Mini Review

Transient Receptor Potential Vanilloid 1 Agonists as Candidates for Anti-inflammatory Agents

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The transient receptor potential vanilloid-1 (TRPV1) cation channel is a receptor that is activated by heat, acidosis and a variety of chemicals, including capsaicin. With these properties, TRPV1 has emerged as a polymodal nocisensor of nociceptive afferent neurons. As many proalgesic pathways converge on TRPV1 and it is upregulated and sensitized by inflammation and injury, TRPV1 is thought to be a central transducer of hyperalgesia and a prime target for the pharmacological control of pain. However, there is conflicting evidence to date as to whether TRPV1 agonists promote or inhibit inflammation. We recently demonstrated that SA13353 [1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea], a novel TRPV1 agonist, inhibits tumor necrosis factor-α production through the activation of capsaicin-sensitive afferent neurons and reduces the severity of symptoms of kidney injury, lung inflammation, arthritis and encephalomyelitis in disease models. These results suggest that TRPV1 agonists may act in an anti-inflammatory manner *in vivo* in certain inflammatory diseases.

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Introduction

Voltage-dependent Ca2+ channels are well known for causing Ca2+ influx into the cell. Recently, a family of closely related cation channels, known as transient receptor potential (TRP) channels, was discovered. They act as molecular sensors for distinct pain, temperature, chemesthesis and taste modalities. The implication of TRP channels in pain and sensation was first heralded in 1997, when the vanilloid receptor-1 (renamed transient receptor potential vanilloid-1; TRPV1) was identified at the genetic and functional level[1]. TRPV1 is expressed mainly in capsaicin-sensitive sensory nerves, which also express the neuropeptides calcitonin gene-related peptide (CGRP), substance P (SP) and somatostatin[2]. Analysis of the molecular and functional properties of TRPV1 has shown that this ion channel is a polymodal nocisensor, which is subject to allosteric modulation by many proalgesic pathways. This and its ability become sensitized by proinflammatory mediators have raised enormous interest in TRPV1 as a prime transducer of pathological pain. At the same time, however, it has emerged that TRPV1 has important functions in homeostasis, for example, in thermoregulation. The role of TRPV1 in inflammation is under debate; several studies have demonstrated a proinflammatory effect[3,4], while other studies have identified a protective role for TRPV1 in systemic inflammation and sepsis[5-7].

The physiological role of TRPV1 in the circulatory system and kidneys

The role of TRPV1 receptors in the circulation has been studied extensively. TRPV1 is responsible for the Benzold-Jarisch reflex, which causes hypotension, bradycardia and apnea, and occurs following the arterial injection of capsaicin[8]. TRPV1 was shown to be cardioprotective, mediating the release of CGRP in response to low pH and lactic acid[9]. TRPV1deficiency in mice has also been sown to impair the recovery process after ischemia/reperfusion-induced cardiac dysfunction[10]. TRPV1 expression is seen in a high percentage of primary afferent neurons that project to cardiovascular and renal tissues[11]. It has been recently demonstrated that the TRPV1 protein is present at high levels in the renal pelvis and exclusively regulates neuropeptide release from primary renal afferent nerves in response to mechanostimulation[12]. Moreover, TRPV1 protein is abundantly present in renal tubules of the medulla, although its functional roles are unknown[12]. The renal medulla contains nephron segments that are most susceptible to ischemic injury. We have recently obtained evidence that the TRPV1 agonists capsaicin, resiniferatoxin and SA13353 attenuate renal tumor necrosis factor (TNF)-α mRNA expression, increase renal interleukin (IL)-10 mRNA expression and improve the condition of ischemia/reperfusion-induced renal injury in rats[13,14]. SA13353 [1-[2-(1-adamantyl)-ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea] is a novel transient receptor potential vanilloid 1 (TRPV1) agonist, which has been demonstrated to have reduced oral toxicity compared with capsaicin in rodents[15,16]. Based on the results from binding, enzyme inhibition and functional assays, SA13353 appears to be a near-pure TRPV1 agonist[14]. The activation of TRPV1 leads to the release of neuropeptides, such as SP, CGRP and somatostatin[17]. CGRP is strongly coexpressed in many TRPV1-expressing nerve fibers, including sensory fibers that innervate the dural vasculature[18], and it has been suggested to act as a counterbalance to the development of hypertension[19]. In addition, previous studies have demonstrated that neuropeptides such as CGRP[20-22] and somatostatin[23] inhibited lipopolysaccharide (LPS)-induced TNF-α production in vivo and in vitro. The release of CGRP by capsaicin-sensitive sensory neurons increased endothelial cell production of prostaglandin I2, which may contribute to the attenuation of the inflammatory response[24]. We suggest that activation of capsaicin-sensitive afferent neurons by TRPV1 agonists and the resultant release of neuropeptides may modify the inflammatory reactions after ischemia/reperfusion. Therefore, TRPV1 agonists are a new class of drugs that have benefits in renal pathology, particularly in ischemia/reperfusion-related kidney injury[25]. Further studies are required to establish a definite role for these agents in the protection from and treatment of renal pathology.

The physiological role of TRPV1 in airway inflammation and disease

The afferent activities arising from sensory terminals in the lung and airways are conducted primarily by branches of vagus nerves, which project to the nucleus tractus solitarius in the medulla. Among these sensory nerves, TRPV1 is expressed predominantly in nonmyelinated afferent C fibers[26], which represent >75% of the afferent fibers in the pulmonary branch of the vagus nerve. One prominent anatomical feature of these sensory nerves is the axonal arborization of their endings that either extend into the space between epithelial cells or form a network-like plexus immediately beneath the basement membrane of the epithelium[27,28], suggesting a role for these afferents in regulating airway responses to inhaled irritants[29]. When these TRPV1-expressing nerve endings are activated by inhaled irritants or by endogenous TRPV1 activators, centrally mediated reflex responses are elicited, including reflex bronchoconstriction and mucus hypersecretion via the cholinergic pathway, accompanied by the sensation of airway irritation and the urge to cough. Activation of TRPV1 also triggers Ca2+ influx and release of tachykinins and CGRP from the sensory terminals. These sensory neuropeptides elicit the local axon reflexes, such as bronchoconstriction and protein extravasation[30]. Furthermore, somatostatin is released, which displays anti-inflammatory and antinociceptive actions. There is an increasing amount of evidence supporting the hypothesis that the expression, activation and modulation of TRPV1 in sensory neurons appears to be an integral component of the cough pathway, although the precise contribution of TRPV1 to human disease has yet to be determined[31-33]. In a bleomycin-induced scleroderma model in mice, activation of TRPV1 and release of CGRP exert protective actions against fibrosis[34]. We investigated the effects of orally administered TRPV1 agonists on leukocyte infiltration in LPS-induced acute lung injury and ovalbumin-induced allergic airway inflammation[35]. In LPS-induced lung injury, capsaicin and SA13353 attenuated neutrophil infiltration and the increase of TNF-α and cytokine-induced neutrophil chemoattractant (CINC)-1 levels. In allergic airway inflammation, SA13353 tended to inhibit leukocyte infiltration and attenuated the increase in IL-4 and IL-12p40. These results suggest that at least somatosensory TRPV1 may play an anti-inflammatory role in lung inflammation. Inducing the cough reflex and modifying airway inflammation may be important functions of TRPV1 in body homeostasis.

The physiological role of TRPV1 in autoimmune diseases

Current evidence for the role of TRPV1 in arthritis models is somewhat conflicting. Some groups have demonstrated that TRPV1 plays a potential role in acute and chronic inflammation in the knee joint[4,36]. In contrast, other groups have shown that a TRPV1 agonist[37] and somatostatin[38] attenuate knee joint inflammation. However, there have been no reports using the collagen-induced arthritis model, one of the most important autoimmune models for human rheumatoid arthritis. We investigated the effects of a TRPV1 agonist, SA13353, on the development of arthritis in collagen-induced arthritis in rats[15]. Post-onset treatment of SA13353 strongly reduced the hind paw swelling and joint destruction associated with collagen-induced arthritis. We believe one of the mechanisms behind the attenuation of arthritis development by SA13353 is the inhibition of TNF-α production from inflammatory cells that were exposed to neuropeptides released from TRPV1-expressing afferent C fibers. In experimental autoimmune encephalomyelitis (EAE), another important autoimmune model, agents activating cannabinoid and vanilloid receptors exhibit beneficial effects in rats[39]. We also investigated the effects of a TRPV1 agonist on the development of EAE in mice using SA13353[40]. SA13353 attenuated the clinical signs of EAE and associated histopathological changes, possibly by reducing inflammation in the spinal cord and cerebellum. We found that SA13353 also reduces the levels of a number of cytokines, including TNF-α, IL-1ß, IL-12p40, IL-17 and interferon (IFN)-γ. In addition, SA13353 attenuated the increase of IL-17 production in splenocytes, implying that SA13353 inhibits the growth of Th17 cells and the development of EAE. The attenuation of TNF-α, IL-1ß and IFN-γ levels by SA13353 may also help inhibit EAE. Further studies to clarify the role of TRPV1 in autoimmune diseases are necessary.

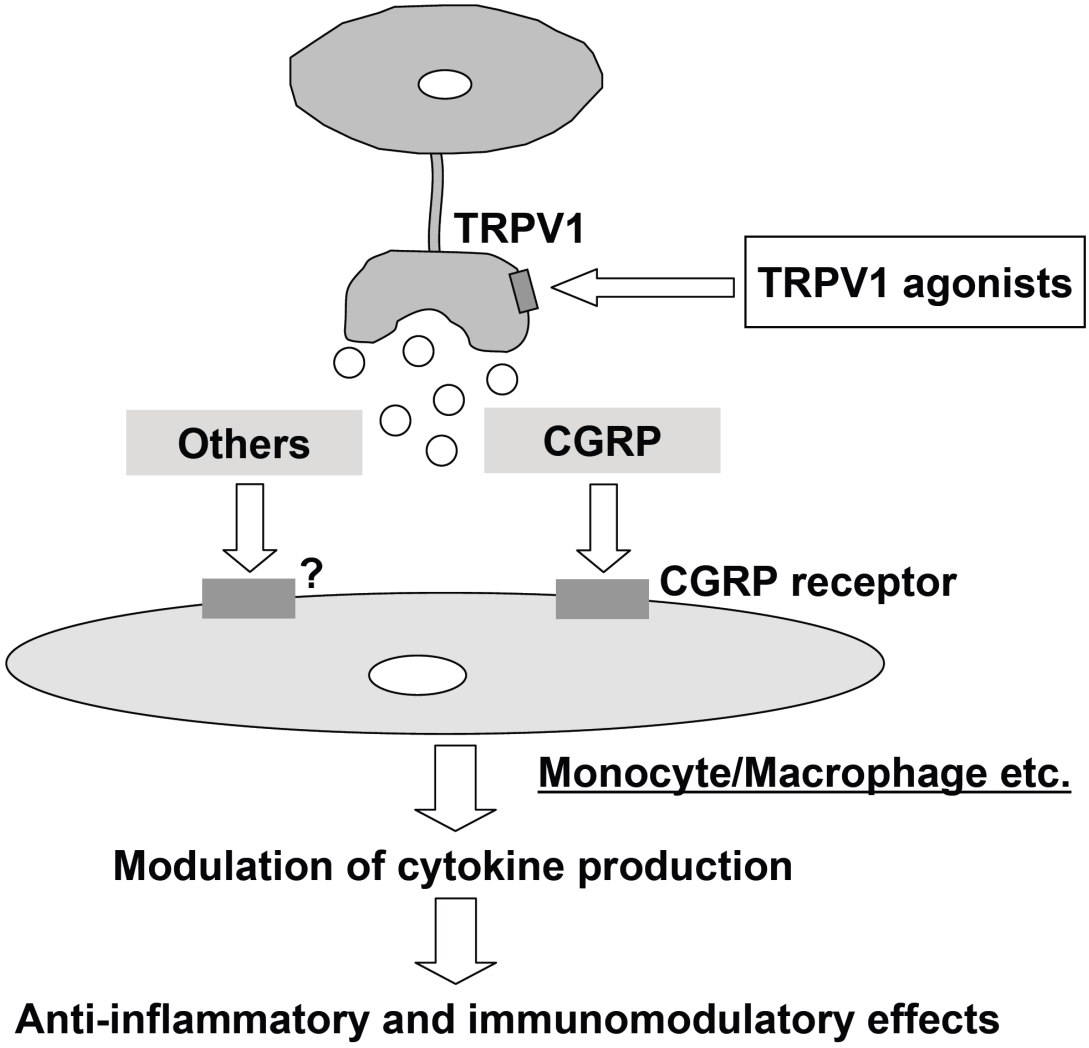

Fig. 1. Mechanism of the anti-inflammatory and immunomodulatory effects of SA13353.

Therapeutic potential of TRPV1 agonists

As mentioned above, TRPV1 agonists may act as anti-inflammatory and immunomodulatory agents in certain inflammatory diseases. We believe that TRPV1 agonists modulate cytokine production via neuropeptide release from afferent C fibers and show anti-inflammatory effects (Fig.1). With numerous studies suggesting that TRPV1 agonistic effects are associated with pain and inflammation[41], many pharmaceutical companies have developed TRPV1 antagonists[42]. However, many TRPV1 antagonists were withdrawn due to their potential to cause hyperthermia or due to the important physiological functions of TRPV1 in the peripheral and central nervous system[43]. Since the antagonist-induced hyperthermia is an on-target effect and a hurdle for the development of TRPV1 antagonists as therapeutics, future clinical trials of this class of molecules may include: i) a preference to develop TRPV1 antagonists with shorter half-lives; ii) co-dosing of antipyretic agents such as acetaminophen; and/or iii) exclusion of patients who are susceptible to frequent pyrexia[44]. Other efforts have targeted the optimization of TRPV1 agonist-based therapies, primarily to inactivate nociceptive nerve fibers[45]. Data from several Phase II studies of TRPV1 agonists indicate potential efficacy in pain relief associated with postherpetic neuralgia, diabetic neuropathy, osteoarthritis, bunionectomy, Morton's neuroma and post-sur-

gical pain following orthopedic surgery. Table 1 shows the current clinical trial status of TRPV1 agonists developed by different drug discovery companies. We have also identified another potential application of TRPV1 agonists; in the modulation of immune responses at doses lower than are required for nerve inactivation. Some of the effects of TRPV1 agonists observed to date and currently attributed to the inactivation of nociceptive nerve fibers may in fact be caused by their immunomodulatory effects. Should afferent C fibers indeed release a critical mediator associated with anti-inflammatory and immunomodulatory effects, it would serve as a target for the treatment of autoimmune diseases. We believe that such a finding justifies the re-evaluation of the value of TRPV1 agonists for clinical applications as analgesic and anti-inflammatory agents.

Table 1. Current clinical trial status of TRPV1 agonists developed by different drug discovery companies.

Compound name	Company	Route of administration	Indication	Stage
NGX-4010 (Qutenza)	NeurogesX	Patch formulation	Neuropathic Pain	Registerd
WL-1001 (Civanex)	Winston Labs	Topical cream	Osteoarthritis	Pre-Registered
4975 (Adlea)	Anesiva	Injection	Knee replacement	Phase III
SA13353	Santen	Oral	Rheumatoid arthritis	Phase II

Conclusion

TRPV1 agonists may act as anti-inflammatory agents *in vivo* in certain inflammatory diseases. Further studies to clarify the role of TRPV1 in inflammation are therefore necessary.

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