The Intricacies of Pruritus

Arvindh Sekaran[1]

Abstract
Pruritus refers to the colloquial term 'itch', an unpleasant sensation that stimulates the desire to scratch. A plethora of aetiologies have been described for itch, however the complexities of the biological interactions that underlie the sensation have not been fully elucidated. Nevertheless, significant progress has been made in solving the conundrum of why we itch and scratch.

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[1]School of Clinical Medicine, University of Cambridge, Cambridge, UK
***Correspondence to**: Arvindh Sekaran, as2466@cam.ac.uk

Pruritus refers to the colloquial term 'itch', an unpleasant sensation that stimulates the desire to scratch. A plethora of aetiologies have been described for itch, however the complexities of the biological interactions that underlie the sensation have not been fully elucidated. Nevertheless, significant progress has been made in solving the conundrum of why we itch and scratch. Accordingly, this review will unpick the peripheral and central interactions between molecules, cells and pathways involved in pruriceptive itch, as this is the most extensively researched, with some exploration of neuropathic and psychogenic pruritus. Where applicable, the current and future therapeutics for pruritus will be highlighted.

1. Introduction

An itch (pruritus) can be defined as an unpleasant cutaneous sensation that elicits the desire to scratch [1]. Evolutionarily, the itch-scratch reflex developed in mammals as a defence mechanism to aid removal of harmful environmental threats such as irritant plant fibres or parasites from the surface of the skin [2]. However, although pruritus is often experienced acutely, in some instances the sensation can persist for more than six weeks leading to a burdensome chronic itch. Affecting one in five people in their lifetime, chronic pruritus significantly reduces quality of life and can be as debilitating as chronic pain [3], which is markedly reflected in the Chinese proverb, "Pain is easier to endure than an itch".

The aetiologies of pruritus are overwhelmingly diverse, but can be split into the following broad categories: pruriceptive, neuropathic, neurogenic and psychogenic. Pruriceptive itch is the most common and occurs when sensory afferent nerve fibres innervating the skin are activated by various exogenous or endogenous pruritogens (mediators of itch). In addition to dermatological disorders, such as atopic dermatitis, systemic conditions such as cholestatic hepatic disease are also associated with pruriceptive itch. In contrast, neuropathic itch results from neural dysfunction as a consequence of anatomical damage whereas neurogenic itch results from a change in neurochemical dynamics involved in itch perception, in the absence of anatomical damage. Damage to neurones and subsequent neuropathic itch can arise via an array of conditions including malignancy, shingles and multiple sclerosis. This differs from neurogenic itch, which is associated with various systemic conditions such as chronic kidney disease. Lastly, psychogenic itch is often associated with underlying mental health illnesses such as depression and obsessive-compulsive disorders [4, 5]. Although there have been recent improvements in the pathophysiological understanding of pruritus, there is a clinical need for non-toxic, effective pharmacotherapies which show efficacy against all aetiologies.

2. Peripheral processing of itch

A plethora of inflammatory and non-inflammatory substances have been established to evoke pruritus experimentally through an array of genetic, electrophysiological, behavioural and psychophysical studies. These studies have also led to the speculation of several theories, which serve to explain how itch is coded in conjunction with its sister sensory modality - pain.
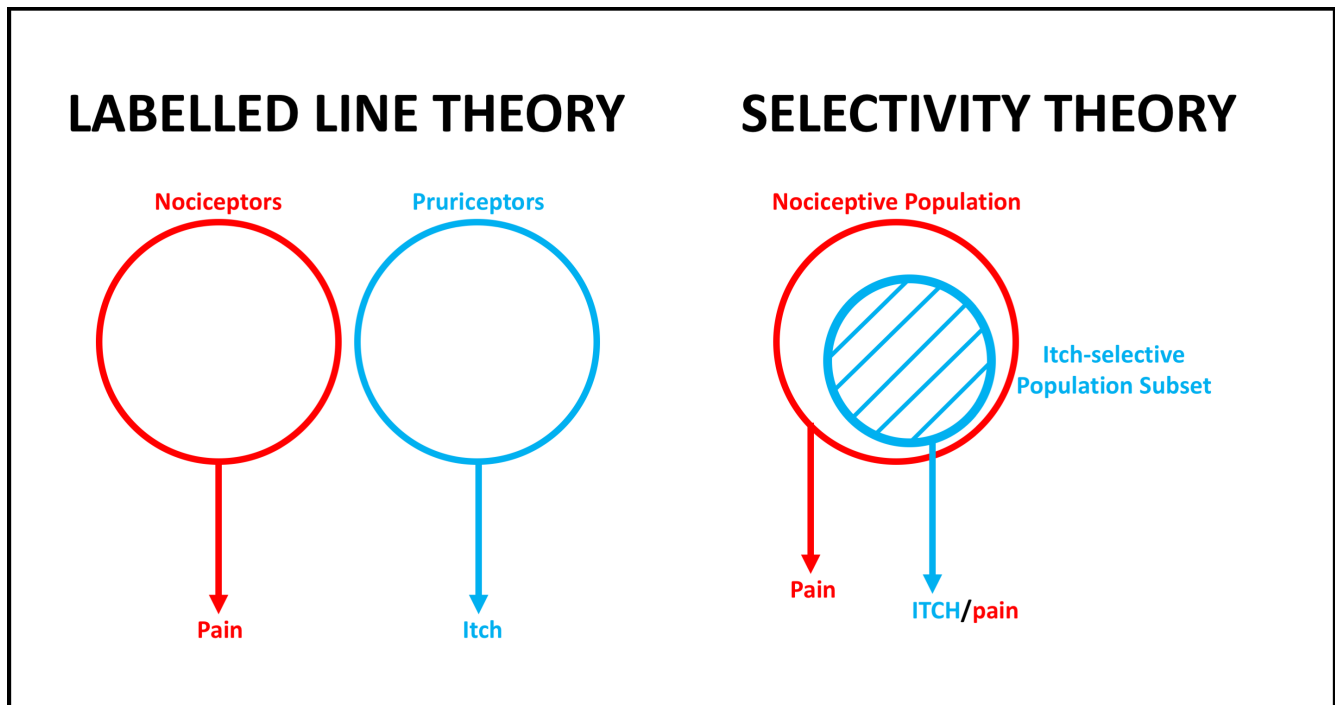
Figure 1. Labelled Line Theory vs Selectivity Theory

2.1 Histaminergic itch

The most extensively studied pruritogen is histamine, which was originally studied for its effects on vasculature. Early on, histamine was demonstrated to elicit itch after being injected intracutaneously into humans in a dose-dependent manner [6]. Subsequent studies also showed that histamine is a key inflammatory pruritogen released after insect bites and allergic reactions [7, 8].

Histamine binds to widely expressed G-protein couple receptors (GPCRs) designated H1 to H4. H1, expressed by peripheral neurones, is the main subtype that mediates itch with some contribution from H4 [9]. Anti-histamines targeting either one of these receptors attenuate itch both experimentally and clinically, thereby further supporting their involvement in acute pruritus [10]. As histamine receptors do not themselves conduct ions, in order to elicit an action potential they must couple to ion channels. Using electrophysiological and heterologous expression studies, it has been shown that the transient receptor potential vanilloid receptor-1 (TRPV1) mediates inward currents secondary to H1 activation [11]. Interestingly, TRPV1 is also activated by capsaicin and noxious thermal stimuli, illustrating how itch and pain are physiologically intertwined.

The particular subpopulations of peripheral neurones implicated in histamine-mediated itch are unmyelinated mechanically-insensitive C fibres (C-MIAs) and a few myelinated A-δ fibres, which reside at the epidermal-dermal junction of the skin [12, 13]. These fibres were considered to be similar yet distinct to those that transmit pain, which led to the proposal of the 'labelled-line theory'. This theory postulates that two distinct and separate neuronal populations carry itch and pain - pruriceptors and nociceptors respectively. It was established that 30% of C-MIAs were responsible for carrying histamine-induced itch with subsequent studies revealing that this subset of neurones also weakly responds to a variety of chemical mediators that elicit pain. These results refuted the 'labelled-line theory' and instead favoured another theory, which is garnering increasing support - the 'selectivity theory'. This theory suggests that pruriceptors predominantly respond to itch, but can also respond to pain, thus making them a subset of nociceptors [14, 15] - (Figure 1).

2.2 Non-histaminergic itch

However, although histamine has a clear role in acute pruritus, the insensitivity of chronic pruritus to anti-histamines suggests that the complete nature of pruritus does not involve the histamine pathway alone [16]. A well-characterised initiator of histamine-independent signalling is mucunain, a highly pruritogenic proteolytic enzyme derived from the seedpods of cowhage (*Mucuna pruriens*) [17]. Unlike histamine-induced itch, H1 receptor antagonists do not inhibit cowhage-induced itch in humans. In fact, cowhage stimulates a distinct subset of nociceptive C-fibres known as mechanical and heat-sensitive C fibres (CMHs) [18]. Thus, specific subtypes of nociceptor C-fibres can signal itch in response to different pruritogens, further supporting the theory of selectivity - (Figure 2). Mucunain acts on protease-activated receptors (PARs), specifically PAR2 and PAR4. PARs are GPCRs, which activate via proteolytic cleavage of an extracellular domain to create a 'tethered ligand', which binds intra-molecularly to the cleaved recep-
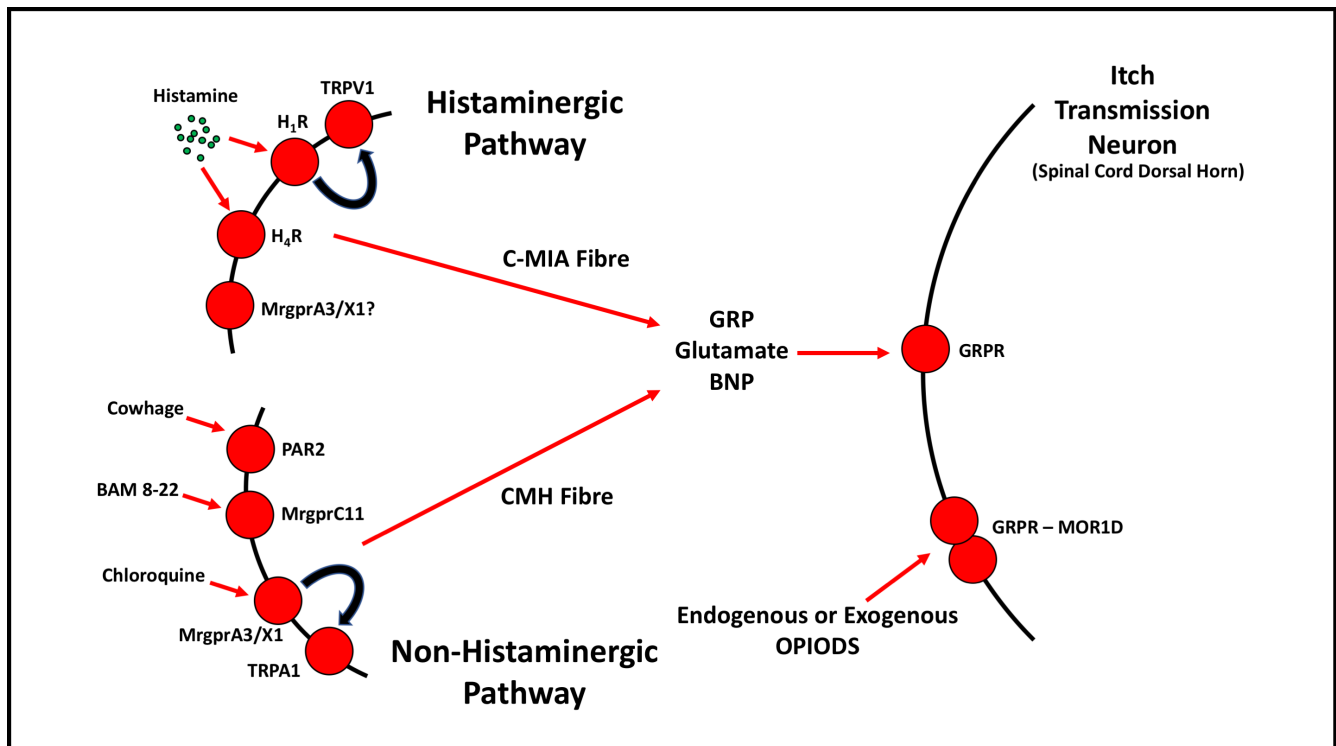
Figure 2. Components of histaminergic and non-histaminergic itch transmission

tor [19]. Accordingly, the development of PAR2-specific antagonists could help alleviate pruritus in those refractory to anti-histamines.

The Mas-related GPCRs (Mrgprs) are another class of GPCRs implicated in itch perception. The four main subfamilies of Mrgpr (MrgprA-MrgprD) in mice and the orthologous subfamily MrgprX in humans have been shown to be key mediators of itch [20]. Mice lacking a cluster of Mrgpr genes were found to have a significant deficit in itch upon injection with chloroquine, an anti-malarial drug with a common adverse effect of pruritus, suggesting an additional pathway for histamine-independent itch perception. Using heterologous expression studies, it was determined that chloroquine specifically activates MrgprA3 and human MrgprX1, which are exclusively expressed on peripheral sensory neurones. These MrgprA3$^+$ neurones were also found to be responsive to histamine and coexpressed MrgprC11, which mediates itch induced by the endogenous opioid derivative, bovine adrenal medulla peptide (BAM 8-22) [21]. The downstream target of these receptors is suggested to be the ion channel, transient receptor potential ankyrin 1 (TRPA1), as TRPA1-deficient mice displayed normal histamine-evoked responses, but significantly diminished responses to chloroquine and BAM 8-22 [22]. Furthermore, in an elegant *in vivo* study, TRPV1 was selectively expressed in murine MrgprA3$^+$ neurones. For these mice, capsaicin, an agonist for TRPV1 that normally evokes pain, strikingly evoked scratching behaviour instead. In mice lacking MrgprA3$^+$ neurones, scratching

responses to histamine and non-histamine substances were diminished, while pain behaviours were unaffected [23]. This suggests that MrgprA3$^+$ neurones cover a wide range of pruritogens and may exclusively signal for pruriceptive itch, thereby providing support for the labelled-line theory.

2.3 Non-neuronal modulation of itch

Although neurones clearly play a large role in itch perception, other cell types such as keratinocytes, mast cells and type 2 T-helper cells (T$_h$2) also contribute to peripheral itch [24] - (Figure 3). The predominant cell of the epidermis is the keratinocyte, which serves a barrier function as well as aiding the propagation of immune responses. One pro-allergic cytokine released by keratinocytes is thymic stromal lymphopoietin (TSLP), which has been implicated in the development of atopic dermatitis. The heterodimeric receptor for TSLP (TSLPR) is expressed by a subset of peripheral afferent nerve fibres and the injection of TSLP into the cheeks of mice elicited TRPA1-dependent scratching behaviour [25].

Keratinocytes also release chemokines such as interleukin 8 (IL-8) and chemokine ligand 5 (CCL5) which recruit immune cells such as histamine-releasing mast cells and have notably been found to be elevated in psoriatic patients [26]. Therefore, keratinocytes may be partially implicated in generating pruritus in certain dermatological conditions. Consequently, the investigation of keratinocytes has provided several therapeutic potentials. However, tezepelumab, a monoclonal antibody which impedes the inter-
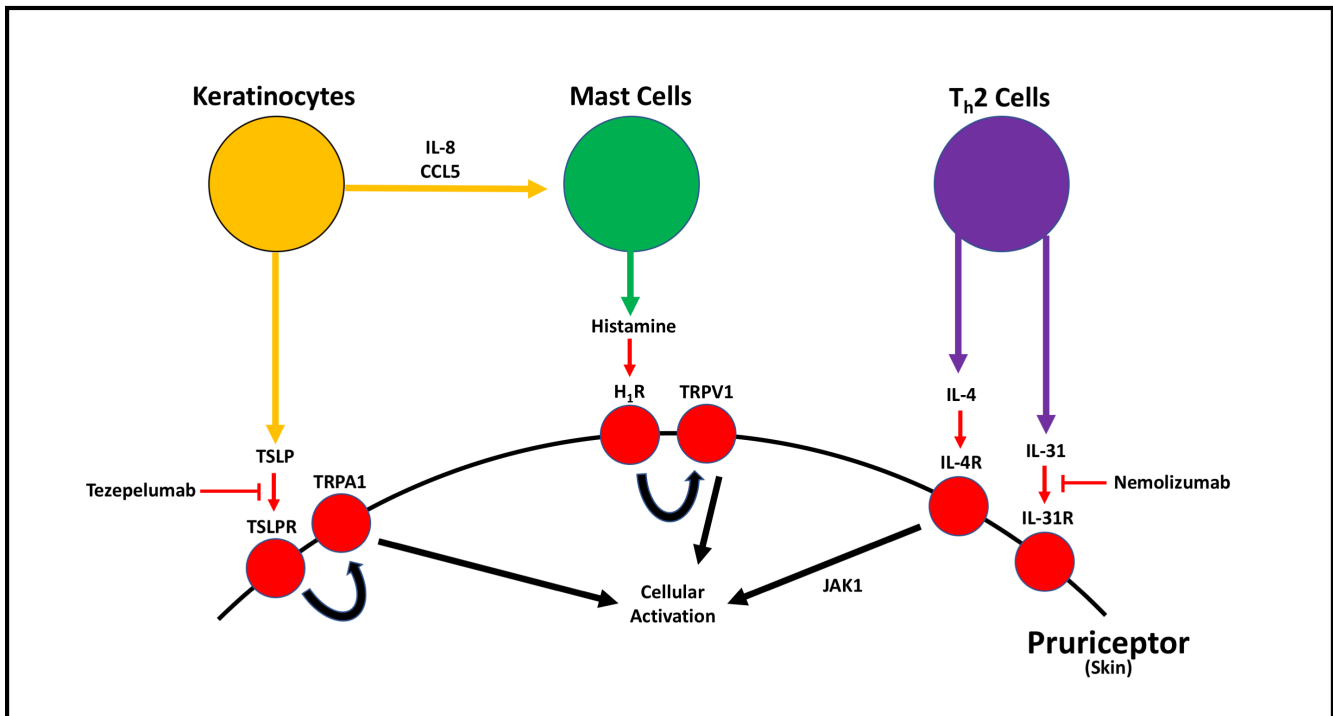
Figure 3. Non-neuronal components of pruriception

action between TSLP and TSLPR, disappointingly did not help a Phase 2a clinical trial (NCT02525094) to meet its primary endpoint of reducing the severity of atopic dermatitis when using a measuring tool called the Eczema Area and Severity Index (EASI) [27]. Nevertheless, a promising fusion protein antagonist targeting TSLPR with high affinity has recently been described [28].

Further important mediators of pruritus include interleukins released by T_h2 cells. For example, as interleukin 31 (IL-31) and its receptor (IL-31R) have been observed to be upregulated in the skin of patients suffering from atopic dermatitis, their role in pruritus has been investigated [29]. Targeting the IL-31/IL-31R axis has had recent success in a Phase 2 trial of nemolizumab, a humanized antibody blocking IL-31R, which led to significant reductions in pruritus among atopic dermatitis patients [30]. Another T_h2 interleukin, IL-4, has been recently found to directly activate pruritogen-sensitive sensory neurones expressing the IL-4 receptor (IL-4R) in both mice and humans. Further analyses using knockout mice showed that a kinase, Janus kinase 1 (JAK1), acted downstream of IL-4R to mediate scratching behaviour. Encouragingly, tofacitinib, a JAK inhibitor, reduced itch scores in patients with chronic idiopathic pruritus who were refractory to all other treatments. The blockade of IL-4R and JAK1 could therefore offer a potential therapeutic target to alleviate chronic pruritus [31, 32].

2.4 Mechanical itch
Thus far, the chemical basis of peripheral itch perception has been addressed. However, pruriceptive itch also encompasses a discrete mechanical component such as that evoked by an insect crawling over skin. A recent human psychophysical study showed that the vibration of hairs on participants' faces could induce mechanical itch. Through microneurographic studies, it was highlighted that this signal may be carried by low-threshold mechanoreceptor C-fibres [33, 34]. Therefore, as further work is still required to establish the putative membrane receptor(s) for mechanical itch, it is clear that the complete intricacies of itch perception are not yet fully elucidated [35].

3. Central processing of itch

Downstream of the complex interactions that occur at the epidermis, much work has been done to unravel the central neurophysiology of pruritus and the relationship between dorsal root ganglion (DRG) neurones and spinal interneurons. C and $A\delta$ fibres are DRG neurones, and those that carry signals of pain and itch from the skin synapse in lamina I-II of the dorsal horn of the spinal cord [24].

3.1 Peripheral and central neuronal networks
Gastrin-releasing peptide (GRP) has been shown to be key to the communication between DRG neurones and spinal neurones. Its expression has been detected in a subset of C and $A\delta$ fibres similar to those that transmit itch, suggesting GRP may signal in itch-specific fibres [36]. The
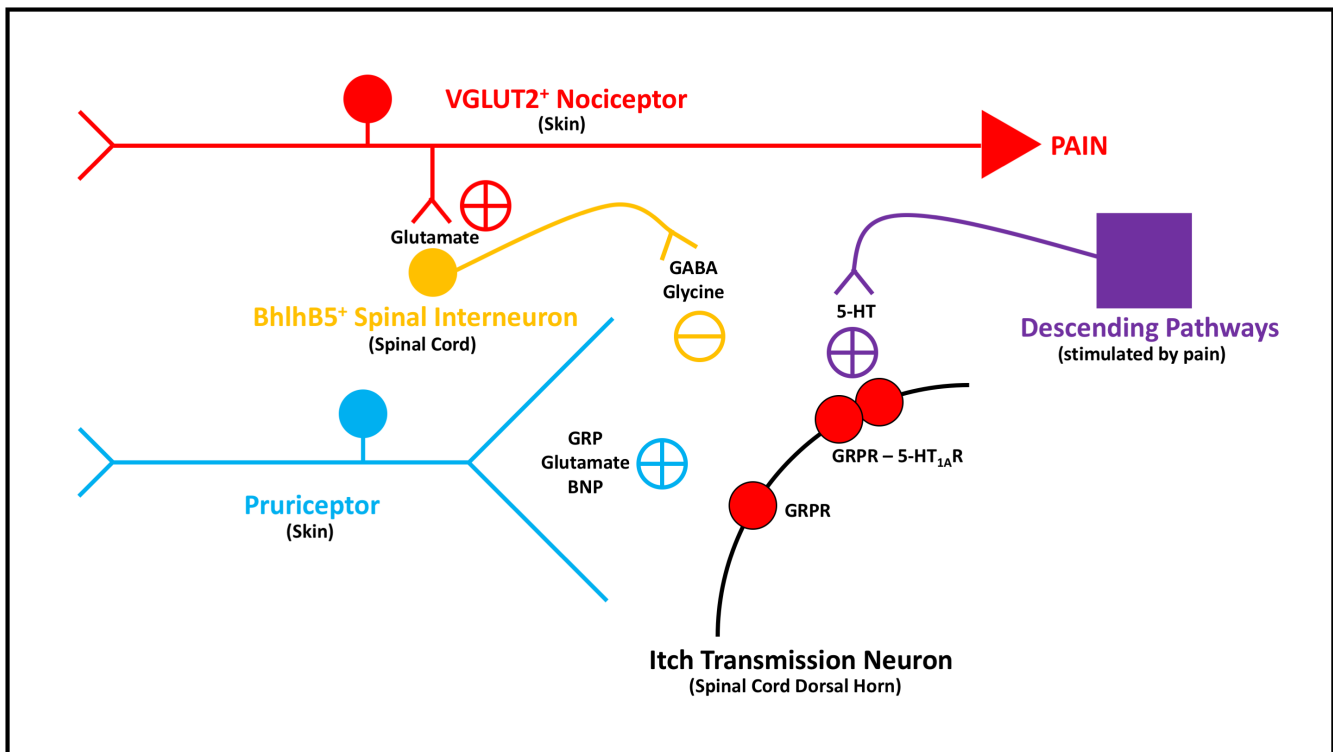
Figure 4. Neuronal circuits involved in the itch-scratch cycle

GRP receptor (GRPR) was also localised to lamina I-II of the dorsal horn and ablation of GRPR+ neurones in mice led to a near complete loss in histaminergic and non-histaminergic scratching behaviour, with no change in pain responses [37]. Together, this indicates that GRP-GRPR signalling may allow itch-specific signalling, which thus supports the labelled-line theory. Intriguingly, an isoform of the μ-opioid receptor (MOR1D) has been revealed to form a heterodimer with GRPR, allowing opioids to cross-activate GRPR+ neurones [38]. This may partly explain why pruritus is a common adverse effect of opioids such as morphine and further emphasizes GRPR's role in transmitting itch.

Another recently identified neuropeptide involved in itch transmission is B-type natriuretic polypeptide (BNP). Putative pruriceptors, which possess both TRPV1 and MrgprA3/C11, have been shown to express BNP. Furthermore, BNP knockout mice exhibited a deficit in scratching behaviour to a wide variety of pruritogens but retained pain-related behaviours [39]. Nevertheless, further studies are still required to dissect the relationship between BNP and GRP in itch perception in order to determine if they constitute parallel or interwoven pathways.

3.2 Why does scratching relieve an itch?

Scratching provides a noxious mechanical stimulus, which commonly alleviates pruritus. Fortunately, genetic knockout studies in mice have provided an insight into the inhibitory effect of scratching-induced pain on itch - (Figure

4). Deletion of either vesicular glutamate transporter 2 (VGLUT2) from peripheral nociceptors or the transcription factor Bhlhb5 from dorsal horn spinal neurones leads to augmented pruritic responses from mice [40, 41]. These studies support a model whereby glutamatergic nociceptors activate Bhlhb5-expressing interneurons, which in turn inhibit itch perception, providing an explanation as to why scratching relieves pruritus [42].

Unfortunately, lichenification and excoriations of the skin seen in many chronic pruritic conditions occurs as a consequence of the vicious itch-scratch cycle. Evidence suggests that the cycle itself is underpinned by GRPR in conjunction with a widely studied neurotransmitter, serotonin (5-HT) [43]. Using pharmacological and behavioural screening it has been shown that the mechanical pain evoked by scratching stimulates the release of 5-HT from descending neuronal pathways. 5-HT then activates 5-HT_{1A} receptors expressed by spinal neurones, which inhibits the processing of pain but facilitates the processing of itch. GRPR-5-HT_{1A} heteromeric complexes were found to activate GRPR signalling, thus amplifying itch perception and creating the urge to scratch more. Therefore disrupting this cross-talk may generate a useful anti-pruritic therapy [44]. However, the interactions between spinal neural circuits and their relative contributions need to be fully ascertained before targeted therapeutics can be developed for central mediators of itch.

4. Neuropathic and psychogenic pruritus

Although our knowledge of pruriceptive itch has blossomed in the past ten years, neuropathic and psychogenic itch remain substantially unresolved. Neuropathic pain has been associated with axonal degeneration and the loss of glial cell support, leading to pruriceptive neural circuitry dysfunction with the disinhibition and sensitisation of pruriceptors [45]. The treatments for neuropathic itch are comparable to that for neuropathic pain, such as pregabalin, which remarkably reflects the extent to which these two sensory modalities are interlinked. Importantly, pruritus does not solely involve peripheral processes, but also integrates higher cortical processing of somatosensory, cognitive and emotional components, which may become deranged in psychogenic pruritus [46]. A key example is delusional parasitosis, a psychodermatological disorder in which individuals incorrectly believe they are infested with parasites and subsequently have an urge to scratch excessively. Magnetic resonance imaging studies have demonstrated an association of this disorder with disruption of the prefrontal cortex, which is involved in behavioural judgment, and the somatosensory cortex [47]. Patients with similar psychoses often require antipsychotics such as risperidone to alleviate their symptoms, yet the atypical antipsychotic class of drugs, from which risperidone is from, is also often associated with the exacerbation of pruritus [48]. Crucially, an integrated multidisciplinary team comprised of dermatologists, psychiatrists and social workers is required to adequately manage the complexity of psychogenic pruritus.

5. Conclusion

In Dante's *Inferno*, inexorable itch is the punishment for those in the penultimate circle of Hell. Unfortunately, this may be the current plight of those suffering from chronic itch due to the lack of effective anti-pruritic therapies. Substantial progress has been made in illuminating the complex web of molecules, cells and neural circuitry involved in pruritus and discriminating the interconnected yet distinct modalities of itch and pain. However, numerous unanswered questions still remain which will inevitably steer the direction of future research. For example, investigating a larger range of pruritic mediators such as the involvement of autotaxin in cholestatic pruritus and abnormal astrocytes in atopic dermatitis may enable the development of more specific anti-pruritic therapies [49, 50]. Although briefly mentioned, unravelling the influence of the sensitisation of peripheral and central neural circuitry on pruritic conditions may also provide us with a deeper understanding of neuropathic and psychogenic pruritic disorders. Due to the multifactorial nature of itch, a universal effective treatment is unlikely, however, targeted therapies are emerging on the horizon that may hold promise in the management of debilitating pruritus in the future.

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