release is believed to exert a trophic function on epithelial cells [Tanaka et al., 1993; Paus et al., 1995]. In keeping with this hypothesis, ablation of cutaneous peptidergic neurons by capsaicin administration at supratherapeutic doses interferes with wound healing [Smith and Liu, 2002] and leads to the formation of skin ulcers [Maggi et al., 1987]. Conversely,
overproduction of SP has been suggested to play a role in the pathobiology of psoriasis [Naukkarinen et al., 1993; Raychaudhuri et al., 1998]. Indeed, topical capsaicin cream is beneficial in patients with psoriasis [Bernstein et al., 1986], although it is still unclear to what degree this beneficial action may be attributed to the anti-pruritic effect of capsaicin [Arkai and Paus, 2006]. Nonetheless, there is anecdotally evidence that cutaneous nerve damage results in the clearance of psoriatic plaques [Farber et al., 1990]. Interestingly, psoriatic keratinocytes are known to produce large amount of nerve growth factor (NGF) [Raychaudhuri et al., 1998], a potent activator of TRPV1 [Chuang et al., 2001]. Last, deregulated CCRF and SP release from capsaicin-sensitive neurons has most recently been linked to both obesity and diabetes, implying therapeutic potential for TRPV1 ligands for weight control and blood glucose regulation [Ganapathy et al., 2003; Streit and Szallasi, 2007; Tsui et al., 2007]. Indeed, the TRPV1 antagonist BCTC was reported by investigators at NovoNordisk to prevent aging-related weight gain and resultant type-2 diabetes in the rat [Ganapathy et al., 2007] when released on masse, sensory neurons initiate the biochemical cascade collectively known as neurogenic inflammation [Geppetti and Holzer, 1998]. At the same time, an impulse is generated and propagated into the CNS via the central fibers that enter the dorsal horn of the spinal cord. The pivotal role of TRPV1 in the initiation of the neurogenic inflammatory response and the transduction of pain is firmly established [for the foundation for the use of TRPV1 antagonists as anti-inflammatory and analgesic drugs [Geppetti and Holzer, 1996; Szallasi et al., 2006, 2007]. Importantly, TRPV1 homozygous null mice (knockouts) are devoid of the thermal hyperalgesia that occurs in response to acute hind paw thermal test of pro-inflamatory agents (e.g., complete Freund's adjuvant [CFA]), predicting a clinical value for TRPV1 antagonists as novel analgesic drugs [Caterina et al., 2000; Davis et al., 2000]. This beneficial effect is mimicked by conditional knockdown of TRPV1 via siRNA in wild-type animals [Christoph et al., 2006; Kasama et al., 2007].

TRPV1 is also widely present in brain nuclei [Szallasi and Di Marzo, 2000; Steenland et al., 2006; Di Marzo and Maione, 2007] and non-neuronal tissues (Gunthorpe and Szallasi, 2007). As to the biological roles of TRPV1 receptors in these tissues, speculations are abundant, but conclusive evidence is still absent. In the brain, recent behavioral studies imply a role for TRPV1 in fear and various cognitive functions [Marsch et al., 2007]. Furthermore, TRPV1 is co-localized with tyrosine hydroxylase in basal ganglia, identifying these neurons as dopaminergic [Mezei et al., 2000]. Indeed, there is preliminary evidence linking TRPV1-expressing basal ganglion neurons to a rat model of Parkinson's disease [Fernandez-Ruiz and Gonzalez, 2005; Di Marzo and Maione, 2007]. With regard to non-neuronal tissues, an exciting but very controversial area of research is the possible connection between TRPV1 and cancer [Gunthorpe and Szallasi, 2007; Prevarskaya et al., 2007]. TRPV1 is apparently expressed in various cancers but authors disagree whether TRPV1 ligands are tumorigenic or, conversely, anti-carcinogenic. Until this controversy is resolved, there are a few basic observations to keep in mind. First, bladder biopsies obtained from both experimental animals and patients undergoing chronic capsaicin or RTX treatment are unremarkable [Dasgupta et al., 1998; Avelino and Cruz, 2000; Apostolides et al., 2005]. Second, there is no published report of increased incidence or formation in animals whose TRPV1 receptors have been ablated either chemically (e.g., neonatal capsaicin administration) or genetically (e.g., TRPV1 ko mice). These negative findings warrant caution in interpreting the biological significance of TRPV1 expression in cancers. Most studies employ high-dose capsaicin treatment in order to delineate the outcome of TRPV1 activation in tumor cells, which is usually apoptosis. Capsaicin is nonspecific, however, for TRPV1 in the high concentrations used in these studies [Szallasi and Blumberg, 1999]. Indeed, some investigators interpret their findings as a direct (TRPV1-independent) activation by capsaicin of apoptotic pathways [Athanasiou et al., 2007]. Of note, similar cautions apply to the putative CNS effects of TRPV1 activation: neither capsaicin, nor the first-generation TRPV1 antagonist, capsazepine is selective for TRPV1. Clearly, these experiments need to be replicated using the new generation of more selective TRPV1 agonists and antagonists. In vivo, a firm conclusion can be reached as to the role of TRPV1 in cancer and higher brain functions.

There is mounting evidence that TRPV1 expression may be altered during disease conditions [Szallasi et al., 2007]. Recognized patterns include (1) up- or downregulation of native TRPV1; (2) ectopic expression of TRPV1 in tissues where it is not normally present; and (3) epigenetic changes by enzymatic modification of the receptor protein (e.g., phosphorylation by kinases, in particular, protein kinase C). Representative examples are discussed below. Upfront, one needs to emphasize that it is unclear whether these alterations are pathogenic or represent adaptive/protective mechanisms.

TRPV1 expression is bidirectionally regulated in sensory neurons both at the transcriptional and
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posttranscriptional levels. A well-established example of upregulated TRPV1 expression is the presence of increased TRPV1 protein levels in animal models of inflammatory hyperalgesia [Wilson-Gerwing et al., 2005]. Importantly, this is in agreement with the increase in TRPV1-like immunoreactivity in a variety of painful human disease conditions that encompass such diverse conditions like caries [Morgan et al., 2005], reflux esophagitis [Matthews et al., 2004; Bhat and Bielefeldt, 2006], inflammatory bowel disease [Yiangou et al., 2001], fecal urgency/irritable bowel syndrome [Chan et al., 2003], vulvodynia [Tympanidis et al., 2013], mastalgia [Gopinath et al., 2005], and burning mouth syndrome [Yilmaz et al., 2007]. Conversely, a diffuse loss of TRPV1-positive axons was reported in patients with painful peripheral neuropathies [Lauria et al., 2006]; this loss may explain the less than satisfactory results obtained in many clinical trials using topical capsaicin for the indication of diabetic neuropathy [Hautakappe et al., 1994; Knottova et al., 2007].

In animals, TRPV1 is downregulated via vanilloid (capsaicin or RTX) desensitization of sensory neurons [Szallasi and Blumberg, 1999]. This downregulation is both long lasting (up to 4 weeks following administration of a single RTX dose) and fully reversible [Szallasi and Blumberg, 1999]. It was suggested that agonist-induced TRPV1 downregulation is part of the phenotypic switch [Ueda, 2006], referred to as “vanilloid-induced messenger plasticity,” that occurs following vanilloid treatment [Szallasi, 1996]. During this switch, the expression of pro-inflammatory neuropeptides (e.g., SP and CGRP) is suppressed, whereas the levels of endogenous analgesic peptides (e.g., galanin) are elevated [Buck and Burk, 1986; Szallasi and Blumberg, 1999]. The end-result of this phenotypic switch is a lasting refractory state.

Ectopic TRPV1 expression was first observed in sensory neurons and non-neuronal tissues. For example, TRPV1 is ectopically expressed on A5 fibers during nerve injury-induced thermal hyperalgesia [Hudson et al., 2001; Rashid et al., 2003] and in diabetic neuropathy [Rashid et al., 2003; Hong and Wiley, 2005]. As discussed above, in non-neuronal tissues, ectopic TRPV1 expression was detected in various cancers, the significance of which is yet to be delineated.

In feline interstitial cystitis, the phosphorylation state of TRPV1 appears to be disease-specific [Sculptoreanu et al., 2005]. If so, it may have important implications for drug development since the pharmacological activity of some agonist/partial antagonist compounds is affected by the phosphorylation state of TRPV1 [Wang et al., 2003; Lizanecz et al., 2006]. Theoretically, such TRPV1 antagonists can be synthesized that selectively target disease-specific (phosphorylated) TRPV1 but spare normal TRPV1 [Szallasi and Blumberg, 2006].

MOLECULAR PHARMACOLOGY OF TRPV1: IMPLICATIONS FOR ANALGESIA AND THERMOREGULATION

Similar to other members of the TRP superfamily, TRPV1 is a putative six-transmembrane spanning protein with a pore region localized between transmembrane segments 5 and 6 [Caterina et al., 1997]. The pore is thought to form a nonselective cation channel with a preference for Ca²⁺ that is directly activated by capsaicin and noxious temperatures with an activation threshold in vitro of about 43°C [Caterina et al., 1997]. These data suggest that TRPV1 is probably inactive at normal body temperature with one notable exception: TRPV1 involved in core temperature regulation seems to have an endogenous role [Gavva et al., 2007a], as evidenced by the hypothermic response to TRPV1 antagonists [Swanson et al., 2005].

The involvement of TRPV1 in heat sensation and body temperature regulation is an exciting, but still controversial, area of research [Caterina, 2007]. It was firmly established more than a half century ago that acute capsaicin administration results in a rapid drop in body temperature [Issekutz et al., 1950; Jancsó, 1955]. The hypothermic action of capsaicin was later linked to the preoptic area of the brain [Szolcsányi et al., 1975], and it may reflect the “cold seeking behavior” of the animal to counteract the acute, pro-inflammatory effects of capsaicin administration [Almeida et al., 2006]. Indeed, no hypothermia response is observed if capsaicin-treated animals are kept in ambient temperature environment [Jancsó, 1962]. Quite the contrary, animals suffer heat stress if they are transferred to a heated chamber [Jancsó, 1989; Szallasi and Blumberg, 1989]. These findings may be interpreted to imply a pivotal role for TRPV1 in regulation of body temperature. However, no difference in circadian body temperature regulation was described in TRPV1 knockout mice compared with controls [Iida et al., 2005].

The clinical significance of the hypothermic response to TRPV1 antagonists remains to be delineated. In the rat, this hypothermic response is modest (1°C), transient (i.e., attenuates upon repeated TRPV1 antagonists administration), and can be easily managed by such common antipyretic drugs as acetaminophen [Gavva et al., 2007]. Yet, Amgen effectively terminated the third molar extraction clinical trials with its lead compound after phase 1...
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after the core temperature reached 40°C in one patient [Gavva, 2007]. The question awaiting answer is: “The capsaicin receptor TRPV1: Is it a pain transducer or a regulator of body temperature?” [Gavva, 2007].

The findings in animals are confusing and provide little guidance in patient management. If TRPV1 blockade is hypothermic, it should exacerbate the febrile response to bacterial lipopolysaccharide (LPS).

However, TRPV1 knockout mice not only show an attenuated fever in response to bacterial LPS [Iida et al., 2005] but also demonstrate enhanced hypothermia, hypotonia, and peritoneal edemas in a murine model of sepsis [Clark et al., 2007]. Based on these observations, pessimists may argue that TRPV1 antagonists can have deleterious effects in hospitalized patients by inducing fever and increasing vulnerability to septic shock. But this is not necessarily true. The relationship between LPS and TRPV1 is questionable.

Indeed, it was suggested that LPS-induced fever is mediated by a capsaicin-sensitive mechanism that is independent of TRPV1 [Dogan et al., 2004]. In support of the hypothesis, capsaicin was shown to block the febrile response to LPS in the chicken [Mahon et al., 2007] although chicken TRPV1 is insensitive to capsaicin because it lacks the capsaicin-recognition domain [Jordt and Julius, 2002]. Even more confusing is the effect of TRPV1 ablation on sepsis appears to be strikingly species-dependent. In the mouse, genetic deletion of TRPV1 exacerbates the harmful components of sepsis [Clark et al., 2007]. By contrast, in the rat chemical ablation of TRPV1 not only prevents mortality but also ameliorates sepsis-induced metabolic effects [Bryant et al., 2003]. Clearly, more research is needed to determine whether TRPV1 antagonists are beneficial or harmful in patients with sepsis.

TRPV1 functions as a polymodal nociceptor with a dynamic threshold of activation and is thought to mediate the phenomenon of “peripheral sensitization” [Julius and Basbaum, 2001; Messeguer et al., 2000]. Even considering the role of TRPV1 as a polymodal nociceptor, it is amazing how diverse agents can activate (or sensitize) TRPV1. An incomplete and ever-growing list of TRPV1 activators include (1) heat and protons [Caterina et al., 1997; Tominaga et al., 1998; Jordt et al., 2000]; (2) bradykinin and nerve growth factor [Chung et al., 2001]; (3) arachidonic acid metabolites such as anandamide [Zygmunt et al., 1999; Mohaved, 2005]; N-arachidonoyl-dopamine and N-oleylidopamine [Huang et al., 2002]; (4) lipoxigenase products (12- and 15-HPETE) [Hwang et al., 2001]; (5) leukotriene B4 [Shin et al., 2002]; (6) prostaglandins [Moriyama et al., 2005]; (7) adenosine and ATP [Kwong et al., 2000]; (8) prokinetics [Negri et al., 2006]; (9) polyamines [Ahern et al., 2006]; (10) ethanol [Trevisani et al., 2002]; (11) plant natural products such as capsaicin [Caterina et al., 1997], RTX [Szallasi and Blumberg 1998], evoxidine [Pierce et al., 2004], camphor [Hu et al., 2005], and phorbol esters [Premkumar and Ahern, 2000]; (12) jellyfish [Cuyvers et al., 2006] and spider venoms [Siemens et al., 2006]; (13) negatively charged air pollutants [Agopyan et al., 2004]; and (14) hydrogen sulfide [Trevisani et al., 2005]. Some of these agents activate TRPV1 directly by interacting at specific residues in the receptor protein, whereas others act indirectly via enzymatic modification of TRPV1 function.

The capsaicin-binding domain was first described by Julius and colleagues [2002]. This is in partial overlap with the residues that are responsible for the high-affinity [3-H]RTX binding [Johnson et al., 2006]. These ligand recognition sites are intracellular. A third intracellular domain was localized to the pore region: this is involved in capsaicin-gating but not heat and/or protons activation [Sutton et al., 2005; Johnson et al., 2006]. By contrast, the pH sensor in TRPV1 is extracellular [Tousova et al., 2005]. The N-terminus acidic repeats of TRPV1 contain a multivalent domain [Liao et al., 2007] whereas the ATP binding site was localized to the C-terminus of TRPV1 [Grycova et al., 2007]. Given this complex structure of ligand activation, it is hardly surprising that TRPV1 antagonists show selectivity in their pharmacological profile. Indeed, it was postulated that TRPV1 antagonists fall into two broad categories: class A antagonists, which prevent TRPV1 activation both by capsaicin and protons, and class B antagonists, which are selective for capsaicin [Gavva et al., 2005].

The activation state of TRPV1 also depends on its phosphorylation state, which reflects a dynamic balance between phosphorylation by kinases and dephosphorylation by phosphatases [Corti and Szallasi, 2004; Lee et al., 2005; Huang et al., 2006]. Most studies agree that receptor protein phosphorylation by kinases (e.g., protein kinase C [Numazaki et al., 2003; Premkumar et al., 2004] and protein kinase A [Mohapatra and Nau, 2005]) of TRPV1 causes sensitization, whereas dephosphorylation by protein phosphatases (e.g., calcineurin [Mohapatra and Nau, 2005]) promotes TRPV1 desensitization. Notable exceptions include reports that (1) protein kinase C may directly activate TRPV1 [Premkumar and Ahern, 2000], and (2) both protein kinase A [Bhave et al., 2002] and C [Liu et al., 2004] may play a role in desensitization. Both pro-inflammatory/aggressive and analgesic agents can affect these pathways. For instance, bradykinin [Lee et al., 2005] and nerve growth factor [Zhang et al., 2005] reduce the activation threshold of TRPV1 via protein kinase C-dependent phosphorylation. Conversely, morphine blocks TRPV1
sensitization by preventing its phosphorylation by protein kinase A [Vetter et al., 2006].

Of the protein kinase C isozymes, protein kinase Cε appears to be the most important: this isozyme has been linked to sensitization of TRPV1 to noxious heat [Cesare et al., 1999]. Compounds that selectively inhibit protein kinase Cε abolish heat hyperalgesia [Zhang et al., 2007], mimicking the phenotype of mice whose TRPV1 has been deleted by genetic recombination [Caterina et al., 2000; Davis et al., 2000].

The effect of phosphorylation of 4,5-biphosphatase [abbreviated as PtdIns(4,5)P2 orPIP2] on TRPV1 is complex and less well understood [Brachot et al., 2007; Qin, 2007]. Originally, Julius and colleagues suggested that TRPV1 is under the inhibitory control of PIP2 [Chuang et al., 2001; Prescott and Julius, 2003], which would be consistent with the lack of endogenous TRPV1 tone except for temperature regulation. They also proposed that (1) cleavage by phospholipase C of PIP2 may contribute to the pharmacological mechanism of TRPV1 activation [Chuang et al., 2001], and (2) functional recovery of TRPV1 from desensitization requires PIP2 resynthesis [Ertel et al., 2005]. Subsequent studies, however, paint a far more complicated picture. In excised patches, PIP2 activates TRPV1 [Lukacs et al., 2007]. Furthermore, capsaicin activates phospholipase C in TRPV1-expressing cells, resulting in PIP2 depletion and subsequent desensitization. Importantly, the phospholipase C inhibitor, U73122, prevents capsaicin desensitization of TRPV1 [Lukacs et al., 2007]. How can we reconcile these conflicting findings? Rohacs and coworkers [Lukacs et al., 2007] believe the PIP2 may have both inhibitory and potentiating effects on TRPV1 depending on the cellular milieu. This biphasic behavior is hardly unprecedented: both some natural products (e.g., cinnamaldehyde [Szallasi et al., 1999]) and synthetic compounds [Wang et al., 2001] can inhibit TRPV1, depending on their dose and/or the phosphorylation state of the receptor.

An emerging area of TRPV1 modulation is the heteromeric assembly of TRPV1 subunits [Garcia-Sanz et al., 2004; Hellwig et al., 2005] and the interaction of TRPV1 with its splice variants and other intracellular proteins that may play a role in the shuffling of TRPV1 among various subcellular compartments [Courtright and Szallasi, 2004; Szallasi and Blumberg, 2006; Szallasi et al., 2007]. As first predicted by its large radiation inactivation size inconsistent with a single protein [Szallasi and Blumberg, 1991], TRPV1 probably exists in a multimeric form, most likely a tetramer [Garcia-Sanz et al., 2004]. This model is entirely consistent with the positive cooperative nature of the ligand binding properties of TRPV1 [Szallasi and Blumberg, 1999]. TRPV1 is actively transported between the cell membrane and intracellular compartments [Morenila-Palao et al., 2004]; it was suggested that upon phosphorylation by protein kinase C, TRPV1 is directed to the membrane [Zhang et al., 2005] and then the dephosphorylated protein is reshelved to the intracellular depot.

COMPETITIVE TRPV1 ANTAGONISTS OBTAINED BY CHEMICAL MODIFICATION OF AGONISTS

The very existence of TRPV1 predicted the existence of painful endogenous compounds, the so-called endovanilloids [Kwak et al., 1993; Szallasi and Blumberg, 1999; Di Marzo et al., 2002; Walker et al., 2003]. It can be argued that if endovanilloids are involved in the development of pathologic pain, competitive TRPV1 antagonists should be analgesic by blocking the access of pro-algesic endovanilloids to the receptor. This concept has gained strong experimental support by the absence of inflammatory thermal hyperalgesia in mice whose TRPV1 had been deleted by homologous recombinant (~−/−) [Caterina et al., 2000; Davis et al., 2000].

The first competitive TRPV1 antagonists, as exemplified by capsaicin (2) (Fig. 1), were derived directly from structural modification of TRPV1 agonists by researchers at the Sandoz (now Novartis) Institute for Medical Research in an attempt to dissociate the intolerable irritant and pungent properties of capsaicin derivatives from their analgesic activity. [Walpole and Wiengart, 1993]. Capsazepine is a conformationally constrained capsaicin analogue and extensive NMR and X-ray crystallographic studies gave rise to a proposal of different binding modes for agonist versus antagonist [Walpole et al., 1994]: agonists bind to the TRPV1 receptor in an extended conformation, whereas the antagonists prefer a L-shaped orientation. Wiengart and Wiengart (1993) capsazepine is still the most widely used pharmacological tool in studies involving TRPV1 despite its many unfavorable properties, including low potency, metabolic instability, and interaction at receptors other than TRPV1 (e.g., nitrergic acetylcholine receptors and voltage sensitive calcium channels) [Szallasi and Blumberg, 1999]. One must use caution when interpreting positive or negative results with capsazepine. Since capsazepine is a class B TRPV1 antagonist, that is, it does not inhibit all types of TRPV1 activators [Gavva et al., 2005], a lack of inhibition by capsazepine does not necessarily imply that TRPV1 was not involved in the response. Conversely, a block of response by capsazepine may be mediated by targets other than TRPV1.

It was with serendipity that it was discovered by investigators at Novo Nordisk that halogenation, and
more specifically iodination, of TRPV1 agonist may provide potent antagonists [Wahl et al., 2001]. For example, iodination of RTX [Wahl et al., 2001] and nonivamide [Appendino et al., 2003] in the homovanillyl moiety results in potent TRPV1 antagonists. Interestingly, the position of iodine is critical for determining the pharmacological activity of the molecule. For instance, introduction of iodine at C-5' position in RTX (3) or at C-9 position in nonivamide (4a) (Fig. 1) resulted in complete reversal, whereas the converse produced either less potent antagonist or partial agonists [Appendino et al., 2005a,b,c]. It is unclear how halogenation works at the molecular level as iodination of vanillic- and dihydroferulic-RTX analogues has no impact on TRPV1 agonism [Appendino et al., 2007]. Halogenated TRPV1 antagonists are a useful tool in in vitro assays, but not much is known about their in vivo efficacy, mostly because they are not considered as drug candidates.

Other examples of TRPV1 antagonists obtained by chemical modification of existing TRPV1 antagonists include the thiourea-based KJM 429 (5) and JYL 1421 (6) (Fig. 1) (also known as SC0030) [Wang et al., 2002; Lee et al., 2003; Kang et al., 2007]. These antagonists were obtained by specific substitution in the aromatic region of the corresponding agonist. KJM 429 was obtained via replacement by a methane sulfonamide group of the 3' phenolic hydroxyl group in the terminal benzyl ring of the corresponding agonist. JYL 1421 is a result of an additional fluoro-substituent at C-2' of KJM 429. JYL-1421 was assessed in various bioassays in the rat where it behaved as a TRPV1 antagonist, both more potent and more selective than capsaicin [Jakab et al., 2005].

**POTENT, SMALL-MOLECULE TRPV1 ANTAGONISTS**

The molecular identification of TRPV1 in 1997 [Caterina et al., 1997] paved the way to the launching of large pharmaceutical companies of high-throughput screening and combinatorial chemistry programs aimed at the identification of novel antagonists with better efficacy, safety, and pharmacokinetic profiles.

**Pyridyl Piperazine Carboxamides**

BCTC (N-(4-tert-butyphenyl)-4-(3-chloropyridin-2-yl)piperazine-1-carboxamide) (7) (Fig. 2) is the most studied member of the piperazine carboxamide class of TRPV1 antagonists [Bakhavatchalam, 2002; Dax et al., 2002; Yura et al., 2003; Rami et al., 2003; Lee et al., 2003; Sun et al., 2003; Tafesse et al., 2004]. In the patent literature, this class was first disclosed by Aurogen, followed by Johnson & Johnson, Bayer, GlaxoSmithKline (GSK), and Abbott and Purdue Pharma [Bakhavatchalam, 2002; Dax et al., 2002; Yura et al., 2003; Rami et al., 2003; Lee et al., 2003; Sun et al., 2003; Tafesse et al., 2004]. BCTC is a promising preclinical candidate molecule. It is a potent antagonist of rat TRPV1 (rTRPV1) activation by both acids

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**Fig. 2.** Piperazine carboxamides and benzinimidazoles.
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(1) IC$_{50}$ = 4.8 nM and capsaicin (IC$_{50}$ = 35 nM), that is, it is a class A antagonist. Moreover, it shows a much better selectivity profile as compared to capsaazine against a panel of ion channels, receptors, enzymes and transporters of clinical relevance. Importantly, BCTC is bioavailable per os (5–15%) with a plasma half-life of nearly 1.0 h and is active in rat models of acute inflammatory and neuropathic pain [Pomoni et al., 2003] with significant penetration into the CNS [Valenzano et al., 2003].

BCTC, however, showed significant shortcomings in preclinical studies, most importantly, it blocked (87% inhibition at 1 µM) hERG channels expressed in HEK-293 cells [Tafesse et al., 2004]. Inhibitors of hERG channels are known to produce potentially fatal cardiovascular effects such as prolongation of the cardiac QT interval causing ventricular arrhythmias and fibrillation [Rodin et al., 1996].

Of note, Johnson & Johnson developed a 4-(3-trifluoromethylpyridin-2-yl)-1-(5-trifluoromethylpyridin-2-yl)piperazine-1-carboxamide (9) (Fig. 2) as a close analogue of BCTC [Swanson et al., 2005]. This compound functioned as a potent human TRPV1 (hTRPV1) antagonist against capsaicin (IC$_{50}$ = 6 nM) and other modes of activation such as low pH (IC$_{50}$ = 16 nM) and also exhibited excellent oral bioavailability (100%) and plasma half-life (7–8 h) [Swanson et al., 2005]. The hyperthermia produced by this compound prevented its further development [Swanson et al., 2005].

In summary, the piperazine carboxamide class contains highly potent TRPV1 antagonists whose clinical potential is limited by a combination of complex pharmacokinetics, low aqueous solubility, metabolic stability, hyperthermia, and potential cardiovascular side effects (the latter mediated by hERG channels).

Piperazine carboxamides and Bicyclic Benzimidazoles

AMG-2674 (10) (Fig. 2), a highly potent TRPV1 antagonist belonging to the series of 2-[(4-pyridin-2-yl)piperazin-1-yl]-1H-benzo[d]imidazoles, was discovered at Amgen as a modified piperazine amide [Ognyanov et al., 2006]. The compounds in this class are modified BCTC analogues where the N1-carboxanylidene group of BCTC has been cycled to form a benzimidazole moiety. The introduction of lipophilic groups such as 3,4,5-trifluorophenyl on the benzimidazole ring and polar head groups such as hydroxymethyls on the pyridine ring restores the high potency of these antagonists, implying the existence of a large hydrophobic pocket in the TRPV1 receptor. Similar to the BCTC series, introduction of a methyl group with R-configuration on the piperazine ring enhances the potency of these compounds. AMG-2674 was obtained by a stepwise modification of the BCTC scaffold. This compound demonstrated potent activity in vitro in capsaicin- and pH-induced activation of rTRPV1 (IC$_{50}$ = 0.9 nM). In vivo, oral administration of AMG-2674 to rats blocked capsaicin-induced flinching (EC$_{50}$ = 8.8 mg/kg) and thermal hyperalgesia by 46% following intraplantar application of complete Freund's adjuvant [Ognyanov et al., 2006].

Piperazine Carboxamides to Biaryl Carboxamides to Aminoquinazolines

A collaborative effort between Neurgen and Merck identified a series of biaryl carboxamides as TRPV1 antagonists with high potency and metabolic stability [Zheng et al., 2006]. This series featured bioisosteric replacement of the piperazine ring from the piperazine carboxamide series with a phenyl ring. Structure–activity relationships were similar to those of the piperazine carboxamide series. Compounds 11–14 (Fig. 3) showed excellent potency (IC$_{50}$ values of 0.6–2.6 nM) for human as well as rat TRPV1. Compound 13 (Fig. 3) was the most potent compound in this class with a mean IC$_{50}$ of 6 nM at hTRPV1 against capsaicin activation. However, these compounds still suffered from poor aqueous solubility and bioavailability. Introduction of a heteroatom such as nitrogen in the phenyl ring (see compounds 15–18; Fig. 3), in an attempt to decrease the lipophilicity and, in turn, improve aqueous solubility of the compounds led to a significant decrease in the potency. By contrast, a dramatic increase in potency was observed upon cyclization of the carbonyl group to the central phenyl ring that yielded the aminoquinazoline derivative 19 (Fig. 4) [Zheng et al., 2006]. Combined, these studies indicate that co-planarity of the carboxamide group with the central phenyl ring is essential for high potency. Recently, compound 22 (Fig. 4) highly potent at hTRPV1 (IC$_{50}$ = 0.1 nM) and rTRPV1 (IC$_{50}$ = 1.4 nM) but also exhibited long half-life (8.1 h) and excellent oral bioavailability (99%) attributed to its low clearance (23 ml/min/kg) and may be to some extent to its conformational rigidity. A phase 2 clinical study was initiated in October 2006 to assess the safety, tolerability, and efficacy of NGD-8243/MK2295 (structure not disclosed) compared with ibuprofen in patients with postoperative dental pain.

d. 1,3-Disubstituted urea compounds

Several pharmaceutical companies (e.g., Abbott, GSK, Bayer) are actively investigating 1,3-disubstituted urea compounds. A series of 5-aminooquinoline urea derivatives was reported by Johnson & Johnson as potent TRPV1 antagonists [Jetter et al., 2004]. This
series resulted from a systematic modification and optimization of the TRPV1 agonist 4-pentylpyridin-3-yl-benzamide 20 (Fig. 5). Replacement of the pyridine group with isoquinoline led to a reversal of agonist activity to an antagonist activity in compound 21. Further modification of the carboxamide (21) to a urea (22) (Fig. 5) and subsequent lead optimization of the urea resulted in a highly potent TRPV1 antagonist, 1-(4-trifluoromethylphenyl)1,2,3-triazole urea (23) (IC_{50} = 3.0 nM) (23) (Fig. 5). This urea derivative (23) was developed independently as an optimized lead compound, now known as A-425619 [Gomisyan et al., 2005]. However, the lead for A-425619 was a hydroxynaphthalene urea derivative (24) (Fig. 5), coming from high-throughput screening of Abbott’s compound library. Bioisosteric replacement of hydroxynaphthalene group was required since the hydroxy group, although essential for activity, was also a potential site for metabolism and hence a liability for pharmacokinetic properties. Several bicyclic heterocycles, based on their comparative charge distribution studies, were considered. Isoquinoline turned out to be the most suitable heterocycle for this series. A-425619 blocked capsaicin-evoked increases in intracellular Ca^{2+} concentrations in HEK293 cells expressing recombinant hTRPV1 receptors with a potent IC_{50} value of 5 nM [El Louh et al., 2005]. A-425619 showed similar potency (IC_{50} = 3.4 nM) in blocking TRPV1 receptor activation by anandamide and N-arachidonoyl-dopamine [El Louh et al., 2005]. In vivo, A-425619 reduced capsaicin-induced mechanical hyperalgesia dose-dependently with an ED_{50} of 45 μmol/kg when given p.o. A-425619 was effective in models of inflammatory pain and postsurgical pain. For instance, A-425619 potently reduced CPA-induced chronic inflammatory pain orally [Honore et al., 2005].

### Substituted Aminoethyl Ureas

This series of TRPV1 antagonists also belong to the 1,3-disubstituted urea class. Investigators at GSK described a substituted aminoethyl urea derivative, SB-452533 (25) (Fig. 6) that showed good potency as TRPV1 antagonist against capsaicin, heat and low pH-mediated activation [Rami et al., 2004]. This urea derivative, however, could not be developed further due to its high intrinsic clearance determined by in vitro rat and human liver microsomes. The high intrinsic clearance was attributed to the N-dealkylation of the N-ethyl group. To circumvent this problem, the N-ethyl group was cyclized on to the adjacent phenyl.
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Aryl Cinnamides

Researchers at GSK identified SB-366791 (29) (Fig. 7) by screening an in-house compound library as a potent competitive inhibitor of both hTRPV1 and rTRPV1, endowed with superior target selectivity compared to capsazepine [Gunthorpe et al., 2004]. Subsequently, investigators at Amgen described AMG-9810, (E)-3-(4-t-butylphenyl)-N-(2,3-dihydrobenzo[b][1,4] dioxin-6-yl)acrylamide (30) (Fig. 7), as a potent TRPV1 antagonist by random screening of its synthetic compound library [Doherty et al., 2005]. AMG-9810 functions as a competitive antagonist of capsaicin activation (IC$_{50}$ = 17 nM for hTRPV1) and blocked all known modes of TRPV1 activation, including protons, heat, and endogenous ligands, such as anandamide, N-arachidonyl dopamine, and oleoyldopamine [Doherty et al., 2005]. In vivo, AMG-9810 was also effective at preventing capsaicin-induced eye wiping in a dose-dependent manner reversing
Fig. 7. Aryl cinnamides.

thermal and mechanical hyperalgesia in a model of inflammatory pain induced by intraplantar injection of CFA. However, it showed poor oral absorption and metabolic stability in rat. A stepwise optimization strategy was undertaken to come up with a clinical candidate having the desired efficacy, safety and pharmacokinetic profile. The lead structure was divided into three sections (benzodioxan-2-yl system, acrylamide core, aryl group) that were independently optimized to obtain analogues 31 and 32 (Fig. 7). In vitro, both analogues were highly potent (ED<50 μM) in capsicain as well as pH-mediated activation of hTRPV1. Their pharmacokinetic profile in Sprague-Dawley rats was also encouraging with compound 32 demonstrating low clearance (0.8 L/h/kg), high volume of distribution (2,800 ml/kg) and favorable half-life (2.9 h). While undoubtedly improved in terms of pharmacokinetic profile, the lack of oral bioavailability of both analogues awaits validation in vivo. 3D-QSAR models (CoMFA and CoMSIA) developed for the aryl cinnamides predict binding modes which are consistent with the previously developed models. It is predicted that these molecules also bind in the TM3/4 region of the TRPV1 channel [Vishwanathan et al., 2007].

Additional TRPV1 Antagonists From Diverse Chemical Classes

The race for launching a clinically useful molecule in a broad therapeutic area such as pain for a novel therapeutic target has spurred tremendous research activity within the pharmaceutical industry. Although most of the molecules discovered can be broadly classified into the categories described above, a diverse class of chemical structures do not fit the classification. However, some common features such as the tert-butyl phenyl, the difluoromethyl phenyl, quinoline, isoquinoline and their bioisosteres can still be found amongst these diverse classes with different set of linkers such as the pyrimidine, pyridazine, quinazoline, piperidine, indazolone and some others. Essentially, in most cases, the carbonyl or thiocarbonyl group, a key group for activity, has been incorporated as ring nitrogen in the above-mentioned linkers.

The chemical diversity in compounds 33-50 (Fig. 8) is evident from the structures listed above. A number of second generation TRPV1 antagonists such as AMG-517 (51) (Fig. 9) from Amgen [Doherty et al., 2007; Gavva et al., 2007; X. Wang et al., 2007; Y. Wang et al., 2007] and A-784168 from Abbott [Cui et al., 2008] belong to this chemical class. These compounds are under active investigation for pain management. The 7-amino modification of the acrylamide group of AMG-9810 to a pyrimidine ring with an oxygen linked heterocycle. This modification has led to improvement in the overall pharmacokinetic profile of acrylamide class of TRPV1 antagonist. AMG-517 acts as a potent, competitive and orally available antagonist of TRPV1 in humans, monkeys, rats and mice (IC50<2 nM), with greater than 4,000-fold selectivity over other TRP channels, a panel of G-protein-coupled receptors, and various ion channels [Doherty et al., 2007; Gavva et al., 2007; X. Wang et al., 2007; Y. Wang et al., 2007]. AMG-517 demonstrated antihyperalgesic efficacy in animal models of inflammatory pain, including carrageenan- and CFA-induced thermal hyperalgesia. Like other TRPV1 antagonists, AMG-517 caused transient hyperthermia that attenuated after repeated dosing [Gavva et al., 2007]. Further
Fig. 8. Chemical diversity of TRPV1 antagonists.
optimization of AMG-517 led to highly potent trisubstituted pyrimidines [Wang et al., 2007] with improved solubility profiles. A-784168 (52) (Fig. 9) is a modified piperazine-carboxamide analogue wherein the piperazine is replaced by tetrahydropyridine. This modification appears to conserve the desired conformation of the molecule to retain in vitro potency. A-784168 inhibited capsaicin induced activation of hTRPV1 with an IC_{50} value of 23 nM and also blocked capsaicin-induced acute nociceptive behavior in vivo. In the CFA model of chronic inflammatory pain, A-784168 inhibited both thermal hyperalgesia and mechanical allodynia following oral administration [Cui et al., 2006]. To assess the role of CNS in broad-spectrum analgesia, the efficacy of A-784168 was compared with another TRPV1 antagonist, A-795614 (53) (Fig. 9) in models, presumably mediated by central sensitization, including CFA- and capsaicin-induced mechanical allodynia and osteoarthritic pain [Cui et al., 2006]. In these models, the potency of the two compounds was similar after intrathecal administration. However, when administered p.o., A-784168, with good CNS penetration, was more potent than A-795614. These results demonstrate that TRPV1 receptors in the CNS play an important role in pain mediated by central sensitization. In addition, these results demonstrate that significant CNS penetration is necessary for a TRPV1 antagonist to produce broad-spectrum analgesia [Cui et al., 2006].

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CONCLUSION

The worldwide analgesic drug market was estimated at US $38 billion in 2002 and is expected to nearly double by the year 2010. An estimated 50 million Americans suffer from chronic pain conditions, often requiring a combination of complex and expensive medical and surgical approaches to provide some relief. More than $10 billion is lost annually due to chronic pain (insomnia, depression, over-compensation, and lost productivity), and this number is sure to rise. At the level of the individual, chronic pain adversely affects patient well-being, level of function, and quality of life. Chronic pain is often undertreated, and the unfilled needs are well recognized. Consequently, chronic pain is subject to intensive research and significant resources are devoted to the development of new analgesic drugs. TRPV1 antagonists represent a new paradigm in the development of analgesic drugs. Unlike traditional analgesic drugs that block the inflammatory response and the propagation and transmission of pain, TRPV1 antagonists prevent pain by silencing a nociceptor in the periphery where pain is generated [Szallas et al., 2006, 2007]. In animals, there is strong evidence that TRPV1 antagonists can relieve inflammatory, cancer, and neuropathic pain [Krause et al., 2005; Immke and Cavaa, 2006; Cottright et al., 2007]. Additionally, TRPV1 antagonists may be useful in the management of urinary incontinence, cough, pruritus, migraine, diabetes, and obesity [Anish and Szallasi, 2007; Gunther and Szallasi, 2006; Szallasi et al., 2007].

In summary, TRPV1 antagonists are very promising drug candidates in animal models but their clinical future is uncertain. Apparently, the hyperthermic response to TRPV1 antagonists that can be easily managed in experimental animals may reach dangerously high levels in patients. Another frequently voiced concern is the possibility of "silent myocardial infarction" in patients on TRPV1 antagonists for chronic pain due to long-QT syndrome. The widespread TRPV1 expression in the CNS and in non-neuronal tissues, where the biological functions of TRPV1 are essentially unknown, is also an area of concern. Yet, alone or in combination with other analgesic drugs, TRPV1 antagonists may prove clinically useful drugs to relieve chronic pain.

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