

## **Summary**

**Janos Szolcsányi**

### **Hot peppers, pain and analgesics**

Capsaicin, the hot component in chilli peppers due to its selective excitatory and desensitizing effects on polymodal nociceptors, has opened new horizons in the pharmacology of analgesics and antiinflammatory agents. A historical survey of the chain of discoveries that led to the cloning of the TRPV1 receptor, the first temperature-gated ion channel, is summarized. TRPV1 as an integrative, nociceptive membrane protein that serves as a target molecule for drug research. Structural differences in capsaicin and resiniferatoxin molecules for gating the TRPV1 ion channel are outlined. The importance of new functions of nociceptors discovered with the aid of capsaicin is emphasized. Neurogenic inflammation is mediated by tachykinins released from the capsaicin-sensitive nerve endings. Somatostatin released from these nociceptors induces systemic sensocrine antiinflammatory and analgesic effects.

**Key Words:** Capsaicin, capsazepine, history, neurogenic inflammation, nociception, polymodal nociceptor, preoptic area, resiniferatoxin, ruthenium red, sensocrine function, somatostatin, tachykinin, TRPV1, vanilloid receptor.

## **Summary**

**Makoto Tominaga**

### **Structural determinants of TRPV1 functionality**

The capsaicin receptor TRPV1 is predicted to have six transmembrane domains and a short, pore-forming hydrophobic stretch between the fifth and sixth transmembrane domains. Many regions and amino acids involved in TRPV1 functions (multimerization, capsaicin binding, proton actions, thermal sensitivity, desensitization, permeability, phosphorylation, and modulation by lipids) have been identified since the cloning of this receptor in 1997. Given the fact TRPV1 is a key molecule in peripheral nociception, these regions and amino acids could prove useful for the development of novel anti-nociceptive or anti-inflammatory agents.

**Key Words:** Agonist binding, desensitization, multimerization, permeability, phosphorylation, sensitization.

## **Summary**

**Janet Winter**

### **TRPV1 distribution and regulation**

TRPV1 protein is distributed widely throughout the peripheral nervous system, in sensory neuron cell bodies, in nerves and nerve terminals supplying peripheral target organs and in central afferent terminals in the spinal cord. It is now also known to be expressed in intrinsic cells of the central nervous system and outside the nervous system in epithelial cells in tissues such as gut, skin, lung and bladder. Depending on the cell type and location of TRPV1, this non-selective cation channel may not only play a role in somatic and visceral pain sensation, headaches and migraine, but also contribute to regulation of cough, apoptosis and cardiac reflexes, and in some cases may have protective, trophic actions.

## **Summary**

**Peter M. Blumberg, Derek C. Braun, Noemi Kedei, Jozsef Lazar, Vladimir Pavlyukovets, Larry V. Pearce**

### **Insights into TRPV1 pharmacology provided by non-capsaicin ligands**

The identification of resiniferatoxin, a natural product derived from *Euphorbia resinifera*, has helped drive the on-going robust medicinal chemical effort into research on capsaicin. Resiniferatoxin showed that it was possible to greatly enhance potency and to dissociate activity for different biological endpoints, such as pungency and desensitization. Resiniferatoxin further made possible for the first time the identification and characterization of the capsaicin receptor through radioligand-binding assays. A great diversity of pharmacological opportunities in the capsaicin field is now emerging. Compounds with somewhat diverse structures, both natural and synthetic, show high affinity as capsaicin analogs. Substantial species differences in structure-activity relations, correlated with differences in capsaicin receptor (TRPV1) sequences, have been defined. Multiple patterns of response of TRPV1 to diverse ligands have been described. Multiple modulators of the function of TRPV1 are being identified. Distinct functions and structure-activity relations for TRPV1 depending on its cellular location have been suggested. For the capsaicin receptor, as with many other therapeutic targets, natural products have led the way in drug discovery.

**Key Words:** Agonist, antagonist, calcium uptake, capsaicin, partial agonist, phorbol ester, resiniferatoxin, TRPV1.

## **Summary**

**Ruth A. Ross**

### **Endocannabinoids and vanilloid TRPV1 receptors**

*N*-Arachidonoyl-ethanolamide (anandamide) is known as an endocannabinoid, as defined by its ability to be produced endogenously and to bind to and activate cannabinoid CB<sub>1</sub> and CB<sub>2</sub> receptors. Since its discovery, anandamide has been shown to have numerous physiological actions that encompass cardiovascular, immune, gastrointestinal, and nervous systems. The pharmacology of anandamide is complex, its actions being mediated by cannabinoid CB<sub>1</sub> and CB<sub>2</sub> receptors and by putative non-CB<sub>1</sub>, non-CB<sub>2</sub> receptors. The search for endogenous TRPV1 receptor activators, or endovanilloids, is on-going and recent advances suggest that anandamide may be one such compound. A large body of evidence now exists to substantiate that certain endocannabinoids activate TRPV1 receptors. Anandamide and *N*-arachidonoyl-dopamine (NADA) appear to be low-intrinsic-efficacy TRPV1 agonists, behaving as partial agonists in tissues with low receptor reserve; whereas, in tissues with high receptor reserve and in circumstances associated with certain disease states, they behave as full agonists. Recent findings indicate that the apparent low efficacy of anandamide and NADA in certain circumstances may be due to limited access to the intracellular environment. When released intracellularly, anandamide activates TRPV1 receptors in the same concentration range at which it is known to activate the CB<sub>1</sub> receptor.

**Key Words:** Anandamide, cannabinoid, CB<sub>1</sub>, endocannabinoid, NADA, TRPV1.

## **Summary**

**Zoltán Sándor and Arpad Szallasi**

### **Vanilloid receptor-mediated hyperalgesia and desensitization**

Capsaicin is unique among the naturally occurring irritant compounds in that the initial excitation it causes is followed by a lasting refractory state in which the previously stimulated neurons are resistant not only to capsaicin but also to unrelated stimuli. This refractory state is traditionally referred to as desensitization. Capsaicin evokes these actions by interacting at its receptor, TRPV1. TRPV1 is a molecular integrator of noxious stimuli (heat, acids, etc.); also, it is a target for pro-inflammatory agents produced during tissue damage. There is a large body of evidence indicating that both sensitization and hyperalgesia involve complex intracellular mechanisms including: (1) dynamic changes in TRPV1 phosphorylation by protein kinases and phosphatases; (2) recruitment of TRPV1 from intracellular stores; (3) changes in the transcription of the TRPV1 gene; and (4) novel expression of TRPV1 on nerves that do not normally express this receptor. Sensitization of TRPV1 by phosphorylation is particularly interesting in that it links TRPV1 to the actions of common algescic/pro-inflammatory substances like bradykinin and nerve growth factor. The border between reversible desensitization and irreversible neurotoxicity is, however, not well-defined. The focus of this chapter is on recent advances in our understanding of mechanisms underlying TRPV1-mediated hyperalgesia and desensitization.

**Key Words:**  $\text{Ca}^{2+}$ -calmodulin complex, capsaicin, dephosphorylation, desensitization, kinase, neurotoxicity, phosphatase, phosphorylation, resiniferatoxin, RTX, sensitization, transient receptor potential channel, TRPV1, vanilloid subfamily member 1.

## **Summary**

**Lars Arendt-Nielsen and Ole K. Andersen**

### **Capsaicin in human experimental pain models of skin, muscle and visceral sensitization**

This chapter will focus on the assessment of hyperalgesia and specifically describe how hyperalgesia can be induced in a standardized way by capsaicin. Moreover, the stimulation and assessment methods available to evaluate quantitatively the different aspects of capsaicin-induced hyperalgesia will be reviewed. The majority of studies have focused on topical and intradermal applications, whereas only few experimental studies have applied capsaicin intramuscularly or to the viscera. Experimental investigations of peripheral and central aspects of capsaicin-induced hyperalgesia may increase the knowledge associated with diseases such as neuropathic pain. In this chapter capsaicin-induced cutaneous, muscular and visceral hyperalgesia are described separately.

**Key Words:** Capsaicin, C-fibers, human pain model, hyperalgesia, muscle, neuralgia, skin, TRPV1, viscera.

## **Summary**

**Peter Holzer**

### **TRPV1 in Gut Function, Abdominal Pain and Functional Bowel Disorders**

Capsaicin, the pungent ingredient in red pepper, has been used since ancient times as a spice, despite the burning sensation associated with its intake, and traditional medicine has relied on red pepper to stimulate appetite, cure indigestion and relieve ulcer pain. Following the

neuropharmacological characterization of its action, capsaicin proved to be a most valuable tool to probe the roles of primary sensory neurons in digestive activity. Its receptor, TRPV1, is expressed by vagal and spinal afferent neurons supplying the gastrointestinal tract. In addition, TRPV1-like immunoreactivity has been described to occur in enteric neurons and epithelial cells of the gut. In view of its unique properties as a polymodal nociceptor that can be sensitized by acidosis and other painful stimuli, TRPV1 is envisaged as an important factor in gastrointestinal pain. Up-regulation of TRPV1 in abdominal hypersensitivity and the beneficial effect of TRPV1 down-regulation in functional dyspepsia and irritable bladder make this nociceptive ion channel an attractive target for novel therapies of gastrointestinal inflammation and hyperalgesia. However, TRPV1 blockers may not only dampen hyperalgesia but also compromise gastrointestinal mucosal protection.

**Key Words:** Abdominal hyperalgesia, capsaicin, dorsal root ganglia, enteric neurons, epithelial cells, functional bowel disorders, functional dyspepsia, gastrointestinal tract, irritable bowel syndrome, mucosal blood flow, mucosal protection, nodose ganglia, primary afferent neurons, TRPV1, visceral nociception.

### **Summary**

**Maria G. Belvisi and Peter J. Barnes**

#### **TRPV1 in the airways**

Sensory nerves in the airways regulate central and local reflex events, such as bronchoconstriction, airway plasma leakage, mucus secretion and cough. Sensory nerve activity may be enhanced during inflammation such that these protective reflexes become exacerbated and deleterious. A characteristic feature of many nociceptive sensory fibres is their sensitivity to capsaicin. However, until recently the molecular mechanism involved in activation of sensory nociceptive fibres was unknown. The capsaicin receptor has recently been identified and has been named the type 1 vanilloid receptor (VR1; or TRPV1). It has previously been suggested that there is an up-regulation of TRPV1 expression in inflammatory diseases and that inappropriate activation of this receptor may lead to sensory nerve hyper-responsiveness or hyperaesthesia. Thus it would appear that airway inflammatory diseases (e.g. asthma and chronic obstructive pulmonary disease) and chronic cough may respond to treatment with effective and selective inhibitors of TRPV1, and to this end much work is being carried out to develop novel inhibitors.

**Key Words:** A $\delta$ -fibres, airway, asthma, capsaicin, C-fibres, chronic obstructive pulmonary disease, COPD, cough, lung respiratory, nerve growth factor, neurotrophins, sensory nerves, TRPV1.

### **Summary**

**Keith R. Bley and Annika B. Malmberg**

#### **TRPV1 agonist-based therapies: mechanism of action and clinical prospects**

Capsaicin and related pungent molecules have been used as topical treatments for a variety of pain syndromes for many centuries. The initial effect of topical capsaicin is the activation of nociceptive sensory neurons, via agonist activity at TRPV1, resulting in a burning sensation, erythema and an increased sensitivity to painful stimuli. However, after prolonged exposure, there is a decrease in the sensitivity not only to capsaicin, but also to heat and noxious stimulation. The pain-relieving effect of topical capsaicin treatments appears to correlate with

reduced sensitivity of cutaneous nociceptors to thermal stimuli and a decrease of immunohistochemical markers for the peripheral endings of small-diameter afferent nerves. Although systemic TRPV1 agonist-based therapies are unlikely to be viable – as the side-effect profile of widespread nociceptor desensitization is unlikely to be acceptable – optimized TRPV1 agonist-based therapies directed to discrete regions or organs may emerge as an effective treatment to control localized pain or inflammation.

**Key Words:** Capsaicin, C-fibers, epidermal nerve fibers, desensitization, inflammation, nerve growth factor, neuropathy, NGF, nociceptors, PGP 9.5, TRPV1, vulvodynia.

## **Summary**

**Francisco Cruz, Carlos Silva and Paulo Dinis**  
**TRPV1 agonist therapies in bladder diseases**

Experimental and clinical data indicate that high urinary frequency, urge and urge incontinence occurring in patients with neurogenic and non-neurogenic forms of overactive bladder depend upon the facilitation of a capsaicin-sensitive spinal micturition reflex, usually inactive in normal adults. Intravesical application of capsaicin or resiniferatoxin in these patients has proven effective in ameliorating urinary symptoms and decreasing involuntary bladder contractions. In addition, some evidence suggests that intravesical TRPV1 agonists may decrease bladder pain in patients with bladder hypersensitive disorders. Intravesical TRPV1 agonists may work through a decreased expression of several C-fiber receptors, namely TRPV1 and P2X3.

**Key Words:** Bladder, bladder outlet obstruction, capsaicin, intravesical treatment, overactive bladder, resiniferatoxin, spinal-cord injury, TRPV1.

## **Summary**

**Kenneth J. Valenzano, James D. Pomonis and Katharine Walker**  
**TRPV1 antagonists and chronic pain**

The small-molecule TRPV1 agonist, capsaicin, is currently used for a number of painful clinical syndromes, including intractable neuropathic pain, osteoarthritis and pruritus. To date, TRPV1 antagonists have yet to reach the clinic as pain therapeutics. While the classic TRPV1 antagonist, capsazepine, has proven useful to better understand the molecular pharmacology of TRPV1, *in vivo* studies with this compound have had limited success due to poor pharmacokinetic properties and species-selectivity issues. With the cloning of TRPV1 in 1997, the pharmaceutical industry has been provided with a molecular target for small-molecule drug discovery. As a result, resurgence in the interest of TRPV1 antagonists has given way to many new pharmacological agents that may provide better tools for unraveling the role of TRPV1 in chronic pain states. This review will focus on the most recent TRPV1 antagonists, their molecular pharmacology and *in vivo* activity in animal models of chronic pain.

**Key Words:** Antagonist, arthritis, BCTC, capsaicin, capsazepine, chronic pain, inflammatory pain, neuropathic pain, resiniferatoxin, ruthenium red, SC0030, TRPV1.

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