Drugs Affecting TRP Channels

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Abstract

Chronic obstructive pulmonary disease (COPD) and asthma are both common respiratory diseases that are associated with airflow reduction/obstruction and pulmonary inflammation. Whilst drug therapies offer adequate symptom control for many mild to moderate asthmatic patients, severe asthmatics and COPD patients symptoms are often not controlled, and in these cases, irreversible structural damage occurs with disease progression over time. Transient receptor

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potential (TRP) channels, in particular TRPV1, TRPA1, TRPV4 and TRPM8, have been implicated with roles in the regulation of inflammation and autonomic nervous control of the lungs. Evidence suggests that inflammation elevates levels of activators and sensitisers of TRP channels and additionally that TRP channel expression may be increased, resulting in excessive channel activation. The enhanced activity of these channels is thought to then play a key role in the propagation and maintenance of the inflammatory disease state and neuronal symptoms such as bronchoconstriction and cough. For TRPM8 the evidence is less clear, but as with TRPV1, TRPA1 and TRPV4, antagonists are being developed by multiple companies for indications including asthma and COPD, which will help in elucidating their role in respiratory disease.

Keywords
'Chronic obstructive pulmonary disease' (COPD) • 'Transient receptor potential' (TRP) • Asthma • Cough • TRPA1 • TRPM8 • TRPV1 • TRPV4

1 Transient Receptor Potential Channels

Transient receptor potential channels are a superfamily of 28 transmembrane cation permeable channels that can be subdivided into seven families – namely, TRP ankyrin (TRPA), canonical (TRPC), melastatin (TRPM), mucolipin (TRPML), NOMPC (TRPN), polycystin (TRPP) and vanilloid (TRPV) – on the basis of sequence homology. With the exception of TRPN channels, which have only been detected in fish, 27 of these ion channels spanning the other six TRP families are expressed in mammals.

In general, TRP channels share certain properties, namely, they are generally Ca^{2+}-preferring cation channels (albeit with varying selectivities), and possess six transmembrane domains with a pore region between the fifth and sixth transmembrane regions (Clapham 2005; Szallasi et al. 2007). Collectively, the TRP ion channel family form an array of cellular sensors for a huge range of endogenous and exogenous chemical and physical stimuli, and their ability to coordinate and integrate a spectrum of physiological stimuli has implicated them with key roles in the pathogenesis of many mammalian diseases. For the purposes of this chapter, we will focus on those TRP channels that have been heavily implicated with roles in asthma and chronic obstructive pulmonary disease (COPD), namely, TRPA1, TRPV1, TRPV4 and TRPM8. We will first briefly summarise the characteristics of COPD and asthma. The structural and functional properties of each TRP channel will then be briefly discussed, along with the evidence for the channels involvement in asthma and/or COPD. Then the drugs affecting that channel will be highlighted, with a particular emphasis on those drugs currently in, or aimed for, clinical trials. Finally the fortunes of current TRP channel drug development will be summarised, and the future merits and prospects of TRP channel drug development will be considered.

1.1 COPD

Chronic obstructive pulmonary disease (COPD) is a prevalent and debilitating respiratory disease with associated systemic comorbidities. It is a leading cause of death and disability worldwide, and disease incidence is predicted to continue increasing, such that COPD is predicted to be the third leading cause of death by 2020 (Vestbo et al. 2013). COPD is characterised by irreversible and progressive reduction of airflow, measured as a decline in lung function through spirometry (Barnes and Stockley 2005; Rabe et al. 2007; Paredi et al. 2010). Current treatments provide essentially only moderate symptomatic relief and do not halt progression of the disease (Barnes 2013). The airflow limitation in COPD is accompanied by an abnormal inflammatory response to noxious inhaled particulates or gases, for example, tobacco smoke, which is thought to be one of the primary causative agents for the initiation of COPD (Barnes and Stockley 2005; Rabe et al. 2007; Salvi and Barnes 2009). Typically such exposures must take place over a long duration before the symptoms of COPD appear – hence most diagnoses of COPD are made when patients are in middle age.

Chronic cough is often one of the first complaints that patients present with prior to a diagnosis of COPD: such that the recent GOLD strategy for diagnosis, management and treatment of COPD notes that patients presenting with chronic cough accompanied by a decline in actual compared to predicted spirometry values should be considered for a diagnosis of COPD (Vestbo et al. 2013). Indeed, cough was found to be the most commonly experienced symptom, as reported by 70% of 3,265 COPD sufferers interviewed, and occurring daily in 46% of the same population (Rennard et al. 2002).

One of the primary characteristics of COPD is an abnormal inflammation of the airways that is unresponsive to standard anti-inflammatories, including the gold-standard treatment of corticosteroids (Barnes 2013). It is thought that chronic exposure to noxious gases/particles drives inflammation in the lungs (Decramer et al. 2012). Cigarette smoke (CS), for example, stimulates multiple pulmonary immune cells (in particular macrophages, but also neutrophils, and $CD4^+$ Th1 and $CD8^+$ Tc lymphocytes) to release many inflammatory mediators, which recruits further inflammatory cells (in particular neutrophils, but also macrophages and $CD4^+$ Th1 and $CD8^+$ Tc lymphocytes) to the airways (Barnes 2008). It is thought that this positive feedback loop, along with repeated stimulation provided by chronic CS exposures, drives a persistent and progressive inflammation. This inflammation, along with exposure to the damaging components of CS, causes destruction of the alveolar structure and enhances mucus production (via goblet cell hyperplasia and hypertrophy) and fibrosis, resulting in reduction in the surface area for gas exchange, reduced elastic recoil and increased airflow obstruction (Hogg et al. 2004; Barnes 2008; Lai and Rogers 2010). The exact proportion of these structural changes may vary between patients, as COPD is an umbrella term that covers several interrelated lung diseases, including chronic bronchitis, small airway disease (SAD) and emphysema (Barnes 2004; Sturton et al. 2008). Whatever the

proportion in an individual patient, these inflammatory-driven structural changes contribute to the reduction in airflow, as assessed by spirometry.

1.2 Asthma

Defining asthma is somewhat difficult, as there is no single definitive genetic or environmental cause or trigger for development of this disease (Hargreave and Nair 2009). However, broadly speaking, asthma is a chronic inflammatory disease of the airways, characterised by sudden but transient decreases in airflow associated with dyspnea, cough and wheeze, which are generally fully reversible by bronchodilator treatment (Morosco and Kiley 2007). It has been estimated that 300 million people worldwide may suffer from asthma, with the highest incidences in the Americas, Europe and Australia of 5–10% of the population (Masoli et al. 2004).

Sudden bronchospasm of airway smooth muscle in asthmatics ('asthma attack') causes breathlessness and wheeze. Bronchospasm may be triggered by many stimuli, which in normal subjects would be innocuous, including dust and other allergens, pollen, air pollution, exercise and cold air (Eder et al. 2006). This airway hyperresponsiveness (AHR) is driven either by chronic airway inflammation and/or structural changes to the airways induced by this inflammation (Lommatzsch 2012). Whilst the chronic inflammation in asthma also involves an abnormal activation of multiple immune cells, it is different from the inflammation observed in COPD in that in the majority of asthmatics it is suppressed by anti-inflammatory therapy and involves different cell types, including $CD4^+$ Th2 cells, mast cells and eosinophils (Barnes 2008).

2 TRPV1

TRPV1 is well known as the receptor responsible for the perception of heat, particularly so for mediating the 'spicy hot' effects of capsaicin, the active constituent of chilli peppers from piquant *Capsicum* spp. plants, which activates TRPV1 on sensory nerves (Caterina et al. 1997). However, TRPV1 is a polymodal receptor, responding to capsaicin, its ultra-potent structural analog resiniferatoxin, and also xenobiotics, noxious heat (>42°C), acidic conditions/protons (low pH), as well as endogenous agents such as anandamide and inflammatory eicosanoids such as bradykinin and PGE_2 (Fig. 1) (Caterina et al. 1997; Vriens et al. 2009; Grace et al. 2012). Some of these agents, such as capsaicin, heat, acid and anandamide, activate TRPV1 via a direct interaction with the channel to cause a lowering of its voltage dependency, leading to opening of the pore domain (Caterina et al. 1997; Zygmunt et al. 1999; Jordt et al. 2000; Vriens et al. 2004). By contrast, other activators of the channel, such as PGE_2 and bradykinin, act indirectly by second messengers, in these cases released subsequent to activation of G-protein-coupled receptors (respectively the B_2 and EP_3 receptors) (Maher et al. 2009; Grace et al. 2012).

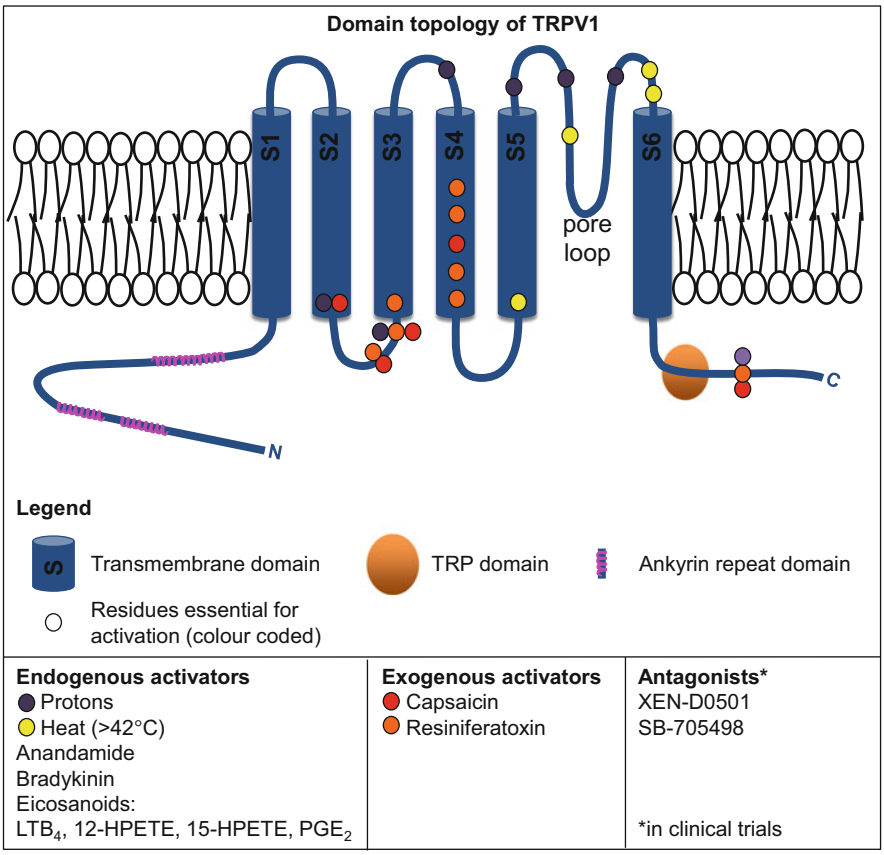

Fig. 1 Diagram showing domain topology and residues important in activation of TRPV1, along with selected endogenous/exogenous TRPV1 activators and TRPV1 antagonists in clinical trials for respiratory indications (Szolcsányi and Sándor 2012)

2.1 TRPV1 Roles in Airway Disease

TRPV1 receptors are predominantly expressed in the peripheral nervous system and, relevant to the control of airway functions, in a subset of vagal (both jugular and nodose origin) ganglia sensory neurons, as well as pulmonary innervating dorsal root and nasal trigeminal ganglia neurons (Banner et al. 2011). TRPV1-positive fibres innervate multiple tissue types, including the nose, trachea, parenchyma, alveoli and vessels, throughout the respiratory tract (Grace et al. 2014). Classically, TRPV1 is thought to be expressed on a capsaicin-sensitive subset of slow-conducting unmyelinated C-fibres (Coleridge and Coleridge 1984); however it is now acknowledged that there is a wider population of TRPV1-expressing neurons which includes the fast-conducting myelinated Aδ-fibres (Adcock et al. 2014). Due to their expression in these nerve fibres innervating the lung,

TRPV1 receptors in the airway have received particular attention for their ability to provoke cough in both animal species and human subjects. Indeed, the threshold for cough provocation by capsaicin has been found to have been lowered in various populations of asthmatics and COPD patients who have chronic cough compared to healthy control subjects (Choudry and Fuller 1992; Wong and Morice 1999; Doherty et al. 2000; Weinfeld et al. 2002; Blanc et al. 2009; Belvisi et al. 2016). Furthermore, a lowered capsaicin cough threshold, or rather increased sensitivity to capsaicin, is one of the key clinical measures which define a population of patients proposed to have cough hypersensitivity syndrome (Chung 2011; Millqvist 2011).

As well as playing a role in eliciting cough, TRPV1-expressing C-fibres have been demonstrated to release pro-inflammatory neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) which mediate neurogenic inflammation via their retrograde release from peripheral terminals in rodent airways, although it is unclear if this phenomenon occurs in humans (Belvisi 2003). Indeed, capsaicin inhalation is also associated with parasympathetic bronchoconstriction, mucus hypersecretion, vasodilatation and the sensation of dyspnea (Couto et al. 2013), further implicating the TRPV1 receptor a role in symptoms other than cough in asthma and COPD. Furthermore, administration of the TRPV1 antagonist SB-704498 was found to reduce subsequent airway hyperresponsiveness to histamine in an ovalbumin-sensitised guinea pig model of allergic asthma (Delescluse et al. 2012).

In respiratory disease settings, TRPV1 function in the lung is thought to be modulated by some or all of three main mechanisms: elevated levels of direct TRPV1 agonists or channel openers; sensitisation of the channel by, for example, phosphorylation to induce activation to otherwise innocuous stimuli; and the increase in expression or de novo expression of TRPV1 in individual cells.

In the case of the first two mechanisms, the progressive and persistent pulmonary inflammation observed in asthmatics and COPD patients elevates the levels of multiple TRPV1 activators and sensitisers, including, e.g. inflammatory prostanoids and eicosanoids, neurotrophins, lowered pH and proteases (PAR2 agonists) (Adcock 2009; Grace et al. 2014; Veldhuis et al. 2015).

It should be noted that it is difficult in some cases to make a distinction between a ‘sensitiser’ and an ‘activator’ of TRPV1, with some GPCR agonists, having been shown to both sensitise TRPV1 to subsequent stimuli and to cause activation of TRPV1 (Fischer and Reeh 2007; Maher et al. 2009). Especially in the context of the inflammatory milieu, it is difficult to determine the exact role a single constituent plays. It is clear however that modulation of TRPV1 by GPCRs is an important factor in inflammatory diseases given that TRPV1 contains domains for binding of proteins, such as A-kinase-anchoring protein (AKAP), that can influence its activity, by, for instance, facilitating interactions with the signalling cascade kinases PKA and PKC (Veldhuis et al. 2015). Interestingly it is thought that the subcellular localisation of TRPV1 along with accessory proteins such as AKAP facilitates the regulation of TRPV1 by a multitude of signalling pathways, allowing TRPV1 to integrate signals to a wide range of stimuli – recently reviewed in Nilius and

Szallasi (2014). Sensitisers are generally thought to enhance the activity of TRPV1 via phosphorylation of specific residues, enabling the channel to respond to normally innocuous stimuli, or even to become activated spontaneously (Nilius and Szallasi 2014).

In addition to the increase in TRPV1 activation currents via elevated levels of activators/sensitisers, expression of TRPV1 may be increased under inflammatory conditions. This may occur in cells that had previously expressed TRPV1, in which case the increased surface expression would be expected to contribute, along with increased levels of activators/sensitisers to increased TRPV1 activation. However, intriguingly Lieu et al. have recently shown in guinea pigs that ovalbumin sensitisation/challenge or neurotrophin administration increases the number of TRPV1-expressing neurons, particularly of Aδ-type fibres, suggesting that the neural pathways innervating the airways are plastic and may be moulded by the inflammatory environment seen in asthma and COPD (Lieu et al. 2012). This data is corroborated by two other studies demonstrating increases in the proportion of TRPV1-expressing neurons in nodose ganglia in both a rat ovalbumin sensitisation/challenge model of allergic asthma and a guinea pig cigarette smoke exposure model of COPD (Zhang et al. 2008; Wortley et al. 2014a). It seems likely therefore that TRPV1 expression can be induced in neurons that previously did not express TRPV1, increasing the number of peripheral sensory inputs which may cause cough or airway hyperresponsiveness. In human subjects with chronic cough and severe asthma, capsaicin cough hypersensitivity has been reported (Doherty et al. 2000; Belvisi et al. 2016), and increased expression of TRPV1-like immunoreactivity has been detected in bronchial biopsies (Groneberg 2004; Mitchell et al. 2005; McGarvey et al. 2013).

By contrast, less evidence has been published regarding the expression of non-neuronal TRPV1. However, preliminary data has suggested that TRPV1 mRNA expression in the whole lung homogenate of emphysema patients is increased compared with healthy nonsmokers and nonsmokers, suggesting that TRPV1 expression may be increased in other tissues as well as neuronal cells (Grace et al. 2014). In addition, the TRPV1 inhibitor JNJ17203212 reduced the release of ATP from human bronchial epithelial cells (HBEC), and in vivo, *TRPV1*$^{-/-}$ mice exhibited less cigarette smoke-induced ATP release and subsequent neutrophilic inflammation in bronchoalveolar lavage fluid (Baxter et al. 2014). Despite these intriguing data, the role of TRPV1 in other lung tissues and cells in respiratory health and diseases such as asthma and COPD is relatively poorly understood (Gharat 2007).

There are no current firm descriptions of TRPV1 variant channelopathies per se (Banner et al. 2011). However Smit et al. more recently described associations between several TRPV1 SNPs and increased risk of usual and nocturnal cough in non-asthmatics, which was also correlated with cigarette smoking and occupational irritant exposures (Smit et al. 2012). Whilst the functional effects of SNPs associated with increased risk of cough are unknown, another SNP variant TRPV1-I585V, which – by contrast – is associated with a reduced risk of current cough or wheeze in asthmatics, is reported to decrease channel activity by 20–30%

(Cantero-Recasens et al. 2010). The associations of these SNPs with either increased risk or protection from cough and wheeze may suggest potential benefit could be derived from the antagonism of TRPV1 in disease, particularly in asthmatics and COPD patients who suffer from these symptoms.

2.2 TRPV1 Channel Antagonists

Of all the TRP channels, antagonists for TRPV1 are the most advanced in terms of drug development and clinical trials. However, development of these compounds has not been as straightforward as was initially hoped. The state of development of TRPV1 antagonists has been well documented in recent reviews (Preti et al. 2012; Nilius and Szallasi 2014), and here we will focus on selected compounds to describe the difficulties in development of TRPV1 antagonists, as well as updating with the latest reports of the most promising compounds, especially those targeted for respiratory conditions.

The main difficulties with TRPV1 antagonist development have been related to its function as a thermosensor for hot temperatures, and in particular this has meant that adverse effects such as increased body temperature and latent withdrawal to noxious hot stimuli have dogged development. For instance, the TRPV1 antagonist AMG 517 was entered into phase 1 and 1b clinical trials, where administration in patients following molar extraction caused significant and long-lasting increases in body temperature to above 40°C (Gavva et al. 2008). Due to safety concerns, these trials were terminated before the analgesic effect could be determined.

Another compound, MK-2295 (or NGD-8243), a Merck/Neurogen compound, entered a phase 2A POC trial also against dental pain, with 182 subjects receiving either drug or placebo (clinicaltrials.gov identifier NCT00387140). In this study the compound was similarly reported to have undesired effects, including causing an increase in body temperature and altering noxious heat sensation threshold (Xia et al. 2011). These adverse effects were correlated with target engagement, and reportedly meant a dose regimen could not be established that would allow efficacy whilst avoiding risk for burn injury, with some subjects reportedly unable to detect potentially harmful hot temperatures (Xia et al. 2011; Moran et al. 2011).

By contrast, the compound PHE377 has completed a phase 1b PoP trial, with the developing company PharmEste reporting that the compound was ‘well tolerated’, has ‘on-target activity’ and ‘does not increase body temperature’ (PharmEste website 2012). Unfortunately we could not find a peer-reviewed publication presenting this data; however the company is reportedly seeking partners for further development in a ‘phase 2 clinical study in chronic pain with different aetiologies’. It seems, therefore, that the development of TRPV1 antagonists which avoid the problem of hyperthermia may be possible, an idea substantiated by the preclinical development of BCTP, which is highly efficacious at inhibiting responses to capsaicin, RTX and heat, yet exhibits only mild effects on body temperature in rats (0.6°C increase) (Nash et al. 2012; Ferrer-Montiel et al. 2012).

Indeed, the GSK candidate SB-705498 recently completed phase 2 clinical trials for chronic refractory cough and was reported to be well tolerated, with no significant increases in tympanic temperature. This was the first TRPV1 antagonist to be examined clinically as an antitussive, but disappointingly, SB-705498 lacked efficacy in improving 24 h cough counts (Belvisi et al. 2014). However, the shift in objectively measured capsaicin-evoked cough, whilst statistically significant, appeared to be slight, and TRPV1 occupancy was estimated to be approximately only 40% (±20% confidence intervals). The targeting of chronic idiopathic cough was based on the observation by Belvisi et al. that cough responses to capsaicin were differential across different disease groups, with COPD and chronic cough patients in particular exhibiting increased cough responses to capsaicin inhalation and additional studies showing that chronic cough patients show high spontaneous cough frequency over 24 h of ambulatory recording compared to other patient groups (Decalmer et al. 2007; Belvisi et al. 2016; Sumner et al. 2013). However, it remains to be seen if higher potency compounds that have greater efficacy at inhibiting capsaicin-evoked cough can be effective at reducing increased cough frequency in chronic idiopathic cough patients or chronic cough of other aetiologies.

Of note, another TRPV1 antagonist, XEN-D0501, has recently been reported to cause increases of only 0.74°C in a phase 1 clinical trial after a single dose, and following twice-daily repeated dosing, this increase above placebo was reduced to 0.3°C (Round et al. 2011). What is more, Wortley et al. have recently shown that XEN-D0501 was approximately 1,000 times more potent than SB-705498 at inhibiting capsaicin depolarisation of human vagus nerve in vitro, and 100 times more potent at inhibiting capsaicin-evoked cough in conscious guinea pigs (Wortley et al. 2014b). XEN-D0501 is currently in ongoing phase 2 clinical trials for both chronic idiopathic cough (clinicaltrials.gov identifier NCT02233699) and cough in COPD (clinicaltrials.gov identifier NCT02233686), which are expected to conclude in 2015.

2.2.1 Other Notable Clinical Candidates Now Discontinued

The sensory neural pathways underlying pain disorders share many similarities with those that cause abnormal cough, and other TRPV1 antagonists which have been in development as analgesics include AZD1386 and GRC-6211 which both were trialled in patients with dental pain following molar extraction and appeared efficacious. It appears however that subsequently both compounds have been discontinued, in the former case due to liver enzyme elevations (Bonney and Carr 2013) and the latter for unspecified reasons following the sale of the compound by Glenmark to Lilly (Lilly press release 2007; Kym et al. 2009; Xia et al. 2011).

3 TRPA1

TRPA1, formerly known as ANKTM1, is currently the only mammalian-expressed member of the TRP ankyrin family and is named for the large number of ankyrin repeat motifs (14–19) on its N-terminus (Nilius et al. 2012). Near this ankyrin repeat domain are residues that enable TRPA1 to be activated by electrophilic compounds, which include a wide range of endogenous and exogenous reactive chemicals and irritants, so implicating TRPA1 with a key role as a noxious chemosensor. This list of TRPA1 activators includes environmental irritants (constituents of cigarette smoke, air pollution and vehicle exhaust fumes), pungent components of foods, hypochlorite (produced endogenously by immune cells and exogenous constituent of warfare agents) and endogenous agents, commonly produced in inflammatory processes (Nilius and Szallasi 2014). The newest addition to the list of TRPA1 activators are components of bacterial cell walls, an intriguing finding that suggests that the peripheral sensory nervous system (which expresses TRPA1 and responds to LPS) can detect and respond to bacterial infections independently of the immune system (Meseguer et al. 2014). A selected list of some of the wide range of the compounds activating TRPA1 is illustrated in Fig. 2. However as well as chemical ligands, TRPA1 was also initially discovered to be a sensor of physical stimuli, responding to noxious cold temperatures (below 17°C) (Story et al. 2003) and contributing to cellular responses to mechanical stresses (Brierley et al. 2011). However there is some controversy surrounding its supposed cold sensitivity, with one group suggesting that rat and mouse TRPA1 expressed in heterologous expression systems *are* activated at cold temperatures (Chen et al. 2013), but that in vivo a TRPA1 antagonist *does not* affect paw withdrawal time to noxious cold (Chen et al. 2011). In support of this latter finding, Zhou et al. report that TRPA1 does not play a role in cold sensation in afferent bronchopulmonary C-fibres (Zhou et al. 2011). This confusion was furthered by two recent contradictory reports, with Chen et al. suggesting that human TRPA1 (albeit in heterologous expression systems) is unresponsive to cold temperatures, whereas Moparthi et al. suggest that human TRPA1 is intrinsically cold sensitive (Chen et al. 2013; Moparthi et al. 2014). It seems therefore that the thermoTRP status of TRPA1 as a cold sensor is far from definitively proven.

3.1 TRPA1 in Asthma and COPD

Although TRPA1 was first identified in human cultured fibroblasts (Jaquemar et al. 1999), expression studies have shown that TRPA1 is predominantly expressed in sensory nociceptive neurons, including, in the respiratory tract, those of vagal and dorsal root ganglia, as well as those of nasal trigeminal ganglia origin (Story et al. 2003; Bandell et al. 2004; Bautista 2005; Nassenstein et al. 2008; Jang et al. 2012).

Recently, however, TRPA1 expression has also been demonstrated in immune cells involved in the inflammatory response in asthma and COPD – such as B cells,

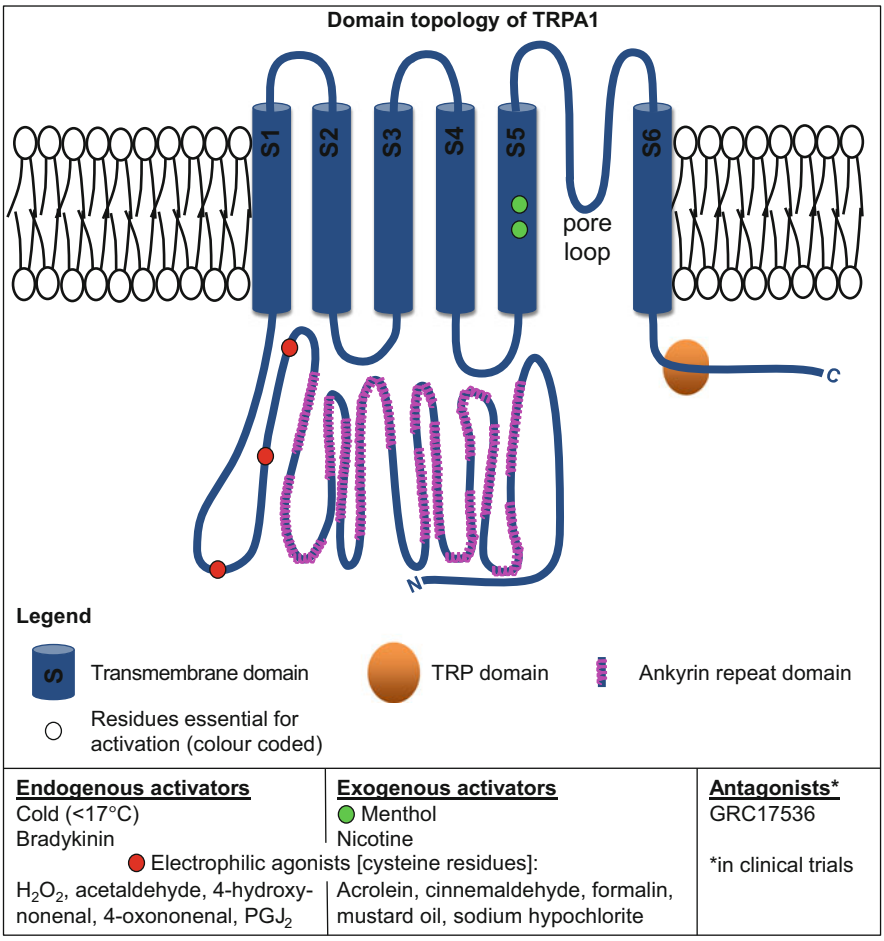

Fig. 2 Diagram showing domain topology and residues important in activation of TRPA1, along with selected endogenous/exogenous TRPA1 activators and TRPA1 antagonists in clinical trials for respiratory indications (Hinman et al. 2006; Macpherson et al. 2007; Bang and Hwang 2009)

$CD4^+$ and $CD8^+$ T cells and mast cells (Prasad et al. 2008; Banner et al. 2011). Additionally, TRPA1 expression has been observed in human lung bronchial epithelial cell lines, and these observations have recently been extended to native pulmonary epithelial cells (Mukhopadhyay et al. 2011; Büch et al. 2013).

Activation of TRPA1 channels has been shown to depolarise vagal pulmonary C-fibres and Aδ-nociceptors in rodent species (Bessac et al. 2008; Taylor-Clark et al. 2008; Nassenstein et al. 2008; Birrell et al. 2009; Andrè et al. 2009; Grace et al. 2012; Adcock et al. 2014), and by extension TRPA1 receptors on these fibre types are thought to mediate cough provoked by TRPA1 agonists in human subjects (Birrell et al. 2009). Indeed, the wide range of exogenous irritants and noxious agents that activate TRPA1, along with its ability to provoke cough, has indicated

TRPA1 with a key role as a key defensive noxious sensor in the lungs (Geppetti et al. 2009; Grace and Belvisi 2011).

Interestingly, in pulmonary vagal ganglia neurons, TRPA1 is expressed almost exclusively in a subpopulation of TRPV1-expressing cells, with up to 98% of TRPA1-expressing cells also expressing TRPV1 (Hondoh et al. 2010). TRPA1 subunits have been demonstrated to form functional TRPA1/V1 heterodimers with TRPV1, although there is no dependency between the two for the formation of functional channels (Akopian 2011). What is more, a recent screen of compounds acting on TRPV1 and TRPA1 suggests that the responsiveness to various agonists may be modulated depending on whether these channels are either expressed individually or together (Sadofsky et al. 2014). It will be particularly interesting and relevant to future clinical development to discover whether native cells that co-express TRPV1/A1 differ in their functional responses to agonists compared to cell populations expressing TRPV1 or TRPA1 alone.

As well as evoking cough, many TRPA1-activating irritants cause asthma-like symptoms, including cough, wheeze and dyspnea, hinting at a role for TRPA1 in asthma (Grace et al. 2014). Indeed, TRPA1 has been linked with a key role in the airway hyperresponsiveness (AHR) and bronchoconstriction characteristic of asthma, with a TRPA1 antagonist (HC030031) reversing the AHR to acetylcholine in an ovalbumin-sensitised mouse model (Caceres et al. 2009) and abolishing the late asthmatic response observed following ovalbumin sensitisation/challenge in rat and murine models of asthma (Raemdonck et al. 2012). Additionally, Trankner et al. recently demonstrated that TRPV1-expressing nerves are essential for the development of allergic AHR in a murine model, with selective ablation of TRPV1-expressing nerve fibres abolishing AHR, and direct optogenetic stimulation of these same fibres induces AHR in non-challenged but sensitised control mice (Tränkner et al. 2014). Given that a TRPV1 antagonist did not block this effect and that TRPA1 is almost only expressed in TRPV1-expressing nerve fibres, this supports the concept that TRPA1 plays a key role in the development of AHR in asthma. Furthermore, recent work by Hox et al. has demonstrated that nonallergic AHR can be induced by a single exposure of hypochlorite (TRPA1 agonist) + ovalbumin in wild-type, but not *TRPA1*$^{-/-}$ mice (Hox et al. 2013).

It is thought that the excessive activation of TRPA1 on sensory nerves in asthma and COPD is due to the increased levels of both endogenous pro-inflammatory signalling molecules (the 'inflammatory soup') and the exogenous stimuli which are implicated in the development of COPD – and to some extent asthma – such as cigarette smoke (Andrè and Campi 2008; Simon and Liedtke 2008; Lin et al. 2010; Kanezaki et al. 2012). However, as well as being excessively activated by pro-inflammatory stimuli, it is also thought that TRPA1 activation itself causes the release of pro-inflammatory agents that help to sustain the persistent inflammation observed in asthma and COPD. COPD-relevant TRPA1 agonist sources include cigarette smoke constituents (including acrolein, crotonaldehyde and nicotine), other potential COPD-causative agents such as wood smoke and ozone as well as endogenous aldehydes produced following oxidative stress exposure, such as 4-hydroxynonenal (Taylor-Clark et al. 2007; Trevisani et al. 2007; Shapiro

et al. 2013). Recent studies have suggested the expression of TRPA1 in non-neuronal pulmonary cell types, including fibroblasts, epithelial cells and smooth muscle cells, and that expression and release of pro-inflammatory cytokines can be induced from these cell types (Nassini et al. 2012).

Whilst there is some evidence that TRPV1 expression is increased under disease conditions and specifically in asthma and COPD (as discussed previously), there is very limited evidence that TRPA1 expression is similarly modulated in inflammatory states. What little information is available indicates that mechanisms of enhanced TRPA1 expression are likely to be tissue-type specific, and to date TRPA1 up-regulation has not been investigated in tissue types or disease models of relevance to COPD (Malin et al. 2011; Bautista et al. 2013).

Again, by comparison to TRPV1, where Smit et al. found an association between TRPV1 SNPs and increased risk of cough and wheeze, the same authors could find no association between 29 TRPA1 SNPs and cough or wheeze in the same population (Smit et al. 2012).

The only known TRPA1 channelopathy is familial episodic pain syndrome, which is associated with functional activation of the channel at normal resting potentials, causing debilitating upper body pain; however there is no data available concerning how this syndrome impacts on the respiratory tract (Kremeyer et al. 2010; Nilius and Szallasi 2014). There are currently no reported associations between SNPs in TRPA1 and susceptibility to airway diseases (Nilius and Szallasi 2014).

3.2 TRPA1 Channel Antagonists

In contrast to TRPV1, TRPA1 antagonists have had less development time (due to the more recent identification of the TRPA1 receptor), and therefore with far fewer candidate compounds, only two candidate compounds have reached clinical trial stages. A recent (and thorough) review of the patent literature however suggests that several companies possess patented TRPA1 antagonists in various states of preclinical/biological testing, including Abbott (two compounds), Merck Sharp & Dohme, Scripps Research Institute, Janssen (two compounds), Glenmark Pharmaceuticals (seven compounds) and Hydra Biosciences (four compounds), with some indicated for asthma and respiratory conditions (Preti et al. 2012).

One of those compounds that has reached clinical trials however is CB-189,625, which was developed by Cubist Pharmaceuticals and Hydra Biosciences. Indicated for acute (perioperative) pain and certain inflammatory conditions, CB-189,625 completed phase 1 clinical trials, with no adverse effects reported apart from those attributed to vehicle (Bokesch et al. 2012; Preti et al. 2012). However, according to a publicly available quarterly financial report in 2013, the compound was discontinued due to ‘solubility concerns’ (Cubist Pharmaceuticals 2013).

By contrast, the Glenmark Pharmaceuticals candidate GRC-17536 appears to have fared better, having completed phase 1 and, recently, phase 2 trials in subjects with painful diabetic peripheral neuropathy (clinicaltrials.gov identifier

NCT01726413). There are to the best of our knowledge no published works on the results of these trials; however a press release indicates that the compound was well tolerated in phase 2, with no adverse effects reported and a statistically significant and clinically relevant positive response observed (Evaluate Group press release 2014).

In addition, and following preclinical data with this compound showing an antitussive effect against CA-provoked cough (Mukhopadhyay et al. 2014), GRC-17536 is currently in another phase 2 clinical trial for chronic refractory cough (clinicaltrialsregister.eu identifier 2013-002728-17). The trial is described as a double-blind crossover placebo-controlled trial of the effect of GRC-17536 on 24 h cough counts in chronic cough patients refractory to treatment, with target engagement judged by GRC-17536 inhibition of CA-induced cough. Interestingly, the compound has been formulated as a dry powder for inhalation, although the reason for this change of formulation from previous clinical trials is unknown. Whilst it is unclear when it is due to conclude, the results of this first clinical trial of a TRPA1 antagonist in a respiratory condition are highly anticipated.

4 TRPV4

TRPV4 was initially discovered to be expressed in rat kidney and was originally identified as a putative osmosensor with sequence similarities to TRPV1 and TRPV2; hence its original designation of VR-OAC, or vanilloid receptor-related osmotically activated channel (Liedtke et al. 2000). TRPV4 is a Ca^{2+}- and Mg^{2+}-permeable nonselective cation channel composed of 871 amino acids with three ankyrin repeats near the NH_2-terminus (Fig. 3). Like TRPA1 and TRPV1, TRPV4 is a thermosensor, although unlike the former two, TRPV4 is thought to be involved in the sensation of tepid to warm temperatures, imbuing TRPV4 with constitutive activity in basal conditions as its activation range of 24–42°C overlaps with normal body temperatures (Nilius et al. 2005; Belmonte and Viana 2008). Again in similarity to TRPV1 and TRPA1, TRPV4 is a polymodal sensor which responds to a range of endogenous and exogenous chemical and physical stimuli including arachidonic acid and derivatives, endocannabinoids, synthetic α-phorbols and mechanical stimuli, such as changes in osmolarity (Watanabe et al. 2003; Vriens et al. 2004; Willette et al. 2008).

4.1 TRPV4 Role in Airway Disease

Its wide tissue expression in tissues all over the body (including heart, lung, kidney, CNS, skin and sweat glands) and variously in multiple neuronal and non-neuronal cell types aligns with the many different cellular functions in which TRPV4 is involved (Vincent and Duncton 2011; Grace et al. 2014).

Unlike that of the TRPA1 and TRPV1 channels discussed previously, the role of neuronally expressed TRPV4 in the lungs is not well characterised (Grace

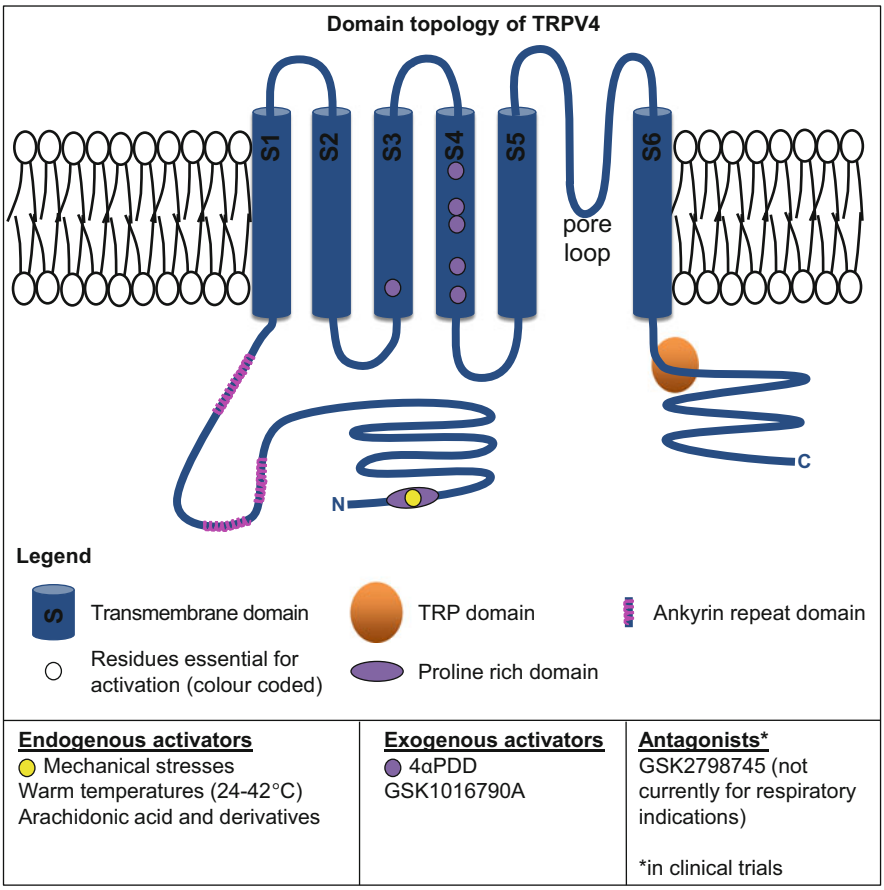

Fig. 3 Diagram showing domain topology and residues important in activation of TRPV4, along with selected endogenous/exogenous TRPV4 activators and TRPV1 antagonists in clinical trials (Vriens et al. 2004, 2007; Vennekens et al. 2008; D'hoedt et al. 2008; Everaerts et al. 2010)

et al. 2014). However, recently it has been demonstrated that airway sensory nerves can be activated by TRPV4 agonists (Bonvini et al. 2016). In this study, TRPV4 agonists evoked cough in guinea pigs and also induced depolarisation or calcium entry into vagal nerves and neurons – specifically nodose but not jugular neurons. This finding means it is possible that TRPV4 could play a role in the abnormal cough response in COPD and asthmatic patients, where the osmolarity of the pulmonary surfaces is altered, and levels of endogenous activators (such as arachidonic acid) are increased, although this idea requires validation with further work (Grace et al. 2014).

Whilst neuronal pulmonary TRPV4 has not been widely investigated, more is known about TRPV4 for its expression and functional role in a wide range of non-neuronal lung tissues, including structural cells such as airway smooth muscle,

epithelial cells, pulmonary vessels as well as in inflammatory cells such as alveolar macrophages and neutrophils (Liedtke et al. 2000; Jia et al. 2004; Yang 2006; Alvarez et al. 2006; Dietrich et al. 2006; Banner et al. 2011). Due to the postulated increased levels of TRPV4 activators present, it is thought that excessive activation of TRPV4 could play multiple roles in the pathology of asthma and COPD, dependent on the specific tissues in which it is expressed.

For example, it has been demonstrated that TRPV4 is expressed in human airway smooth muscle cells (Jia et al. 2004), and a specific TRPV4 agonist elicits significant contraction of both guinea pig and human smooth muscle (via the release of cysteinyl leukotrienes), which is blocked using a selective TRPV4 antagonist, implicating TRPV4 with a role in the variable airflow obstruction observed in asthma (Bonvini et al. 2013; McAlexander et al. 2014). Furthermore, TRPV4 activation in both human airway smooth muscle and human airway epithelial cells has been shown to cause the enhanced release of ATP (Seminario-Vidal et al. 2011; Takahara et al. 2014; Baxter et al. 2014), *TRPV4*$^{-/-}$ mice had reduced pulmonary ATP release and neutrophilic inflammation following CS exposure and TRPV4 expression was upregulated in whole lung tissues from COPD patients (Baxter et al. 2014). What is more, TRPV4 activation has also been suggested to contribute to both neurogenic inflammation via the release of neuropeptides and the stimulation of alveolar macrophages to release reactive oxygen and nitrogen species (Vergnolle et al. 2010; Hamanaka et al. 2010). These data collectively suggest TRPV4 plays a role in the inflammatory processes underlying asthma and COPD pathologies (Esther et al. 2008; Willart and Lambrecht 2009; Mortaz et al. 2010; Riteau et al. 2010; Eltom et al. 2014). What is more, in rodent and murine models TRPV4 activation has been implicated with a role in the formation of pulmonary oedema (Thorneloe et al. 2012), which is thought to be due to its role as a regulator of endothelial permeability (Jian et al. 2008).

Similarly to TRPV1 and TRPA1, TRPV4 can be activated by multiple stimuli including endogenous inflammatory lipids, changes in airway surface osmolarity and mucus production (Vincent and Duncton 2011; Grace et al. 2014). In addition to the evidence that levels of TRPV4 activators are upregulated in asthma and COPD, there is also the suggestion that TRPV4 may be sensitised to subsequent stimulation via phosphorylation of the channel, for example via PKA and PKC activity (Grant et al. 2007; Poole et al. 2013).

Two known diseases are caused by genetic changes resulting in abnormal TRPV4 function: Charcot-Marie-Tooth disease type 2C and scapuloperoneal spinal muscular atrophy (Wu et al. 2010). Whilst there are serious systemic repercussions of both channelopathies (bone dysplasia and peripheral nervous degeneration), there is no evidence linking these channelopathies of TRPV4 with asthma, COPD or other respiratory diseases, although it is unclear whether a gain or loss of function is encoded by the TRPV4 mutant protein (Nilius and Owsianik 2010). As Nilius and Owsianik point out when discussing TRPV4 channelopathies, there appears to be a disconnect between the anticipated problems (osmoregulation, pulmonary hypertension or endothelial dysfunction) and those observed in TRPV4-related channelopathies (Nilius and Owsianik 2010).

By contrast, however, several SNPs of TRPV4 have been found to confer increased susceptibility to COPD pathologies, indicating that the increased activation of TRPV4 may contribute to disease progression in COPD patients (Zhu et al. 2009). Interestingly, the study by Cantero-Recasens et al., which found an association between TRPV1 SNPs and cough/wheeze in asthma, found no similar associations with known TRPV4 SNPs and asthma symptom risk (Cantero-Recasens et al. 2010). It may be, however, that there are other asthma risks (e.g. for exacerbation) that are associated with TRPV4 SNPs that were not considered in the design of this study.

Whilst much work remains to be done to highlight directly the role of TRPV4 in asthma and COPD in the specific context of these diseases, there is evidence that activators of TRPV4 are elevated in disease and that activation of TRPV4 leads to the development of asthma and COPD pathologies in animal models. When taken together with the associations between TRPV4 SNPs and risk for COPD, there seems to be a role for TRPV4 activation in the development of these diseases, providing a rationale for the clinical development of specific antagonists of TRPV4.

4.2 TRPV4 Antagonists

There are few TRPV4 antagonist clinical candidates in advanced stages of development. Currently, the GlaxoSmithKline compound GSK2798745 is in a phase 1 trial to assess safety and tolerance in healthy subjects and stable heart failure patients (clinicaltrials.gov identifier NCT02119260). Otherwise it is unclear whether existing compounds in preclinical testing for respiratory indications will be advanced to clinical trials. Given the channelopathies related to systemic change of function of this channel, and its wide expression profile, it may be that the lungs are ideal target tissues for antagonists of TRPV4, with the potential for compounds to be targeted relatively selectively to the lung using inhaled formulations.

5 TRPM8

TRPM8 is another ‘thermoTRP’, in that, like TRPA1, it is thought to respond to cold – or more accurately cool – temperatures in the range 15–28°C (Peier et al. 2002; McKemy 2013). In this way, TRPM8 is thought to be more a physiological sensor of innocuous cool temperatures, rather than a sensor for the detection of painful noxious cold temperatures (McKemy 2013).

Whilst it is a cold thermosensor, TRPM8 shares little sequence homology with TRPA1 and in particular lacks the N-terminus ankyrin repeat sequence structure of TRPA1, as well its responsiveness to electrophilic noxious compounds (Story et al. 2003; Latorre et al. 2007). Instead, chemical TRPM8 activators, such as menthol, icilin and eucalyptol, in general seem to have the shared characteristic of eliciting a cooling sensation (Peier et al. 2002; Zhou et al. 2011). Menthol itself has been variously reported to be analgesic, to have antitussive properties, to be a

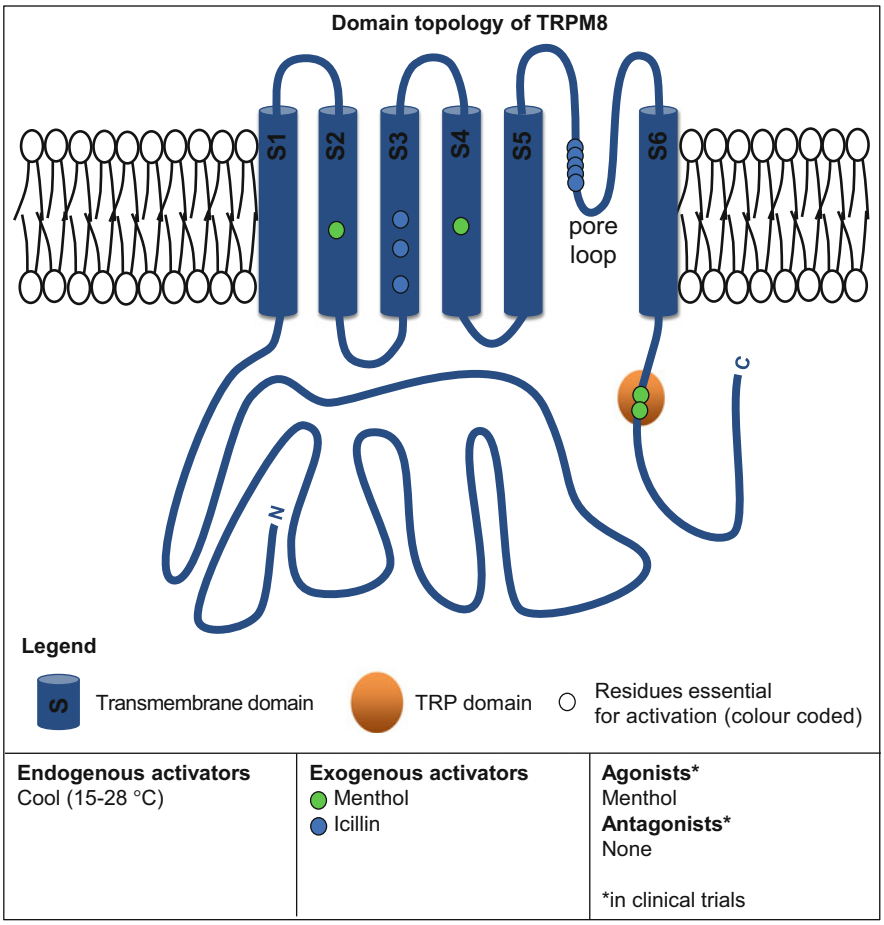

Fig. 4 Diagram showing domain topology and residues important in activation of TRPM8, along with selected endogenous/exogenous TRPM8 activators and TRPM8 ligands in clinical trials for respiratory indications (Latorre et al. 2011)

bronchodilator and to reduce airway irritation and inflammation caused by cigarette smoke irritants (Morice et al. 1994; Wright et al. 1997; Galeotti et al. 2002; Willis et al. 2011; Millqvist et al. 2012). However, whilst menthol is commonly thought of as a TRPM8 agonist, it acts as a TRPA1 agonist at higher concentrations, and may well also activate a host of other targets, including possibly opioid receptors (Galeotti et al. 2002; Karashima et al. 2007). Indeed, data presented recently indicates that the beneficial (bronchodilator/antitussive) effects of menthol in the airways are not due to TRPM8 agonism (Maher et al. 2014). This highlights the particular difficulty in interpreting the literature on TRPM8 due to the use of nonselective ligands (Fig. 4).

5.1 TRPM8 in Asthma and COPD

TRPM8 is primarily expressed in neurons, particularly in subpopulations of neurons originating in the dorsal root and trigeminal ganglia (Clapham et al. 2001; Peier et al. 2002; Story et al. 2003). Interestingly, the subpopulation of TRPM8-expressing neurons appears to be mostly distinct from those subpopulations that express TRPA1, which could imply a distinction in the physiological responses to 'cool' versus 'noxious cold' sensing (Clapham et al. 2001; Peier et al. 2002; Story et al. 2003; Hondoh et al. 2010). It may therefore be relevant to note that whilst TRPA1 expression almost completely overlaps with the well-known pain/cough receptor TRPV1, only about 30% of TRPM8 also express TRPV1 in DRG neurons (Okazawa et al. 2004). Limited TRPM8 expression in vagal ganglia neurons has also been observed in some studies (Xing et al. 2008; Nassenstein et al. 2008), and whilst TRPM8 mRNA has been detected in retrograde-stained airway jugular neurons, it is thought that the proportion of TRPM8-expressing vagal ganglia neurons is much lower than the reported 60% of TRPM8-expressing nasal trigeminal neurons (Hondoh et al. 2010; Plevkova et al. 2013).

Inhalation of cold air can cause bronchoconstriction and cough and induce plasma protein extravasation and mucus production (Yoshihara et al. 1996; Peier et al. 2002; Carlsen and Carlsen 2002; Xing et al. 2008). However, it is unclear whether this is due to the activation of TRPM8, or the noxious cold sensor TRPA1, or some relative proportion of the two channels. Furthermore, contradictory data exists from multiple studies indicating that activation of TRPM8 (mostly via menthol inhalation/application) inhibits cough and bronchoconstriction (Morice et al. 1994; Kenia et al. 2008; Ito et al. 2008; Millqvist et al. 2012; Wise et al. 2012).

There is also the suggestion that activation of TRPM8 by menthol in nasal trigeminal neurons can inhibit the cough reflex, although this may tell us more about the neurological integration of peripheral nervous signals in the CNS than it does about the role of TRPM8 in disease conditions (Buday et al. 2012).

A truncated TRPM8 splice variant has been detected in human bronchial epithelial cells, and this activation of this variant has been shown to induce pro-inflammatory cytokine transcription (Sabnis et al. 2008a, b). Furthermore, TRPM8 activation has been shown to play a key role in mucus production and mast cell activation (Cho et al. 2010; Li et al. 2011; Grace et al. 2014).

It is unknown whether the expression of TRPM8 is altered in disease states. What is more, whilst it is thought that modulators (usually activators) of TRPV1, TRPA1 and TRPV4 are increased in disease states or inflammatory conditions, it is unclear if in a similar manner TRPM8 activity is modulated by the inflammatory milieu, with no known endogenous activators of TRPM8 having been described (Grace et al. 2014).

To the best of our knowledge there are no SNPs of TRPM8 with relevance to asthma or COPD, and likewise there are no known channelopathies that can offer insight into the function of TRPM8 in the airways.

The various apparently conflicting findings of the consequences of TRPM8 activation make it hard to predict whether TRPM8 agonism or antagonism would be of more benefit in asthma or COPD. Perhaps future work with more specific agonists would help to elucidate the role of this channel in various disease states and tissues. Therefore the next section of this chapter will discuss the development and use of both TRPM8 agonists and antagonists.

5.2 Drugs Affecting TRPM8 Channels

Menthol is already currently available and widely used in OTC lozenges, nasal sprays and cough syrups; usually indicated as cough and cold remedies (Morice et al. 1994; Laude et al. 1994; Kenia et al. 2008; Preti et al. 2012). In these OTC remedies, menthol is often ascribed with antitussive properties and increasing airflow (reducing dyspnea). However, whilst clinical studies have found that menthol does inhibit the cough response to inhaled capsaicin and citric acid (Morice et al. 1994; Laude et al. 1994; Wise et al. 2012), appropriate controls for inhalation of menthol have not been established. This makes these data hard to interpret, given the conscious control of the cough reflex, and the demonstrated effect of mindfulness on the cough reflex (Young et al. 2009). What is more, recently menthol has been shown to increase the perception of nasal patency, but no effect on nasal airflow (Eccles 2003; Kenia et al. 2008).

Interestingly, menthol can attenuate respiratory irritation induced by TRPA1 and TRPV1 agonist constituents of cigarette smoke (Willis et al. 2011). However, as menthol is known to activate several receptors besides TRPM8 (as discussed previously), it is hard to know whether to attribute any clinical benefits to TRPM8 agonism.

To the best of our knowledge, currently no TRPM8 antagonists have reached clinical development stages for asthma and COPD. However, the Pfizer candidate PF-05105679 has completed a phase 1 trial (clinicaltrials.gov identifier NCT01393652) and was reported to be generally well tolerated whilst reducing inhibition of pain induced by the cold pressor test (Winchester et al. 2014). It was also reported that around a third of participants receiving PF-05105679 experienced a sensation of ‘feeling hot’; however no effect on core temperature was observed – although the reason for this observation was not established.

Furthermore, antagonists are in development and biological testing by Bayer HealthCare, Glenmark Pharmaceuticals, RaQualia Pharma Inc., Amgen, and Janssen (for more details, see the excellent patent review by Preti et al. 2012). Of note, Janssen and Amgen have specifically mentioned COPD and asthma (respectively) in their patent applications, although Janssen has multiple compounds that are also indicated for ‘respiratory conditions’, although to date there are no published validations of these compounds in preclinical models of asthma or COPD (Preti et al. 2012).

It seems likely that future preclinical biological work to understand the mechanisms of how TRPM8 modulation affects the course of disease is required to 'pathfind' for the preclinical and clinical development of TRPM8 drugs.

6 Discussion

Targeting TRP channels with antagonist drugs may be an effective strategy for reducing the elevated activity of these channels and consequent adverse effects/symptoms in asthma and COPD. Whilst it is apparent from the first generation of antagonists that TRP channels play a role in homeostasis as well as as gatekeepers of these adverse effects, it may be possible to design compounds that can avoid these adverse effects. For example, hot temperature gating of TRPV1 is structurally separate to ligand-gating site(s), and this has allowed the development of specific antagonists that block activation of the ligand-gating site to prevent chemical activators, but allow activation by hot temperatures (it is thought). Such antagonists hold promise that they may allow the desired blockade of adverse effects caused by TRP activation whilst still allowing the activation of the TRP channel by normal endogenous stimuli such as hot temperatures. This offers an optimal clinical profile for patients, especially in the case of TRPV1, for example, allowing the reflexive sensing of dangerous heat for the avoidance of burning.

TRPV4 and TRPM8 channel antagonists are in various stages of preclinical development, and their use in animal models has the potential to tell us much more about the role of the these channels in respiratory disease. By contrast, the clinical trials of TRPV1 and TRPA1 antagonists for the indication of chronic cough in various patient populations are currently ongoing, and the results of these trials may inform us much more about the nature of these channels in human respiratory disease.

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