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Themed Section: The pharmacology of TRP channels

EDITORIAL

The pharmacology of TRP channels

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This themed issue of the *British Journal of Pharmacology* contains review and research articles on recent advances in transient receptor potential (TRP) channel pharmacology. The review articles, written by a panel of distinguished experts, address the rapid progress in TRP channel research in fields as diverse as oncology, urology, dermatology, migraine, inflammation and pain. These reviews are complemented by original research reports focusing, among others, on the emerging roles of TRPV1 in osteoporosis and cystitis and on evodiamine as a lead structure for the development of potent TRPV1 agonists/desensitizers. Other papers highlight the differences in TRPV3 pharmacology between recombinant and native systems, the mechanisms of TRPM3 activation/inhibition and TRPP2 as a target of naringenin, a dietary flavonoid with anticancer actions. New therapeutic opportunities in pain may arise from the strategy to combine TRP channel and cell membrane impermeant sodium channel blockers to inhibit sensory nerve activity.

LINKED ARTICLES

This article is part of a themed section on the pharmacology of TRP channels. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-10

Abbreviations

CXCR2, chemokine CC motif receptor 2; TRP, transient receptor potential; TRPA, TRP channel subfamily A; TRPC, TRP channel subfamily C; TRPM, TRP channel subfamily M; TRPP, TRP channel polycystin subfamily; TRPV, TRP channel subfamily V

The transient receptor potential (TRP) cation channel superfamily is classified into six related subfamilies: the TRP channel subfamily C (canonical, TRPC), the TRP channel subfamily V (vanilloid, TRPV), the TRP channel subfamily M (melastatin, TRPM), the TRP channel subfamily A (ankyrin, TRPA), the TRP channel polycystin subfamily (TRPP) and the TRP channel mucolipin subfamily (Moran *et al.*, 2011; Fernandes *et al.*, 2012). The TRPs are, in general, non-selective cation channels that open in response to changes in temperature, ligand binding and other alterations of the channel protein, but are only weakly sensitive to depolarization (Vay *et al.*, 2012). Animal and human genetic studies have shown that alterations in TRP channel functions – in a pathological context known as TRP channelopathies – are causative for a variety of diseases, such as inherited pain syndrome, multiple kidney diseases and skeletal muscle disorders (Moran *et al.*, 2011).

In this themed issue, we have brought together a number of informative reviews depicting and discussing some of the basic and clinical concepts that emerge from the current TRP channel research. Since the identification of the first mammalian TRP channels in the 1990s, these entities have been addressed as potential targets for drugs, and Kaneko and Szallasi (2014) review the current status of TRP channels from a clinical perspective. Despite accumulating evidence to implicate a number of TRP channels in a wide range of diseases, only 4 of the 28 mammalian TRP channel subunits, namely TRPM8, TRPA1, TRPV1 and TRPV3, have been exploited so far to reach the clinical stage of drug development. One of the substantial drawbacks associated with the

use of TRP ligands is that, due to their wide distribution, activation or inhibition of TRP channels may be beneficial in one organ but at the same time may induce unacceptable adverse effects in another (Holzer, 2008; Kaneko and Szallasi, 2014). As an example, the clinical development of first-generation TRPV1 antagonists was halted because they caused hyperthermia and elevated the heat pain threshold. The article by Kaneko and Szallasi also points out that TRP channels are primary targets for a number of plant-derived products with therapeutic potential. For example, TRPV1 is activated by capsaicin (from hot chilli and other red pepper variants), TRPA1 by allylisothiocyanate (from *Brassicaceae* plants) and the phytocannabinoid cannabichromene, and TRPM8 by menthol. It should not be overlooked, however, that plant-derived ligands very often exert pharmacological effects that are independent of TRP channel activation (Mori *et al*., 2011; Capasso *et al*., 2012; Izzo *et al*., 2012; Bartho *et al*., 2013; Romano *et al*., 2013a). The complex pharmacology of TRP ligands emphasizes the importance of using genetically modified mice to demonstrate response specificity.

TRP channels constitute the largest group of transducer molecules thus far known to be involved in the generation of pain sensation in mammals. Sousa-Valente *et al*. (2014) review the role of TRP channels expressed by primary sensory neurons in the development of pain associated with peripheral pathologies and the possible approaches to translate preclinical data to the development of effective new analgesics. Two possible strategies can be pursued to achieve pharmacological inhibition of pain, the first being the use of receptor antagonists or channel pore blockers. The second strategy is to build on desensitizing agents, in a manner similar to the ability of capsaicin to desensitize TRPV1. However, the potential downside of desensitizing compounds is their propensity to cause, initially, irritation and the requirement of multiple applications. Because there are several activation and sensitization sites in nociception-related TRP channels, inhibiting the activation of the channel is more difficult to achieve than inducing desensitization.

Another review article (Blackshaw, 2014) focuses on visceral sensory pathways that exhibit a particularly abundant supply with TRP channels and for this reason have been subjected to extensive physiological and pharmacological investigations (Holzer, 2011). The take-home message is that TRP channels appear to be of special importance for the function of visceral sensory pathways, which makes them interesting targets for drug development. Although there are robust preclinical data on a variety of TRP channels, including TRPA1, TRPV1, TRPV4 and TRPM8, TRPV1 still represents the only TRP subunit that is clinically targeted in the treatment of sensory bladder dysfunction (Blackshaw, 2014).

Historically, the bladder was the first organ in which a TRP channel ligand was clinically tested. Already several years before the cloning of the first TRP channel gene, intravesical capsaicin instillations were used for the management of neurogenic detrusor overactivity. Since then it has been well established that, in the urinary bladder, TRP channels are densely expressed in, but not restricted to, primary afferent neurons (Avelino *et al*., 2013). Building on these advances, Franken *et al*. (2014) review those TRP channels whose relevance in urology has been clearly defined. Because TRP channels are probably the main molecular sensors that generate bladder sensation, they represent an intriguing target for the development of drugs to be used in lower urinary tract dysfunctions. Research with genetically modified animals and pharmacological tools reveals a crucial role of TRPM8, TRPA1 and TRPV4 in bladder pathophysiology. The current clinical research efforts in the TRP channel field have a particular focus on neurogenic pain treatment and, specifically, address the development of selective antagonists for urological pain syndromes such as painful bladder syndrome and interstitial cystitis.

Migraine and headache are global disabling conditions causing extensive individual suffering, impaired quality of life and working time loss (Wöber-Bingöl, 2013). TRPA1 emerges as an important relay in this disorder, given that TRPA1 activity impacts on cerebral circulation (Earley, 2012) and pain sensitivity. Benemei *et al*. (2014) review the available evidence that identifies TRPA1 as a major contributing factor in migraine pathogenesis and as an emerging target for drug development. Their review presents several fascinating aspects of the TRPA1-migraine connection. For instance, certain foods or exposure to environmental irritants such as chlorine, cigarette smoke, formaldehyde and others – which may provoke migraine-type headaches – can target the TRPA1 subunit. Other enthralling hints portraying a key role of TRPA1 in headache came from the plant kingdom. Thus, the monoterpene ketone umbellulone, isolated from the Californian bay laurel (*Umbellularia californica*) – also known as the 'headache tree' because the inhalation of its vapours can cause severe headache crises – evokes TRPA1-mediated and calcitonin gene-related peptide-dependent neurogenic meningeal vasodilation (Nassini *et al*., 2012). Furthermore, parthenolide, the active ingredient of *Tanacetum parthenium*, a herbal remedy promoted for the prevention of migraine attacks and alleviation of the accompanying symptoms, desensitizes the TRPA1 channel and abrogates nociceptive responses evoked by stimulation of peripheral (meningeal) trigeminal nerve endings (Materazzi *et al*., 2013). Because TRPA1 is activated or sensitized by some migraine triggers and inhibited by analgesic and antimigraine medicines, these TRP channels present themselves as important target for novel drugs to treat migraine and associated primary headaches.

The skin represents probably the most relevant example of an organ in which TRP channels are found not only on sensory neurons, but are also functionally expressed by non-neuronal cell types. Tóth *et al*. (2014) review the emerging evidence that attributes these non-neuronal TRP channels various roles in the regulation of cutaneous functions such as homeostasis, growth control, cell fate and survival as well as immune and inflammatory processes, and describe their emerging implications in widespread skin diseases such as atopic dermatitis, acne vulgaris, hair growth disorders, psoriasis, cutaneous melanoma and non-melanoma cancers. A plethora of robust preclinical data invites clinical studies aiming at the exploitation of the TRP channel superfamily as drug target for skin disorders.

Gautier *et al*. (2014) discuss the accumulating evidence for the expression of TRP channels by cancer cells and tissues; their role in many malignant processes including cell differentiation, apoptosis, angiogenesis, migration and invasion during cancer progression; and the effect of drugs targeting TRP channels in experimental tumour models. It comes quite

as a surprise that a multitude of subunits among the TRPC, TRPV and TRPM subfamilies as well as TRPA1 appear to be involved in various cancer types ranging from glioma, breast, gut, head and neck cancers to lung and prostate cancers. Their widespread expression by cancer cells even led to considering TRP channels as tools for malignant tumour diagnosis and/or prognosis. For example, TRPM8 has been proposed as marker for prostate cancer progression and outcome. In addition, pharmacological TRP channel targeting may have a place in treating cancer-related pain. Although this field of study is undoubtedly rewarding, the relationship between TRP channels and cancer remains a controversial area of research (Kaneko and Szallasi, 2014).

TRP channels are widely distributed in the respiratory tract in which they have both physiological and pathological implications. Grace *et al.* (2014) review the existing data on the role of TRP channels in the airways, with a specific focus on the pathogenesis and symptoms of asthma and chronic obstructive pulmonary disease. In these disorders, TRPA1, TRPV1, TRPV4 and TRPM8 are the TRP subunits that have been explored most thoroughly (Grace *et al.*, 2014). Because TRP channels represent an important part of the pulmonary defence systems and are crucial to the pathogenesis of respiratory diseases, they emerge as molecular targets for novel drug candidates to manage airway diseases. The patent literature highlights TRPA1 and TRPV1 channels as the most advanced therapeutic targets in respiratory disorders, with promising data put forward on the use of TRPA1 (and possibly TRPV1) blockers as anti-tussive/anti-asthma drug candidates (Preti *et al.*, 2012). In addition, TRPV1 has been recently proposed as being crucial in initiating symptoms of rhinitis (Changani *et al.*, 2013).

The review articles represent one core of this themed issue and are complemented by eight original articles that further illuminate the relevance of TRP channel pharmacology. De Petrocellis *et al.* (2014) highlight the importance of chirality and lipophilicity in the functional activity of the TRPV1 agonist evodiamine, a quinazolinocarboline alkaloid isolated from the traditional Chinese medicine *Evodiae fructus*. Owing to its chemical and biological properties, evodiamine represents a useful starting point in the development of new and potent TRPV1 agonists/desensitizers. Using a multidisciplinary approach that includes biochemical, pharmacological and morphological analyses, Rossi *et al.* (2014) provide clear, convincing and elegant evidence for a role of TRPV1 channels in bone resorption. Both genetic deletion of TRPV1 and its pharmacological inhibition/desensitization are able to reduce osteoclast activity *in vitro* and to prevent experimentally induced bone loss in mice *in vivo*. A further study depicts the pivotal role of TRPV1 and chemokine CC motif receptor 2 (CXCR2) in a rat model of cystitis induced by cyclophosphamide (Dornelles *et al.*, 2014). TRPV1 and CXCR2 are up-regulated in the inflamed bladder, and selective TRPV1 or CXXR2 antagonists ameliorate cyclophosphamide-induced inflammation.

TRPV3 represents an attractive pharmacological target in inflammatory and neuropathic pain as well as in skin diseases (Moran *et al.*, 2011; Vay *et al.*, 2012). Grubisha *et al.* (2014) developed medium-throughput recombinant and native cellular assays to assess the detailed pharmacological profile of human, rat and mouse TRPV3 channels. Their findings illustrate both similarities and differences in TRPV3 pharmacology between recombinant and native systems, an issue that is of high relevance in the design and choice of drug candidates for further development.

Two research papers deal with the mechanism of activation or inhibition of TRPM3, another TRP subunit involved in pain perception. Using transcriptional assays as an index of TRPM3 activation or inhibition, Lesch *et al.* (2014) present the first comparative analysis of putative TRPM3 activators and inhibitors in TRPM3-regulated gene transcription. Pregnenolone sulphate is shown to be a powerful activator of TRPM3-mediated gene transcription, whereas mefenamic acid is an inhibitor. These drugs could serve as important tools in future studies of the biological functions of TRPM3. In a different study, Drews *et al.* (2014) characterize the steroid binding site of TRPM3 by analysing the structural and chemical requirements of TRPM3 activation.

Flavonoids are a class of plant polyphenolic compounds that are consumed in large amounts in the daily diet (Romano *et al.*, 2013b). In an attempt to characterize flavonoid effects on TRP channels, Waheed *et al.* (2014) used the slime mould *Dictyostelium* as a cell proliferation model to investigate the molecular mechanisms of action of naringenin, a dietary flavonoid with anticancer actions, and found that TRPP2 mediates the growth inhibitory effects of this flavonoid. Other papers published previously in the *British Journal of Pharmacology* reported that certain dietary flavonoids may activate or block other members of the TRP channel superfamily, in particular TRPV4 and TRPM3 (Ma *et al.*, 2012; Straub *et al.*, 2013). Finally, Brenneis *et al.* (2014) screened caine-type compounds for their ability to activate TRP channels in dorsal root ganglion neurons and found bupivacaine to be the most potent activator. When combined with QX-314 (a cell membrane-impermeant sodium channel blocker), bupivacaine produced a long-lasting blockade of sensory nerve activity.

Overall, this themed issue highlights some of the rapid and significant advances that may facilitate the translation of basic TRP channel research to clinical application. Intimately related to these pharmacological aims, unravelling the physiological and pathophysiological implications of TRP channels continues to be an active area of research, pinpointing the clinical indications and opportunities of TRP-related therapy. The potential of such therapies is continuously expanding as TRP channels emerge as important factors in several highly prevalent pathologies including inflammation, pain and cancer. The biology and pharmacology of TRP channels is overtly complex, which represents both a challenge and a chance for their exploitation as pharmacological targets. For us as editors it has been highly rewarding to witness and guide some of the recent advances in this field into a special issue of the *British Journal of Pharmacology*. Hopefully, this collection of articles will bolster our knowledge and understanding of TRP channel pharmacology and stimulate further research and development in this area.

Conflict of interest

The authors declare that they have no conflict of interest.

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