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Commentary

Analgesic potential of TRPV1 antagonists

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ABSTRACT

The discovery of TRPV1 antagonists as a new class of analgesic agents for the treatment of chronic pathological pain has been pursued aggressively across the pharmaceutical industry. This effort has led to the identification of several TRPV1 antagonists that have entered clinical trials, including ABT-102 (Abbott), SB-705498 (GSK), AMG-517 (Amgen), MK2295 (Merck/Neurogen), and GRC-6211 (Lilly/Glenmark). Using the published structures for ABT-102, SB-705498, AMG-517, and lead compounds representing six additional TRPV1 antagonist chemotypes, a pharmacophore model that describes the common structural features found in potent TRPV1 antagonists was established. The TRPV1 antagonist pharmacophore fits within the pore region of a TRPV1 receptor homology model, with critical hydrogen bond interactions proposed between the TRPV1 antagonist pharmacophore and Tyr 667 on helix six. In spite of the putative common binding site for all TRPV1 antagonists included in this particular TRPV1 pharmacophore, these ligands have demonstrated that they can still offer distinct pharmacological profiles, likely due to differences in their pharmacokinetic profiles. This is highlighted by differences in temperature elevation observed when comparing the clinical candidates ABT-102 and AMG-517.

1. Introduction

Chronic pain remains a widely recognized unmet medical need, and consequently, the search for new analgesic agents is being intensively investigated by the pharmaceutical industry. Given the known limitations of currently available analgesic agents (opioids, NSAIDs, gabapentin, pregabalin, and duloxetine), there is particular interest in identifying novel mechanisms of action that play a role in pain transmission. One relatively new molecular target that has attracted significant attention in the past decade is TRPV1 (transient receptor potential vanilloid type 1) [1]. TRPV1 is the receptor that mediates the effects of capsaicin, the pungent ingredient in hot chilli peppers. In addition to capsaicin, TRPV1 can be activated by endogenous vanilloid lipids, heat, and acidic pH such as that associated with inflammation. TRPV1 null mice (−/−) show attenuation of thermal hyperalgesic responses [2,3], and small molecule antagonists block pain responses in rodents [4,5]. The hypothesis that the TRPV1 receptor is a nexus in pain transmission [6], and that TRPV1 antagonists may deliver broad spectrum efficacy in nociceptive pain by silencing pain signaling pathways has made the discovery of novel TRPV1 antagonists an enticing goal for the pharmaceutical industry [7–9].

2. Biochemical pharmacology: TRPV1 in pain transmission

Activation of TRPV1 results in the release of molecules associated with pain transmission, such as glutamate, bradykinin, calcitonin gene-related peptide (CGRP), and substance P [10,11]. TRPV1 is localized on small- and medium-size sensory neurons in dorsal root and trigeminal ganglia, with peripheral projections innervating the skin, muscles, joints, and gut, and central terminals projecting to the spinal dorsal horn. Within the CNS, TRPV1 functional activity has been demonstrated in the spinal cord and specific sites in the brain including the thalamus, locus coeruleus, periaqueductal grey and cortex [12,13]. TRPV1 selective antagonists are particularly potent and efficacious in preclinical pain models associated with low pH and thermal hyperalgesia such as acute and chronic inflammation [14]. In this regard, the effects of TRPV1 antagonists are in close agreement with the phenotype observed in TRPV1 knockout mice when challenged with inflammatory agents such as carrageenan and CFA, or with capsaicin [2,3].

Activation of TRPV1 triggers an influx of calcium and sodium ions, initiating a cascade of events that results in membrane depolarization, neuronal firing, and transduction of neural impulses [9]. In response to several algesic agents, TRPV1 becomes phosphorylated, resulting in a lower threshold of channel activation (sensitization). Bradykinin (BK), nerve growth factor, and anandamide [15], as well as prostaglandins (notably PGE_2 via

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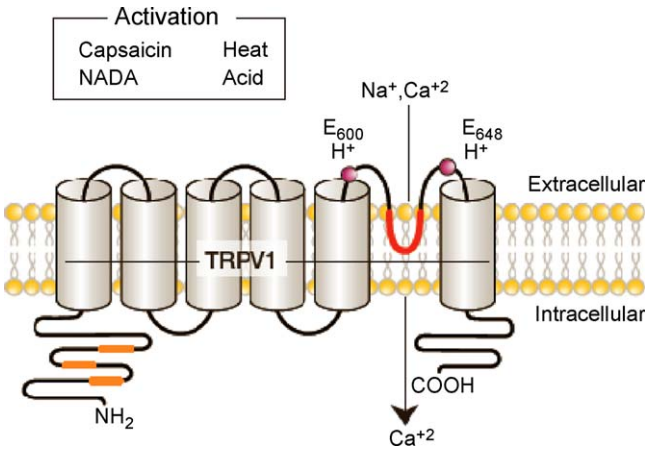

Fig. 1. Representation of TRPV1 highlighting the six transmembrane domains, the two glutamate (E) residues involved proton binding, and the pore-forming loop. The receptor is activated by capsaicin, endogenous vanilloid lipids such as *N*-arachidonyl-dopamine (NADA), heat >43 °C, or protons (pH below 5.5).

EP4 receptors) [16], and protons [17,18] have all been reported to sensitize TRPV1. Activation of TRPV1 results in release of glutamate [19] and the pro-nociceptive peptides CGRP and substance P [20]; in contrast, treatment with TRPV1 antagonists decreases the release of CGRP [21]. Recently, our group reported the finding that the analgesic effects of selective TRPV1 antagonists from different chemotypes are enhanced in animal pain models following repeated administration relative to their acute effects [22]. While data have not been reported that establish the mechanism for the enhanced efficacy with sub-chronic dosing, one hypothesis that has been advanced is that blocking the release of neuropeptides (e.g., BK, CGRP, and substance P) that sensitize TRPV1 leads to interruption of the mechanism that lowers the threshold of TRPV1 activation, resulting in increased efficacy of TRPV1 antagonists.

3. Structure/function of TRPV1

The TRPV1 receptor is the first discovered mammalian member of the TRP superfamily. The members of this superfamily contain six transmembrane helices (TM1–TM6) with a pore domain between helices 5 and 6, and the N- and C-termini on the cytosolic side of cell membrane (Fig. 1). The first low resolution (19 Å), three-dimensional structure of TRPV1, determined by single particle electron microscopy, revealed a protein that is arranged in two distinct domains: a relatively compact domain that is consistent with a six-helix transmembrane protein structure, and a large open basket-like domain that resides in the intracellular compartment [23]. Another important feature of TRPV1 architecture confirmed by this structure was the symmetrical assembly of four TRPV1 subunits to form the channel pore. These data support the generally accepted belief that the structure of TRPV1 is related to other ion channels for which high-resolution X-ray crystal structures have been obtained (Kcsa [24], Kv1.2 [25], and MthK [26]).

Alignment of the sequence of TRPV1 with the sequence of Kv1.2 using hydropathy analysis and conserved interdomain contacts as critical factors, allows the use of the Kv1.2 X-ray crystal structure as a template for homology models of the TRP family and of TRPV1 in particular. Consideration of common and distinct residues across the family of TRP channels provides insights into sequence alignment and contributes to the robustness of the TRPV1 model (Fig. 2).

Ligand placement in ion channel modeling can only be inferred based on other data, since there are no crystal structures of ion channels with relevant ligands. Extensive site-directed mutagenesis of another potassium channel, the human ether-a-go-go (hERG) channel [27], can be used to infer the binding site of ligands in related channels. Many groups have mutated residues in the pore region (helices S5 and S6) and examined the changes in ion currents in cells containing the overexpressed channels. The general conclusion from these studies is that most channel antagonists bind in the pore region, interacting with residues from all four monomers of the tetrameric channel [27].

Although mutagenesis data have identified a number of key residues (Tyr 511, Ser 512, Thr 550, and Tyr 667) important for TRPV1 agonist binding, diverging hypotheses have emerged on the precise locus of the TRPV1 agonist binding site [28–32]. Ligand modeling studies suggest intracellular agonist binding, but there is consensus neither on the transmembrane segments of the channel involved nor on the binding orientation of agonist (typically, capsaicin). Similar questions arise in the case of TRPV1 antagonists, where the extent of overlap that exists with the capsaicin binding site introduces an added layer of uncertainty [32].

4. Pharmacophore model of TRPV1 antagonists

Pharmacophore models can show the important features of a group of ligands that are believed to bind to a common site. The homology model of the TRPV1 channel has been used to filter the

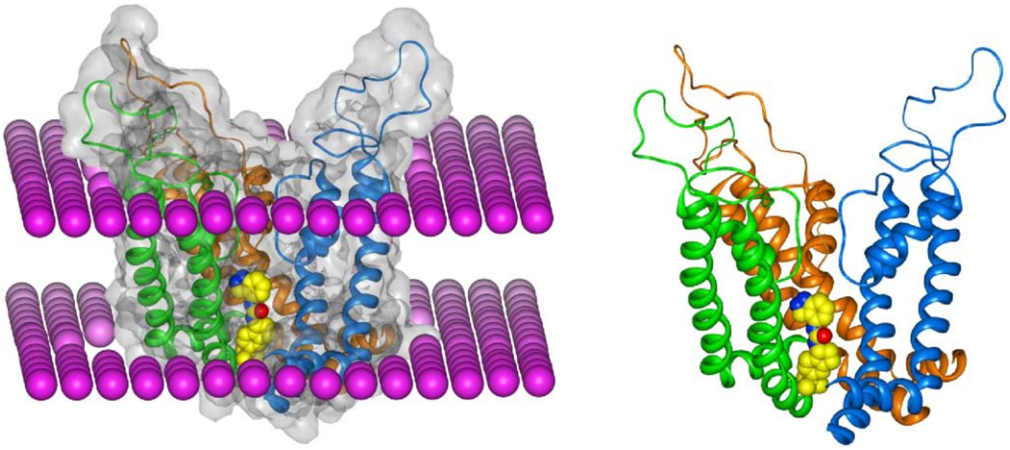

Fig. 2. The homology model of the TRPV1 ion channel with the ribbon of each monomer colored differently (monomer 1 removed for clarity). ABT-102 is depicted in the ligand binding site described in the text.

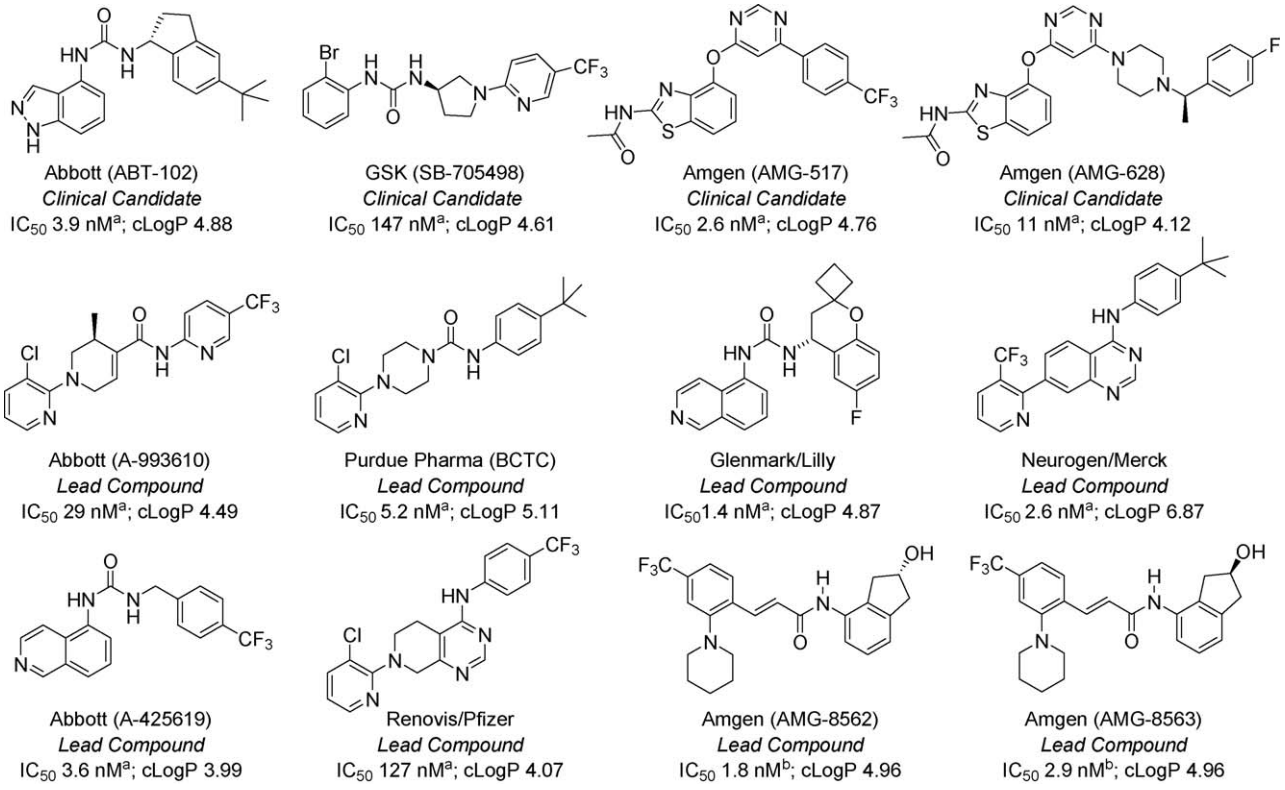

Fig. 3. TRPV1 antagonists used in construction of the TRPV1 pharmacophore model. [a]TRPV1 IC_{50} based on inhibition of calcium flux in response to 50 nM capsaicin in human TRPV1 stably expressed in human astrocytoma 1321 cells. TRPV1 function was monitored using a calcium sensitive dye, fluo-4 and a fluorescent imaging plate reader (FLIPR), Molecular Devices. [b]TRPV1 IC_{50} based on inhibition of $^{45}Ca^{2+}$ uptake in response to 500 nM capsaicin in rat TRPV1 stably expressed CHO cells as described in Ref. [54].

set of possible pharmacophore models both by size and shape of the site and by location of appropriate interacting sites on the protein. The overlap volume of the ligands must fit in the binding site and there should be corresponding hydrogen-bond donors or acceptors located near the hydrogen-bonding features identified by the pharmacophore model.

Using these concepts and the TRPV1 antagonists shown in Fig. 3, a TRPV1 antagonist pharmacophore model has been generated that embodies three essential features: a hydrogen-bond acceptor, a hydrogen-bond donor, and a ring feature. In addition, the TRPV1 antagonists have been superimposed in such a way that they could fit in the volume of the TRPV1 pore (Fig. 4). When the homology model is considered, appropriate interaction sites are found in the pore. The hydrogen-bond acceptor on the pharmacophore is proposed to interact with Tyr 667 (helix S6) as a hydrogen-bond donor, and the hydrogen-bond donor on the pharmacophore is proposed to interact with Tyr 667 on the opposite monomer of the tetramer as a hydrogen-bond acceptor (Fig. 4). The ring feature of the pharmacophore is proposed to fit in the hydrophobic space formed by the aromatic rings of the four Tyr 667 residues of the four monomers. Consistent with the critical role played by Tyr 667 in the interaction with key elements of the TPRV1 antagonist pharmacophore, site-directed mutagenesis studies have shown that exchanging this tyrosine for alanine in the rat TRPV1 receptor (rat Y666A) abolishes functional activity of TRPV1 [33]. The opposite, more lipophilic end in these ligands is more varied in character and volume and interacts with the lower end of transmembrane helices S5 and S6. The intracellular ends of these helices are likely to be flexible, since they extend past the membrane and may be part of the channel opening and closing process. This combined use of a pharmacophore model, assembled from highly optimized TRPV1 antagonists, with a homology model of the protein has enhanced understanding of the observed structure–activity relationships of many series of current TRPV1 antagonists, and should be useful in the discovery of new classes of antagonists.

5. Molecular properties of TRPV1 antagonists

Examination of the antagonists shown in Fig. 3 reveals an average cLogP of 4.81 and polar surface area of 60.1 $Å^2$ [34]. Given

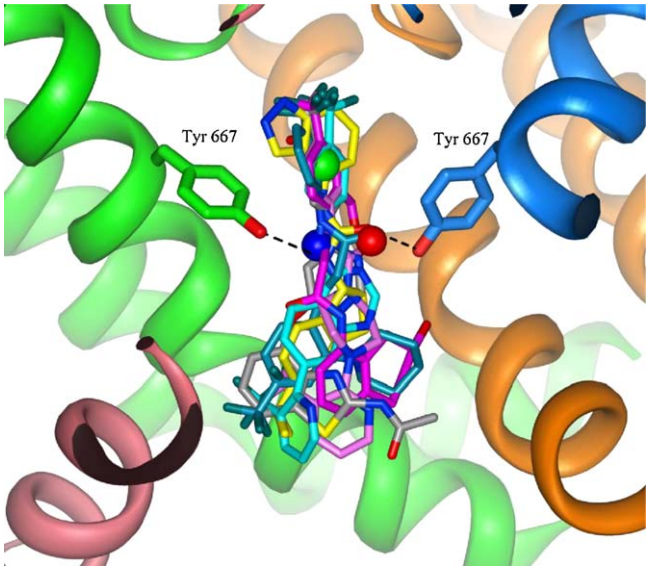

Fig. 4. TRPV1 antagonist pharmacophore model. Tyr 667 of blue monomer donates a hydrogen-bond to all ligands and Tyr 667 of green monomer accepts a hydrogen-bond from most ligands. ABT-102 (yellow carbons) and other ligands occupy the binding site in the center of the pore. Pharmacophore model features are shown as spheres (red: acceptor; blue: donor; and green: ring).

the overall hydrophobic character of the putative TRPV1 antagonist binding domain, it is not surprising that cognate antagonists, possessing highly optimized potency and selectivity, are very lipophilic in nature. Perhaps equally predictable is the wealth of literature evidence that attests to the drugability challenges these types of molecules present, particularly in the form of limited aqueous solubility, poor pharmacokinetic properties across species, and susceptibility to cytochrome-mediated metabolism [35–38]. From a drug discovery perspective, investigators have sought to circumvent these liabilities by incorporation of solubilizing polar functionality (e.g., the piperazine in AMG 628), replacement of the amide/urea linker with a suitable isostere or surrogate spacing group (e.g., the heterobicyclic Neurogen/Merck and Renovis/Pfizer lead structures), and blockade of potential metabolic soft spots (e.g., with halogen and trifluoromethyl groups). However, improvement of either the physicochemical or pharmacokinetic profile of TRPV1 antagonists frequently has been achieved at the expense of potency and selectivity [9].

The early potent and selective antagonists of human and rat TRPV1, BCTC [39] and SB-366791 [40], were exceedingly valuable as structurally novel tool ligands; unfortunately, the poor pharmacokinetic properties of these compounds, like their prototypical TRPV1 antagonist predecessor capsazepine, rendered them unsuitable for further development. On the other hand, the robust microsomal stability ($CL_{int} < 5$ μL/(min mg)) of SB-705498 translated to low *in vivo* clearance, good oral bioavailability, and a high volume of distribution in rat, dog, and guinea pig [32]. The encouraging activity of SB-705498 in preclinical models of pain prompted its subsequent clinical evaluation. SB-705498 was well tolerated at single doses up to 400 mg in humans. In humans, a single oral dose of SB-705498 at 400 mg demonstrated target-specific pharmacodynamic activity in reducing both UV-burn evoked inflammation and the area of capsaicin-evoked flare [41]. However, there was no significant effect on capsaicin-evoked thermal hyperalgesia or on the flare intensity induced by capsaicin or UV-burn irradiation at this dose. Estimates of the terminal elimination phase half-life for SB-705498 ranged from 35 to 93 h, with SB-705498 remaining detectable for the entire 168 h post-dose sampling period [41]. While trials in migraine, rectal hypersensitivity, and post-operative dental pain were initiated in 2005, these trials were terminated in 2006 with no trial data released.

The acylation of the aminobenzthiazole in AMG-517 mitigates metabolic oxidation, which is often problematic in this region of the molecule, but does not compromise the hydrogen-bond donor–acceptor network that is critical for maintaining TRPV1 potency [42]. The 4-oxopyrimidine group presumably enhances systemic exposure relative to a urea, amide, or vinylogous amide (e.g., AMG-8562) linker. In aggregate, these structural features impart low intrinsic clearance (50 μL/(min mg), rat; <5 μL/(min mg), human) and a high volume of distribution (1.6 L/kg, rat), leading to a long half-life in preclinical species (rat, dog, monkey $t_{1/2} > 24$ h). Consistent with allometric scaling projections (human half-life of 60–120 h), a $t_{1/2}$ range of 13–23 days was observed in humans in the Phase I trial with AMG-517 [43]. Interpretation of clinical efficacy in a post-operative dental pain study was complicated by the observation of dose-limiting hyperthermia that occurred at sub-therapeutic doses [43]. Possessing a piperazine fragment in the P1 region of the pharmacophore, the second-generation candidate AMG-628 has increased solubility (200 μg/mL in 0.01N of HCl) and a reduced half-life (rat, dog, monkey $t_{1/2} < 4$ h) compared to AMG-517 [44]. Thus far, no clinical data has been reported for AMG-628.

A number of potent diaryl or *N*-aryl-*N*′-benzyl urea TRPV1 antagonists have been described [45,46], but their untoward physicochemical and pharmacokinetic properties apparently have precluded further development. Replacement of substituted benzyl groups by a conformationally rigidifying indane moiety in a previously described *N*-indazole-*N*′-benzyl urea series led to a number of TRPV1 antagonists with significantly increased in vitro potency (hTRPV1 $IC_{50} < 10$ nM) and enhanced drug-like properties, including the clinical candidate ABT-102 [47]. Although the aqueous solubility of this compound is very low (57 ng/mL at pH 6.8; 100 ng/mL at pH 1), requiring lipid vehicle formulation, it is predicted to be well absorbed in humans based on Caco-2 permeability studies ($P_{app} > 18 \times 10^{-6}$ cm/s). Compared with SB-705498 and AMG-517, the decreased half-life ($t_{1/2}$ 1.7 h, rat; $t_{1/2}$ 1.8 h, dog) of ABT-102 together with acceptable clearance (1.1 L/h kg, rat; 0.62 L/h kg, dog), volume of distribution (2.8 L/h kg, rat; 1.6 L/kg, dog), and oral bioavailability (70%, rat; 60%, dog) in preclinical species are consistent with more favorable predicted pharmacodynamic behavior in the clinical setting [47].

Besides some characterization in the patent literature, relatively little is known about the profiles of GRC-6211 (Glenmark/Lilly) [48] or NGD8243 (Neurogen/Merck) [49], two compounds for which clinical trials have been initiated and subsequently abandoned [50]. Inspection of the chemical classes from which these compounds emanate, leads to the speculation that an inability to adequately balance favorable pharmacology and acceptable drug-like properties in a single entity may have contributed to their demise.

While progression of candidates for clinical proof-of-concept experiments suggests limitations on drugability are not insurmountable, it is clear that these hurdles will persist as the development of small molecule TRPV1 antagonists continues.

6. TRPV1 antagonists and temperature effects

Most TRPV1 antagonists described to date cause modest dose-limited increases in body temperature in preclinical studies [51]. Amgen previously demonstrated that TRPV1 antagonists did not cause temperature elevation in TRPV1 knockout mice [52], thus establishing that the elevated temperature was mechanism based. However, the magnitude and duration of temperature elevation caused by TRPV1 antagonists appeared to be dependent on the specific properties (pharmacokinetic profile, modality specific blockade of TRPV1 activation) of the individual TRPV1 antagonists. Recently, we have reported that temperature elevation caused by the clinical candidate ABT-102 is modest (0.6 °C) [22] compared to the temperature elevation (1.6 °C) observed with AMG-517 [53] in telemeterized rats. In addition, the elevation in temperature observed with ABT-102 in telemeterized rats is self-limiting (maximum increase in core body temperature observed at 10 μmol/kg, p.o.; no further increase upon dosing to 30 μmol/kg), and transient (duration of temperature elevation is only 8 h for ABT-102 [22] compared to 20 h reported for AMG-517 [53]). Importantly, the temperature elevation fully attenuates with repeated dosing of ABT-102 in rats [22], but the temperature elevation observed with AMG-517 in humans only partially attenuates with repeated dosing [43]. In preclinical studies, AMG-517 is reported to have diminished effects on temperature elevation in rats and dogs after multiple days of dosing, however, it is not reported whether repeated dosing of AMG-517 results in full attenuation of body temperature in these species [53]. The temperature elevation associated with AMG-517 is reported to fully attenuate in monkeys that were treated with AMG-517 for 8 days [53]. It is possible that the shorter half-life of ABT-102 relative to AMG-517 may result in attenuation of temperature effects with repeated dosing more rapidly and more efficiently with ABT-102 than with AMG-517.

7. Modality specific TRPV1 antagonists

Most TRPV1 antagonists described to date block all three modes of TRPV1 activation (lipid-based ligands, proton, and heat) individually and in combination. However, TRPV1 antagonists have been reported that block capsaicin and heat activation but not proton activation, or that selectively block only capsaicin activation with no effect on proton or heat activation [54]. With distinct molecular domains for activation by capsaicin, protons, and heat, the opportunity exists to design modality-specific TRPV1 antagonists. Although it is unclear which TRPV1 inhibition profile is preferable for optimal clinical efficacy and safety, the link between stimulus-specific TRPV1 antagonists and differentiated *in vivo* pharmacology has already has been demonstrated. For example, Amgen has described a compound (AMG-8562) that completely blocks TRPV1 activation by capsaicin, but potentiates TRPV1 activation by acidic pH [54]. This compound does not cause the increase in core body temperature that is commonly observed with TRPV1 antagonists that block all forms of TRPV1 activation, but it does reduce CFA-induced thermal hyperalgesia and acetic acid-induced writhing [54]. The discovery that modality-specific TRPV1 antagonists are linked to distinct *in vivo* pharmacology with respect to temperature effects may lead to a new generation of TRPV1 antagonists entering the clinic.

8. Future outlook

While the field of TRPV1 research still awaits disclosure of the first clinical proof-of-concept studies describing the analgesic potential of TRPV1 antagonists, recent advancements in TRPV1 antagonist design have led the field to the doorstep of this important milestone. In particular, two recent findings related to TRPV1 antagonist design may illuminate the path to identifying a successful clinical entity. First, the observation that TRPV1 antagonists can be designed to deliver more manageable effects on core body temperature by adaptation of the pharmacokinetic profile provides evidence that not all TRPV1 antagonists affect body temperature to the same extent. In comparison to AMG-517, ABT-102 demonstrates significantly lower maximal temperature elevation, and the temperature elevation that does occur attenuates rapidly with repeated dosing. Since both of these antagonists are potent blockers of all modes of TRPV1 activation, the differences in temperature profile are presumably related to the contrasting pharmacokinetic profiles of these two clinical candidates. However, the report that SB-705498, another multimodal competitive TRPV1 antagonist, did not result in hyperthermia in clinical trials [55] suggests that additional data is needed with other clinical candidates before the field is fully able to predict the effects of TRPV1 antagonists on core body temperature in humans.

In addition, the discovery of stimulus-specific TRPV1 antagonists suggests the possibility of identifying a new generation of modality-specific TRPV1 antagonists that do not affect core body temperature. While the prospect of temperature neutral TRPV1 antagonists is enticing, there are still significant unanswered questions. Thus far, stimulus-specific TRPV1 blockade has only been characterized using rat TRPV1 preparations, and using rat telemetry and preclinical pain models. The translation of these effects to other species remains to be established. In addition, the breadth of efficacy associated with stimulus-specific TRPV1 antagonists versus multimodal TRPV1 antagonists must be better understood both in rodent preclinical pain models and in higher order species. Ultimately, the relative merits of different classes of TRPV1 antagonists will be determined through clinical trials.

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