# ‘Why do we itch and scratch?’

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## Introduction:

Pruritus is derived from the Latin word pruritic (prʊəˈrɪtɪk) to mean ‘an itching’. The response generated; *the* scratch equates to a physiological protective mechanism to protect the skin barrier from external harmful irritants in an acute setting. However, chronic itch, defined as a persistent pruritic urge lasting longer than six weeks is associated with significant negative impact on ones quality of life. The incidence of chronic itch was seen to increase with age reaching a maximum of 20.3% in a cohort of people aged between 61-70 years (1) The presence of chronic itch was shown to be as debilitating as chronic pain by Kini et al (2) attributed to the lack of effective treatment options available to these patients. Those with chronic pruritus reported experiencing mood and sleep disturbances through the Dermatology Life Quality Index (DLQI) (3) No major classification of pruritus exists but broad classification can be made into four major causes; dermatological, systemic, neuropathic and psychogenic (4). Whether the aetiology is dermatological or not, there exists a secondary dermatological response to the pruritic actions with lichenification and excoriations (5) of the skin which can predispose to an increased risk of infection, particularly from S. Aureus, due to the micro-penetrations of nails introducing the source of infection.

The start of all things '*itch*':

One chronic dermatological condition that I have been exposed to on my dermatology elective placement was Trigeminal Trophic Syndrome (TTS) – the instigator in my fascination with all things *itch*. TTS is a chronic condition that arises from an insult to a peripheral or central component of the trigeminal nerve – usually a stroke involving the trigeminal nucleus centrally. Ulceration and effacement of the dermis to deep tissues and bone can occur to a various intensity due to the unconscious drive to scratch in response to the paraesthesia (6) leading to profound facial disfigurement. Currently no standard methods of care have been proven efficacious, some reports on thermoplastic dressings have been suggested, (7) but new targets must be sought in order to provide efficient care for these patients with a debilitating chronic itch. The lack of primary treatment options for these patients put me in pursuit to know more about the complicated mechanism of itch and how its' complicated pathways has proven to remain enigmatic.

An overview of the pathway:

In the acute setting pruritus is a protective mechanism from external stimuli. This reflex is thought to be modulated neurologically from the level of the skin, with peripheral and/or central neurological signalling components. It is believed to be a sensory modality; similar to pain and touch. Therefore a complex pathway of mediators are involved in the sensation.

Small unmyelinated C fibres that are mechanically insensitive, extremely slowly conducting, and excited by the application of histamine, a known puritogen, were shown to be involved in transmitting the signal from the periphery to the spinothalamic tract (8). These primary afferent neurons synapse with cell bodies located in the dorsal root

ganglia (DRG). A decussation results in the signal reaching certain brain regions (Fig. 1). These pathways were shown to overlap with central regions involved in pain sensation (8)

Anatomically the itch and pain primary afferents are indistinguishable and both sensations can arise from chemical, temperature and mechanical forces. However, itch sensing neurons were believed to be a subpopulation of nociceptive neurons as proposed by the intensity-coding theory. The proposition of this theory was that low firing rates from specific nociceptive neurons generated the sensation of itch but once a higher firing frequency was attained the activity would be centrally interpreted as pain. (9)(10) The current suggestion is that itch neurons are recognised as their own entity of afferents, functionally distinct from those of nociception.

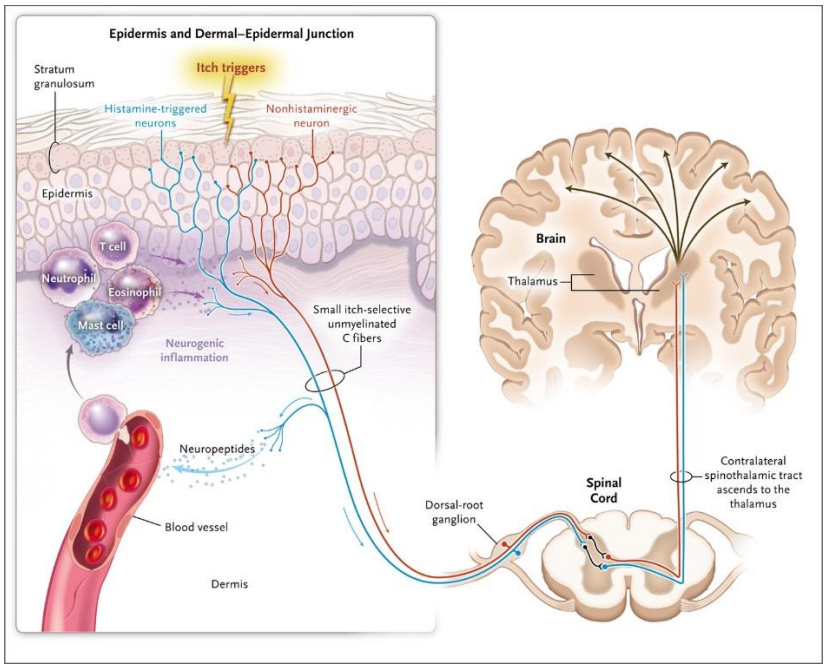


Figure 1. Yosipovitch et al. Chronic pruritus. New England Journal of Medicine. April 2013.

Where it all starts… signalling at skin level:

Cytokines are well established signalling molecules of the immune system. These molecules are the 'middleman' of immunological communication; however they too, are believed to interconnect the immune and neurological system. This interconnection of cytokines allows for pathological inflammatory processes of the skin to be mediated centrally from the primary epithelial cell, the keratinocytes.

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterised by the presence of a chronic itch. According to the Irish Association of Dermatologists (IAD) around 20% of the Irish paediatric population will develop AD and this incidence is increasing annually. This condition can progress to asthma and allergic rhinitis – the process coined 'atopic march'. Signalling between the primary epithelial cell; the keratinocyte, and the immune system via cytokines was shown to be the driver of the atopic march. This cytokine was denoted as Thymic Stromal Lymphopoietin (TSLP) and was shown to promote the robust itch in mouse studies (11). TSLP, a component of Il-2 cytokine family, was originally shown to promote B cell signalling and growth (12) as well as other immune and haematological cell lines but no causative link was initially shown between the activation of TSLP and the neurological response to itch. (13). TSLP is expressed from keratinocytes, with a direct correlation between the GPCR Protease-Activated Receptor 2 (PAR2) activity and TSLP expression. (14) However, recent papers demonstrate the activation of JAK-1 and -2 signalling in response to TSLP in dendritic and CD4+ T cells as the mechanism contributing to nociceptive signalling (15)

Conditions such as AD, which have been shown to have cytokines as the primary driver of their condition, may be confirmatory that itch may start at the level of the dermis due to

cytokines. Monoclonal antibodies such as Dupilumab, a recent FDA approval (March 2017), which targeted signalling at the level of IL-4Rα of Th2 cells produced a marked clinical improvement in the areas of AD distribution and the overall quality of life for the patient. (16) The results of Dupilumab in recent clinical trials and medical use for patients with AD combined with its' known mechanism of action show that molecular cytokine signalling is a responsible driver of chronic itch and inflammation.

Labelled Line Theory or Intensity Theory – The Peripheral Signal:

Afferent fibres express a host of channels and receptors in order to generate and appropriate response to stimuli. A study on mouse DRG demonstrated the expression of three G-protein coupled receptors (GPCR) as three separate classes of itch sensitive afferent neurons; 5-hydroxytryptamine, receptor 1F and Mrgpra3/d (17). However, only Mrgpra3 and Mrgprd were specific to itch sensitive neurons with minimal expression detected elsewhere. Even though the expression of Mrgpr was specific, certain transcripts with known pain signalling function were also seen in the DRG and thus suggesting the existence of a subpopulation of pain neurons specific to itch. (17)

Animal mouse studies also demonstrated that those with deficits in pain sensation with knockout of TRPV1; a known channel involved in pain signalling, produced significantly less scratch response when injected with both histamine and chloroquine; a non-histaminergic puritogen. (18) Not only was pruritus shown to be a response to the well-known puritogen histamine, which mediated many inflammatory conditions, but also to non-histaminergic signals. Different TRP channels were known to mediate either pain or

itch, but as a class, they act as a functional molecular connection in mediating both pain and itch supporting the intensity-coding theory.

The conflicts between these theories was clarified by Han et al. who proposed evidence in his studies on Mrgpra3 signalling that would conflict the intensity theory. Mrgpra3 was shown to represent a subpopulation of nociceptive afferents that exclusively mediated itch, and not pain. (19) Mrgpra3 neurons were shown to exclusively innervate the epidermis and respond to an array of puritogens, both histaminergic and non-histaminergic. Ablation resulted in reduced pruritic response and most importantly pain sensation in such models remained intact. (19)

MRGPRs are a family of receptors expressed in sensory afferents of the DRG, brain and also mast cells. Only some of which selectively mediate itch. Bam8-22, activator of MrgprX1 (20) was shown to produce itch, and pain related symptoms of pricking, stinging and burning sensations in healthy human volunteers. (21) β-alanine, an agonist of Mrgprd and Compound 48/80 an activator of Mrgprb2 were shown to be itch selective with minimal pain symptoms (22,16).

The MRGPRs are known to signal as part of a GPCR mainly αq. (23) These signalling pathways rely on a calcium influx from the external environment which is provided by TRP channels which are located downstream of the Mrgpr signalling pathway (24). TRP channels are a well-known transmitter of pain signals however not all TRP channels that transmit pain transmit itch. This is because only a fraction express Mrgpr channels simultaneously. (25)

Nociceptive firing through the TRP channels have experimentally been shown to block itch and their silencing result in chronic pathological itch through the *gate control theory*.

(26) The afferent nociceptive neurons were shown to activate a set of interneurons that inhibit itch sensation – basic helix-loop-helix b5. The selective mutation in this interneuron resulted in chronic itch with intact pain sensation. (27) These interneurons allow for pain signals to be felt while silencing that of itch afferents.

It is now well established that many receptors are involved in the transmission of *itch signalling* to the level of DRG and spinal cord. However, like many sensory pathways it still is needed to be proven if these signals are relayed centrally, and if so, how!

Labelled line theory – is it going centrally?

Evidence is in support of the labelled line theory in the peripheral afferents with an interneuron connection, like many sensory pathways to allow for overriding signals to pervade. Further evidence has shown that this specificity extends into the central nervous system. Gastrin related peptide receptor (GRPR) and natriuretic peptide A (Npra) were put forth as two receptors that are itch selective neurons in the spinal cord (28,29) as their deletion showed a dramatic reduction in itching in response to histamine but no effects on somatosensory pathways as noxious mechanical and thermal stimuli remained intact (demonstrated through paw withdrawal and tail-flicks in animal studies). (30) The central labelled line specificity was confirmed as GRP analogue bombesin provoked a pruritic reaction in the absence of pain. (31)

The future and *the itch…*

At present, there are no direct treatments targeting the mechanism of itch. However, new advancements may be on the horizon with the development of tofacitinib, a JAK inhibitor that has shown improvements of itch in mouse studies. (32)

JAK signalling occurs in immune cells through type 2 cytokines. (33) JAK too, has been shown to be expressed in puriceptive neurons and phosphorylation occurs with Il-4 stimulation. Oetjen et al. studies showed that the administration of ruxolitinib, another JAK inhibitor, significantly reduced scratching behaviours in animal studies. By blocking the signalling mechanism through type 2 cytokines. JAK inhibition may be put forth as a broad therapeutic strategy in the treatment of itch. This data has been reassured from the use of oral tofacitinib in a small group of patients suffering from chronic idiopathic pruritus (CIP) who showed marked improvement in symptoms of itch. (Figure 2)

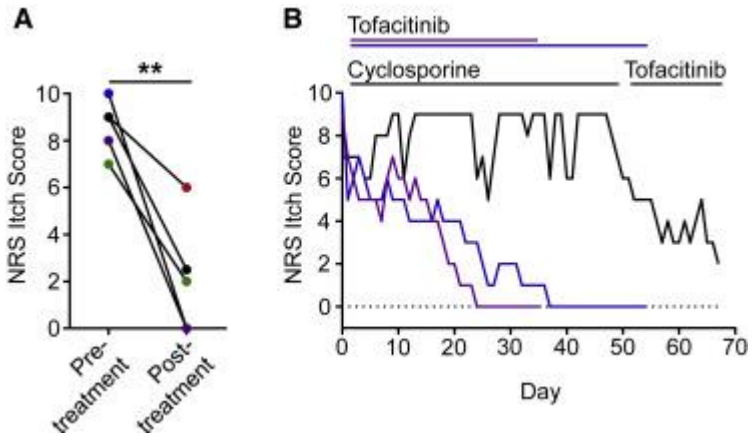


Figure 2: Oetjen et al. Sensory Neurons Co-opt Classical Immune Signalling Pathways to Mediate Chronic Itch. Cell Volume 171, September 2017.

Many of the pathways involved in the signalling mechanism behind pruritus are thought not to be fully elucidated currently. JAK inhibition may be the key process involved in blockade of multiple puritogens signalling through a central, key molecule as seen through the recent studies published in Cell. Many chronic dermatological conditions have shown a beneficial response to the use of JAK inhibition to support this suggestion; alopecia universalis (34) and vitiligo (35).

Conclusion:

Pruritus is a primary symptom of many dermatological conditions with a significant effect on a patient's morbidity. The mechanism is thought to be neuroprotective but the pathways that are involved in its signalling are poorly understand, but ever so slowly being elicited. A peripheral and central signalling pathway is thought to exist after instigation of a signal at the level of the skin, with multiple signalling molecules and receptors involved, including Mrgpr and GRP. The new advances with JAK however, have postulated the existence of a core molecule as the ultimate signal through which multiple puritogenic signals may converge. The exact mechanism is yet to be fully established however if the hypothesis holds, the treatment with JAK inhibitors may be life changing and not solely limited to that of pruritus.

Total word count (2055)

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