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REVIEW

Itch and Cough – Similar Role of Sensory Nerves in Their Pathogenesis

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Summary

Itch is the most common chief complaint in patients visiting dermatology clinics and is analogous to cough and also sneeze of the lower and upper respiratory tract, all three of which are host actions trying to clear noxious stimuli. The pathomechanisms of these symptoms are not completely determined. The itch can originate from a variety of etiologies. Itch originates following the activation of peripheral sensory nerve endings following damage or exposure to inflammatory mediators. More than one sensory nerve subtype is thought to subserve pruriceptive itch which includes both unmyelinated C-fibers and thinly myelinated Aδ nerve fibers. There are a lot of mediators capable of stimulating these afferent nerves leading to itch. Cough and itch pathways are mediated by small-diameter sensory fibers. These cough and itch sensory fibers release neuropeptides upon activation, which leads to inflammation of the nerves. The inflammation is involved in the development of chronic conditions of itch and cough. The aim of this review is to point out the role of sensory nerves in the pathogenesis of cough and itching. The common aspects of itch and cough could lead to new thoughts and perspectives in both fields.

Key words

Cough • Itch • Sensory fibers • C-fibers • A-fibers

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Introduction

Itch is a common sensation that drives an intense urge to scratch. Itch and scratching have persisted in humans and many other species, suggesting that they play an important role in survival (Sanders *et al.* 2019). Mammals have evolved neurophysiologic reflexes such as coughing and scratching to expel invading pathogens and noxious environmental stimuli. It is well established that these responses are also associated with chronic inflammatory diseases such as asthma and atopic dermatitis. However, the mechanisms by which inflammatory pathways promote sensations such as itch remain poorly understood (Oetjen *et al.* 2017). Histological analyses of tissues from atopic patients have revealed striking increases in innervation at sites of inflammation. This was identified early in the skin of patients with atopic dermatitis (Tobin *et al.* 1992) but has now been shown in other tissues such as the lung in asthma (Myers *et al.* 2002). This increase in sensory neuron density is believed to contribute to atopic hypersensitivity, and worsening barrier damage, potentially caused by chronic itching or coughing, has been shown to increase tissue innervation (Valtcheva *et al.* 2015).

Sensory fibers pathways in itching and cough

The sensory nervous system is tasked with

relaying peripheral signals to the brain. It broadly includes the somatosensory nervous system which transmits conscious perception of multiple sensations such as itch, nociception, mechanoreception, and proprioception through unique families of sensory neurons as well as the autonomic nervous system which transmits visceral sensations and homeostatic signals (Bautista *et al.* 2014). To accomplish this, sensory neurons send projections from their cell bodies, located in discrete ganglia throughout the body, toward both the central nervous system (CNS) and barrier surfaces. For example, conscious sensations from the skin of the body are carried along projecting axons of sensory nerves to the dorsal root ganglia (DRG) where their signals are then transmitted to the spinal cord and brain. Initiation of these signals begins in peripheral terminals of sensory neurons with localized depolarization due to activation of neuronal receptors and membrane ion channels. Given a sufficient stimulus, local activation can lead to increased action potential firing of projecting sensory neurons which results in CNS transmission. Thus, determining the function of specific receptors and channels expressed by sensory neurons at barrier surfaces is critical to understanding the mechanisms underlying dysregulated sensory responses (Oetjen and Kim 2018). Sensory neurons that play a role in itch or cough can be classified into two distinct fibers, the thinly myelinated Aδ-fiber and the unmyelinated C-fiber (LaVinka and Dong 2013).

A-fibers in itching and cough

Itch

Pruriceptive itch originates when specific sensory nerve terminals, generally located in the skin, are activated. Pruriceptive itch can also original from certain mucosal surfaces; however, a majority of research on itch has focused on sensory nerve fibers from the skin (Wallengren 2005). The excitation of sensory nerve fibers in the skin leading to pruriceptive itch occurs upon exposure of certain sensory nerve terminals to a pruritic substance and frequently follows skin damage or inflammation. Sensory nerve fibers in the skin originate from the distal processes of primary afferent dorsal root ganglion neurons. Sensory nerve fibers in the skin are broadly classified according to their condition of velocity and the sensory modalities that excite them. Fast conducting myelinated nerve fibers (Aβ) respond to non-noxious mechanical stimulation of the skin, while slow conducting myelinated (Aδ) and unmyelinated (C) nerves fibers respond to noxious stimulation and temperature changes of the skin (McGlone and Reilly 2010). It has been shown in studies involving the known pruritogen cowhage *(Mucuna pruriens)*, that mechanosensitive Aδ-fibers play a role in itch. Cowhage causes intense itching when injected into the skin (Shelley and Arthur 1957). In monkeys, cowhage activates mechanosensitive A-fibers while some mechanoinsensitive A-fibers are activated by another pruritogen, histamine (Ringkamp *et al.* 2011, LaVinka and Dong 2013).

Cough

Aδ-fibers fibers are unique in their lack of response to tissue distension, airway smooth muscle contraction and inflammatory mediators. They are, however, exquisitely sensitive to punctate mechanical stimulation (touch) of the epithelium. These terminals are also sensitive to acid, but only when there is a rapid drop in pH (Kollarik and Undem 2002). The unique structures of these terminals have been described in guinea pig trachea, and nerves with similar structures have recently been described in human bronchi (Mazzone *et al*. 2009, West *et al.* 2015). Physiological studies have revealed that stimulation of these fibers cause a strong cough response, even when an animal is anaesthetized (Canning *et al.* 2004). It stands to reason that these bona fide "cough receptors" provide a selective advantage by reducing the potentially lethal complications of aspiration (Mazzone and Undem 2016).

Aβ-fibers (rapidly adapting receptors - RARs, slowly adapting receptors - SARs, stretch receptors). The vagal afferent fibers terminating in the respiratory tract that conduct action potentials in the Aβ range are by in large sensitive to the lung distention evoked by inspiration (Lee and Yu 2014, Sant'Ambrogio 1987). A subset is also sensitive to the mechanical forces caused by lung deflation (Liu and Yu 2013).

The role of myelinated fibers in cough is much more defined and explored when compared to myelinated fibers' role in itch. What is interesting in both is that these myelinated fibers are not solely responsible for the genesis of itch or cough. In both itch and cough, C-fibers play a role in setting the threshold, controlling the sensitivity of the system (LaVinka and Dong 2013).

C-fibers in itching and cough

Itch is primarily mediated by slower conducting C-fibers innervating the dorsal horn of the spinal cord.

Early itch studies used spicules of cowhage to show that the strongest itch is felt in the dermo-epidermal juncture area, the area where unmyelinated sensory fibers innervate (LaVinka and Dong 2013). Two itch-sensitive pathways exist: a histamine-stimulated pathway that uses mechanically insensitive C-fibers, and a cowhage-stimulated pathway primarily involving polymodal C-fibers. In typical circumstances, pruritogens stimulate skin receptors and activate the peripheral pathway of itch. This provokes a signalling cascade and action potentials in at least two types of C-fibers. These nerve fibers conduct the action potential to the dorsal horn of the spinal cord. The itch pathways are stimulated by histamine and cowhage skin receptors in the epidermis and dermis, respectively. Impulses are transmitted primarily via mechanically insensitive C-fibers and polymodal C-fibers, respectively, to secondary neurons in the dorsal horn. One means of modulation by the pain pathway is through a Bhlbb5 interneuron (Dhand and Aminoff 2014).

Cough

In the respiratory tract, C-fibers are often subclassified as pulmonary C-fibers or bronchial C-fibers, depending on whether the terminations receive blood supply from the pulmonary or bronchial circulation (Coleridge and Coleridge 1984). Operationally a C-fiber is considered to be a pulmonary C-fiber if it responds to a chemical stimulant with short latency when delivered by right atrial injection to the pulmonary circulation. A C-fiber is termed “bronchial” if it is located in the large airways or if it responds with short latency to a chemical stimulant injected directly into the systemic circulation, i.e., into the bronchial artery. Pulmonary C-fibers are thought to terminate largely in the lung interstitium close to the pulmonary capillaries. For this reason, these fibers were referred to as juxtacapilliary receptors or J-receptors (Paintal 1969, Mazzone and Undem 2016).

Vagal C-fibers innervating the respiratory tract have been subclassified based on whether the cell body is situated in the jugular (neural crest-derived) or nodose (placodal-derived) ganglia (Undem *et al.* 2004). Extensive studies in mice and guinea pigs reveal the C-fiber nerve phenotype is distinct between nodose and jugular C-fibers. The jugular C-fibers are more apt to contain sensory neuropeptides than nodose C-fibers. The nodose C-fibers can be stimulated by a wider range of chemical stimuli than jugular C-fibers (Nassenstein *et al.* 2010).

The majority of C-fibers terminating in the large extrapulmonary airways of guinea pigs are jugular C-fibers, with nodose C-fibers comprising only 10-20 % of tracheal C-fibers (Riccio *et al.* 1996). In contrast, similar numbers of nodose and jugular C-fibers terminate in the intrapulmonary tissues (Undem *et al.* 2004). Importantly, where it has been studied, the C-fiber phenotype of a nodose and jugular C-fiber remains constant regardless of where it terminates within the respiratory tract. Therefore, when describing phenotypic subsets of C-fibers, the embryonic history has advantages over the location of the terminations. That embryonic history is important is verified by the observation that the jugular C-fiber phenotype is similar to the C-fibers that arise from neurons within the dorsal root ganglia (like jugular neurons, they too are derived from the neural crest) (Surdenikova *et al.* 2012).

Nodose and jugular C-fibers respond to potentially damaging mechanical forces in a graded fashion. They also respond to inflammatory mediators and tissue acidification (Mazzone and Undem 2016).

Unmyelinated C-fiber afferents comprise the majority of afferent nerves innervating the airways (Coleridge and Coleridge 1984). Afferent C-fibers are distinguished from mechanically sensitive afferents by their conduction velocity and their direct responsiveness to a wide variety of chemical substances acting at both ligand-gated ion channels and G protein-coupled receptors (Widdicombe 2001). The direct sensitivity of this class of afferents to chemical stimuli is inferred by the observation that chemical activation of C-fiber endings in the airways is not inhibited by pretreatment with a bronchodilator. Furthermore, this is supported by expression studies in vagal ganglia preparations which show a wide variety of ion channels and receptors in C-fiber afferents and by the ability of ligands of these receptors to produce action potentials in patch recordings of acutely isolated vagal neurons in culture (Mazzone and Undem 2016). Indeed, bronchodilators such as prostaglandin E_2 (PGE_2) and epinephrine actually enhance afferent C-fiber excitability rather than inhibit it (Lee and Pisarri 2001). C-fibre endings are polymodal, and thus can respond to both chemical and mechanical stimulation; their high threshold for mechanical activation means that C-fibers generally don't fire action potentials throughout the respiratory cycle but rather are recruited in times of tissue injury/inflammation or in the presence of noxious chemicals. Indeed, in addition to the long list of chemicals that can activate C-fibers, many inflammatory mediators can additionally sensitize C-fibers and lower their threshold for activation such that more physiological

stimuli (e.g., bronchoconstriction) may activate C-fibers in the diseased airways (Mazzone and Undem 2016).

A subpopulation of C-fibers synthesize neuropeptides that are subsequently transported to their central and peripheral nerve terminals (Mazzone *et al.* 2009), and this has been exploited to describe the morphology of C-fibers in a variety of species, including rats and guinea pigs. Neuropeptide staining of large airway wholemount preparations or of tissue sections of the lung shows a vast plexus of fine varicose fibers innervating the airway epithelium and effector structures such as airway smooth muscle, glands, the vasculature, and autonomic ganglia within the airway wall. It is important to note that the expression of neuropeptides in C-fibers is both species-dependent (for example, human vagal afferents contain fewer neuropeptides than do guinea pigs or rats) and dependent on the ganglionic origin of the C-fiber (nodose C-fibers largely do not express substance P or CGRP), and as such, it is not clear if the described morphology is true of all C-fibers and in all species (Mazzone and Undem 2016).

The absence versus presence of neuropeptide expression in subsets of C-fibers represents one example of heterogeneity among chemically sensitive afferent neurons. In dogs, airway C-fibers have been classified as "bronchial" or "pulmonary," a distinction based partly on anatomical termination sites and supported by differences in functional responsiveness to stimuli (Coleridge and Coleridge 1984). For example, bronchial C-fibers in dogs, but not pulmonary C-fibers, are responsive to histamine. However, this is not true in guinea pigs, as histamine is without direct effect on any airway C-fibers (Coleridge *et al.* 1978). Nevertheless, C-fiber subtypes have been identified innervating the airways and lungs of mice, rats, and guinea pigs, distinguished based on their ganglionic origin, molecular phenotype, responsivity, and termination sites within the airways (Ricco *et al.* 1996, Mazzone and Undem 2016).

Knowing that itch and cough are mediated by similar sensory neurons, the specifics of activating these fibers can be examined and compared. Two types of receptors are activated on sensory fibers, ionotropic and metabotropic. In both of these categories, itch and cough work through the same receptors in multiple instances (LaVinka and Dong 2013).

TRPV1 receptor

The transient receptor potential, vanilloid 1 (TRPV1) receptor is a membrane-bound, ligand-gated channel. It is a six transmembrane spanning protein that undergoes a conformational change upon binding of a ligand, allowing cations into the nerve and resulting in activation of primary sensory neurons (Caterina *et al.* 1997).

Itch

The most famous TRPV1 ligand is capsaicin. If capsaicin is applied in a punctuate manner to the epidermis, it causes itch (Sikand *et al.* 2009). TRPV1 plays an important role in histamine-dependent itch (LaVinka and Dong 2013). TRPV1 is an important component in multiple itch pathways (Patel *et al.* 2011). TRPV1 expression is increased in itching skin lesions and its activation promotes itch by secreting soluble factors (Steinhoff *et al.* 2003).

Cough

Potential (TRP) family are a large family of ion channel proteins some of which are expressed on airway sensory nerve terminals (Bonvini and Belvisi 2017). TRPV1 is also thought to be a strong effector of the cough reflex in response to many different stimuli (Grace *et al.* 2012). TRPV1 is found in both vagal ganglia as well as throughout the airway (Watanabe *et al.* 2006). Airway mucosal biopsies from patients suffering from chronic cough showed a fivefold increase in TRPV1 expression (Groneberg *et al.* 2004). Capsaicin is a commonly used tussive agent and resiniferatoxin, a strong TRPV1 agonist, causes cough by direct activation of TRPV1 (Laude *et al.* 1993). PGE_2 and bradykinin, which are known to cause cough, depolarize vagal sensory neurons through activation of TRPV1 (Grace *et al.* 2012). Citric acid evoked cough works through activation of TRPV1 and antagonizing the receptor with capsazepine reduces citric acid cough (Lalloo *et al.* 1995).

TRPA1 receptor

The Transient Receptor Potential Ankyrin 1 (TRPA1) channel, originally called ANKTM1 (Story *et al.* 2003), is an ion channel dominantly expressed in a subset of nociceptive somatosensory neurons where it acts as a polymodal sensor for diverse physical and chemical stimuli of extracellular or intracellular origin. There is progress in the identification of various signalling pathways involved in the sensitization of the TRP channels by pro-inflammatory agents (Kádková *et al.* 2017).

Itch

In the skin, histamine-dependent mechanisms contribute to itch; however, several distinct histamine-independent itch mechanisms have also been described. One involves the Mas-gene-related G protein-coupled receptor family, which includes MRGPRA3 and MRGPRC11 (LaMotte *et al.* 2014). Another mechanism involves the bile acid receptor TGR5, also known as GPR130 or GpBAR1 (Alemi *et al.* 2013). TRPA1 has been shown to be important to histamine-independent itch.

MRGPRA3 and MRGPRC11 are expressed by subsets of sensory DRG neurons innervating the skin. Activation of MRGPRA3 by the anti-malarial drug chloroquine, or MRGPRC11 activation by the endogenous pruritogen, bovine adrenal medulla 8-22 peptide (BAM8-22), induces itch. However, it remains unclear if both TGR5 and MRGPR mechanisms co-exist within the same DRG neuronal populations or whether they exist in, and therefore recruit distinct populations of DRG neurons (Castro *et al.* 2019).

Both TRPV1 and TRPA1 are co-expressed in a large subset of sensory nerves, where they integrate numerous noxious stimuli. It is now clear that the expression of both channels also extends far beyond the sensory nerves in the skin, occurring also in keratinocytes, mast cells, dendritic cells, and endothelial cells. In these non-neuronal cells, TRPV1 and TRPA1 also act as nociceptive sensors and potentiate the inflammatory process (Gouin *et al.* 2017).

While TRPV1 and TRPV4 are expressed both by sensory neurons and keratinocytes, it has recently been demonstrated that the specific and selective activation of TRPV1 on keratinocytes is sufficient to induce pain. Similarly, the targeted activation of keratinocyte-expressed TRPV4 elicits itch and the resulting scratching behavior (Talagas and Misery 2019).

Cough

TRPA1 is the only member of the Ankyrin family of TRP channels and was first discovered in cultured human lung fibroblasts (Jaquemar *et al.* 1999) but is now known to be widely expressed in sensory nociceptive neurons in the vagal, jugular and nodose ganglia (Story *et al.* 2003). However, unlike TRPV1, TRPA1 only seems to activate C-fibers and interestingly single-cell PCR experiments identified that although they are often co-expressed in neurons within the jugular and nodose ganglia they are also found separately (Wortley *et al.* 2016). It is a polymodal ion channel shown to be a sensor of noxious cold (Story *et al.* 2003). TRPA1 channels are activated by a range of natural products such as allyl isothiocyanate, allicin and cannabinol, found in mustard oil, garlic and cannabis and by environmental irritants (Bonvini and Belvisi 2017). TRPA1 is also the molecular target for reactive and electrophilic by-products of oxidative stress. This also includes electrophiles such as hypochlorite and hydrogen peroxide (Taylor-Clark 2016). TRPA1 can also be indirectly activated by the inflammatory mediators PGE_2 and bradykinin (Grace *et al.* 2012). In the airways, TRPA1 is highly expressed in neuronal tissue including nasal trigeminals, vagal airway neurons and spinal DRGs (Nassenstein *et al.* 2008, Wortley *et al.* 2016), and is predominantly expressed on C fibers (Robinson *et al.* 2018). Activation of TRPA1 causes activation of vagal bronchopulmonary C fibers (Nassenstein *et al.* 2008) and causes cough in both animals and man (Birrell *et al.* 2009). Unlike TRPV1, TRPA1 has only been shown to activate C fibers and not the more mechanically sensitive Aδ fibers (Robinson *et al.* 2018).

The fact placebo and active had virtually identical effects on the cough counting speak strongly to the idea that blocking TRPA1 in the periphery, and indeed centrally may not have any effect on clinically important endpoints. Similarly, the failure of TRPV1 antagonists to make it to the clinic having shown a high degree of target engagement also suggests that peripheral sensitization is at best a minor feature of cough hypersensitivity syndrome. The recent success in multiple clinical studies of the ATP P2X3 receptor blocker AF219 (Abdulqawi *et al.* 2015) demonstrated that hypersensitization upstream of the vagal nerve terminals underlies the mechanism for cough hypersensitivity syndrome. TRPA1 antagonists may have a role in other disease areas but the current evidence suggests that we are unlikely to fundamentally interfere with the mechanism of cough hypersensitivity through peripheral receptor blockade (Morice 2017).

Inflammatory mediators

Activation of TRP channels leads to release of inflammatory neuropeptides from C-fibers. These neuropeptides include the tachykinins (Substance P, neurokinin A, neurokinin B) and calcitonin gene-related peptide (CGRP) (Holzer 1998). Other inflammatory chemicals, such as bradykinin, may also be released. Neurogenic inflammation has been shown to play roles in both chronic itch and chronic cough (LaVinka and Dong 2013).

Substance P (SP)

Itch

SP and neurokinin 1 receptor (NK1R) play an important role in itch signalling. This is supported by a large and growing body of evidence demonstrating that (i) NK1R is broadly expressed in multiple cell types in the skin, such as keratinocytes and mast cells, as well as the CNS; (ii) in many pruritic dermatological conditions, based on immunohistochemical studies, overexpression of NK1R is seen in the epidermis and increased numbers of SP-expressing nerve fibers and inflammatory cells are found in the skin; (iii) SP binding to NK1R-bearing neurons in the dorsal horn of the spine is a key relay point in itch signalling; and (iv) the blocking of NK1R via the use of NK1R antagonist interrupts transmission of the itch signal. SP and NK1R are overexpressed across multiple chronic itch-inducing conditions and that NK1R antagonism disrupts itch signalling and reduces itch provide a rationale for targeting this pathway as a potential treatment of chronic pruritus across multiple diseases (Ständer and Yosipovitch 2019).

Cough

Substance P and NK1R are implicated in chronic refractory cough pathophysiology. The efficacy and safety of orvepitant, a brain-penetrant NK1R antagonist, in an open-label study in patients with chronic refractory cough were established. Orvepitant resulted in a significant and sustained improvement in objective cough frequency, severity visual analogue scale (VAS), and quality of life; appeared safe, and merits further clinical investigation (Smith *et al.* 2019).

Bradykinin

Itch

In humans, the subjective response to intradermal injection of bradykinin is intense burning pain. Bradykinin injection also led to mild to moderate itch in about 60 % of participants, but the itching was only noticed after cessation of the burning pain. The preference for pain over itch may change in atopic dermatitis where administration of bradykinin in lesional skin causes less pain and a robust itch sensation (Potenzieri and Undem 2012). Itch evoked by bradykinin is histamine-independent (Hosogi *et al.* 2006). Both kinin receptors, B1 and B2, are shown to contribute to itch (LaVinka and Dong 2013).

Cough

The mechanism of angiotensin-converting enzyme (ACE) inhibitor-induced cough remains unclear. Possible protussive mediators include bradykinin and substance P, which are degraded by ACE and therefore accumulate in the upper airway or lung when the enzyme is inhibited; and prostaglandins, the production of which may be stimulated by bradykinin. Bradykinin-induced sensitization of airway sensory nerves has been proposed as a potential mechanism of ACE inhibitor-induced cough (Fox *et al.* 1996). Some evidence has suggested that the therapeutic effect of ACE inhibitors may involve the activation of bradykinin receptors (Ignjatovic *et al.* 2002), and that bradykinin receptor gene polymorphism is associated with the cough that is related to ACE inhibitors (Mukae *et al.* 2000). A dry, persistent cough is a well-described class effect of the angiotensin-converting enzyme (ACE) inhibitor medications (Dicpinigaitis 2006). Bradykinin's tussive effects are tied to the activation of TRPV1 and TRPA1 (LaVinka and Dong 2013).

Histamine

Itch

Histamine is one of the best-characterized pruritogens in humans. It is known to play a role in pruritus associated with urticaria as well as ocular and nasal allergic reactions. Histamine mediates its effect via four receptors. Antihistamines that block the activation of the histamine H_1 receptor, H_1R, have been shown to be effective therapeutics for the treatment of pruritus associated with urticaria, allergic rhinitis, and allergic conjunctivitis. However, their efficacy in other pruritic diseases such as atopic dermatitis and psoriasis is limited. The other histamine receptors may also play a role in pruritus, with the exception of the histamine H_2 receptor, H_2R. Preclinical evidence indicates that local antagonism of the histamine H_3 receptor, H_3R, can induce scratching perhaps via blocking inhibitory neuronal signals. The histamine H_4 receptor, H_4R, has received a significant amount of attention as to its role in mediating pruritic signals. Indeed, it has now been shown that a selective H_4R antagonist can inhibit histamine-induced itch in humans. This clinical result, in conjunction with efficacy in various preclinical pruritus models, points to the therapeutic potential of H_4R antagonists for the treatment of pruritus not controlled by antihistamines that target the H_1R (Thurmond *et al.* 2015).

Cough

The peripheral sensory and autonomic nervous system densely innervates mucosal barrier tissues including the skin, respiratory tract and gastrointestinal tract that are exposed to allergens. It is increasingly clear that neurons actively communicate with and regulate the function of mast cells, dendritic cells, eosinophils, T_h2 cells and type 2 innate lymphoid cells in allergic inflammation. Several mechanisms of cross-talk between the two systems have been uncovered, with potential anatomical specificity. Immune cells release inflammatory mediators including histamine, cytokines or neurotrophins that directly activate sensory neurons to mediate itch in the skin, cough/sneezing and bronchoconstriction in the respiratory tract (Voisin *et al.* 2017). Causing increased cough sensitivity can lead to chronic cough and chronic cough sufferers do have elevated levels of histamine in their sputum and lungs (McGarvey *et al.* 1999, Birring *et al.* 2004).

Serotonin

Itch

5-HT (5-hydroxytryptamine, serotonin) is another endogenous biogenic amine that has been shown to evoke itch in humans (Potenzieri and Undem 2012). Consistent with this, 5-HT stimulates action potential discharge in a subset of human cutaneous C-fibers (Schmelz *et al.* 2003). The itch sensation evoked by 5-HT was weaker than the sensation of itch evoked by histamine (Schmelz *et al.* 2003, Hosogi *et al.* 2006). Although serotonin is a relatively weak pruritogen in normal non-lesioned skin, it should be kept in mind that it is a much stronger pruritogen when administered to lesioned skin from patients with atopic dermatitis (Hosogi *et al.* 2006). 5-HT also evokes scratching behavior in experimental animals and in rats, the scratching behavior to 5-HT is associated with activation of C-fibers, but not faster conducting myelinated nerve fibers (Hachisuka *et al.* 2010). Based on studies with selective 5-HT receptor subtype agonists and antagonists it appears that in mice the 5-HT2 receptor subtype is responsible for 5-HT-induced itch (Yamaguchi *et al.* 1999). 5-HT has also been proposed to be involved in the pathogenesis of pruritus in polycythaemia vera, a myeloproliferative neoplasm associated with intense itching (Diehn and Tefferi 2001). Selective serotonin reuptake inhibitors have displayed beneficial effects in palliative care patients with pruritus of different natures (Xander *et al.* 2013, Luo *et al.* 2015).

Cough

Serotonin stimulates respiratory reflexes (Coleridge *et al.* 1989). In dogs, phenylbiguanide, a 5-HT receptor agonist, activates bronchial C-fibers (Coleridge and Coleridge 1977). Nodose ganglia C-fibers respond to serotonin. The guinea pig also shows activation of the 5-HT3 receptor on intrapulmonary nodose C-fibers (Lee *et al.* 2004). The jugular ganglion C fibers in guinea pigs do not respond to 5-HT (Chuaychoo *et al.* 2005). However, 5-HT does stimulate jugular ganglion C fibers in mice, possibly through a metabotropic 5-HT receptor (Potenzieri *et al.* 2012). It is possible the metabotropic 5-HT2A receptor might be involved because in mouse tracheal preps, serotonin causes tracheal muscle contraction via the 5-HT2A receptor (Weigand *et al.* 2009, Campos-Bedolla *et al.* 2019). This contrasts with activation of the nodose C fibers of mice, which is mediated by the ionotropic 5-HT3 receptor (Potenzieri *et al.* 2012, LaVinka and Dong 2013).

Conclusion

Itch is described as an irritating sensation that triggers a desire to scratch and the chronic itch is defined as pruritus lasting longer than 6 weeks. The pathophysiological mechanisms of chronic itch are poorly understood but likely involve sensitization of itch-signalling pathways. The sensory Aδ- and, more importantly, C-fibers play a pivotal role in itch perception. Tied closely to activation of these sensory fibers is neurogenic inflammation, which involves the release of inflammatory agents like SP and bradykinin as well as products of mast cells, all which result in itch, flares, wheals, and can easily become chronic conditions. All of these individual factors also play roles in cough and the similarities between itch and cough in sensing irritants from the environment can be seen. Cough has an additional factor to incorporate though, movement. While the end result of the itch is scratching, the muscles and joints being used to scratch are not receiving signals directly from the itching skin. With cough, smooth muscle movement is incorporated into the actual cough reflex in order to move the irritant or blockage up the airway and out. It is this additional motility aspect that could result in more specialized involvement of myelinated fibers in cough, a specialization not needed in itch (LaVinka and Dong

2013). Realizing the similarities between itch and cough can lead to new ideas and even perhaps, new ways to apply existing medications to new conditions. Clinically, anti-histamines are often prescribed and have been shown to help with itch and cough. However, by no means do anti-histamines help with all conditions. This indicates a real need to discover the histamine independent pathways involved. Progress has been made recently in histamine-independent itch research with the discovery of MRGPR genes. Future investigations into vagal neuroscience should also provide for novel therapeutic targets and strategies aimed at reducing the suffering of those inflicted with airway-related and also skin-related pathology.

Ethical approval

There are no unpublished experiments and data presented in this review article.

Conflict of Interest

There is no conflict of interest.

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