Why do we itch and scratch?

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Introduction

Itch may be defined as an unpleasant sensation that evokes a scratch response. It is an increasingly common symptom presenting in both dermatology and primary care, which may significantly threaten physical and psychological wellbeing. Despite the prevalence of this sensation, the underlying mechanisms of itch have been poorly characterised until recently. The development of reliable animal models has greatly improved our understanding of the molecular and neural pathways employed in itch signalling. The reasons underpinning itching and scratching may be considered on several levels, which will be considered in turn. On a cellular level it is important to appreciate the interaction of stimulated receptors and neurotransmitters in initiating the itch signal. The underlying source of the pruritogenic stimulus must also be explored, with relevance to clinical conditions. Finally, the functional purpose of this sensation will be assessed.

1. Causes of itch at a cellular level

a) A variation of pain?

The itch pathway shares anatomical similarities with the pain pathway and was initially considered a submodality of pain rather than a sensory modality in its

own right. Early studies demonstrated shared itch and pain spots, leading to postulation of an intensity or pattern theory. It was hypothesised that both sensations were encoded by a common neuronal population but were differentiated by variations in intensity and patterns of neuronal activation. However, this theory was challenged when increased frequency of electrical stimulation failed to result in pain, instead intensifying itch[1]. The opposite was also demonstrated when lower frequency painful stimuli did not result in conversion to an itch[2].

Sensitivity of C fibres to histamine, coupled with insensitivity to mechanical or thermal nociceptive stimuli, promoted the 'labelled-line' theory, where distinct neuronal populations mediate itch and pain[3,4]. This suggested that these two sensations did not simply represent opposite ends of a spectrum, but were functionally distinct modalities sharing a neuroanatomical pathway.

b) Neuronal circuitry

The sensation of itch is conveyed following activation of receptors on peripheral nerve endings by pruritogenic stimuli. This message is relayed predominantly by C fibres[5] in the spinothalamic tract, to the somatosensory cortex. There are two itch-sensitive pathways: a histamine-mediated pathway involving with mechanically insensitive C fibres and a cowage-mediated pathway utilising polymodal C fibres[6]. More recently, the activation of faster conduction velocity Aδ fibres has also been implicated in itch signalling[7].

A variety of peripheral pruritogens activate distinct receptors, as outlined in **Table.1**.

Pruritogen	**Peripheral receptor**
Histamine	HR1, HR4
Chloroquine, β-alanine	Mass-related G-protein coupled receptors
Proteases: tryptase, cathepsins, mucunain.	Protease-activated receptors
TLR 3 TLR 7 (evidence of imiquimod-associated itch[8]).	Toll-like receptors
Serotonin	Serotonin receptors
Endothelin-1	ET_A, ET_B
Interleukin-31	Interleukin-31 receptor
Substance P	Neurokinin-1 receptor
Bile acids	TGR-5

Table.1: Pruritogens and specific receptors

Neurotransmitters facilitate propagation of itch signals to neurons in the dorsal horn. Neuropeptide natriuretic polypeptide b (Nppb) is expressed on a subset of DRG neurons. Scratching behaviour was abolished in Nppb knockout mice exposed to pruritogens and intrathecal Nppb administration conversely provoked scratching responses. Nppb primarily activates natriuretic peptide receptor A (Npra), expressed on a subset of dorsal horn neurons. Specific neurotoxic destruction of Npra+ neurons resulted in a diminished itch response to histamine[9]. While this evidence is seemingly persuasive, cautious interpretation of Nppb ablation studies is required. Npra is not exclusive to

dorsal horn neurons and is also expressed in DRG neurons[10]. Therefore, it is unclear whether Nppb works at the level of the peripheral sensory neuron or in the spinal cord. Gastrin-releasing peptide (GPR) and glutamate have also been hypothesised to function as neurotransmitters in the itch pathway. The signalling role of GPR is strengthened by the association observed between increased levels of bile acids, coupled with higher concentrations of GPR, provoking an itch sensation[11].

Postsynaptic pruriceptors are located within the spinal cord, mediating the central pathways of itch. Mouse studies identified restricted expression of gastrin-releasing peptide receptors (GRPR) in lamina I of the dorsal horn. GRPR knockout mice specifically failed to demonstrate a scratch response to pruritogenic stimuli, with no deficit in pain sensation[12]. A distinct spinothalamic tract neuronal population express NK-1 receptors. Intrathecal administration of the neurotoxin substance P-saporin in rats abolished both itch and pain responses[13].

Therefore, on a molecular level, we itch because a variety of endogenous or exogenous stimuli activate specific receptors in the periphery. Signal propagation to the CNS is subsequently instigated, which can be processed to generate a response.

2. What stimulates release of pruritogens?

While it is relevant to appreciate the molecular mechanisms of itch, it is important to take a step back and consider the underlying source of pruritogens

that activate peripheral receptors, as well as their clinical relevance. Pathological processes, which may be grouped according to their clinical time course **(Figure.1)**, influence the concentrations of diverse pruriceptor agonists.

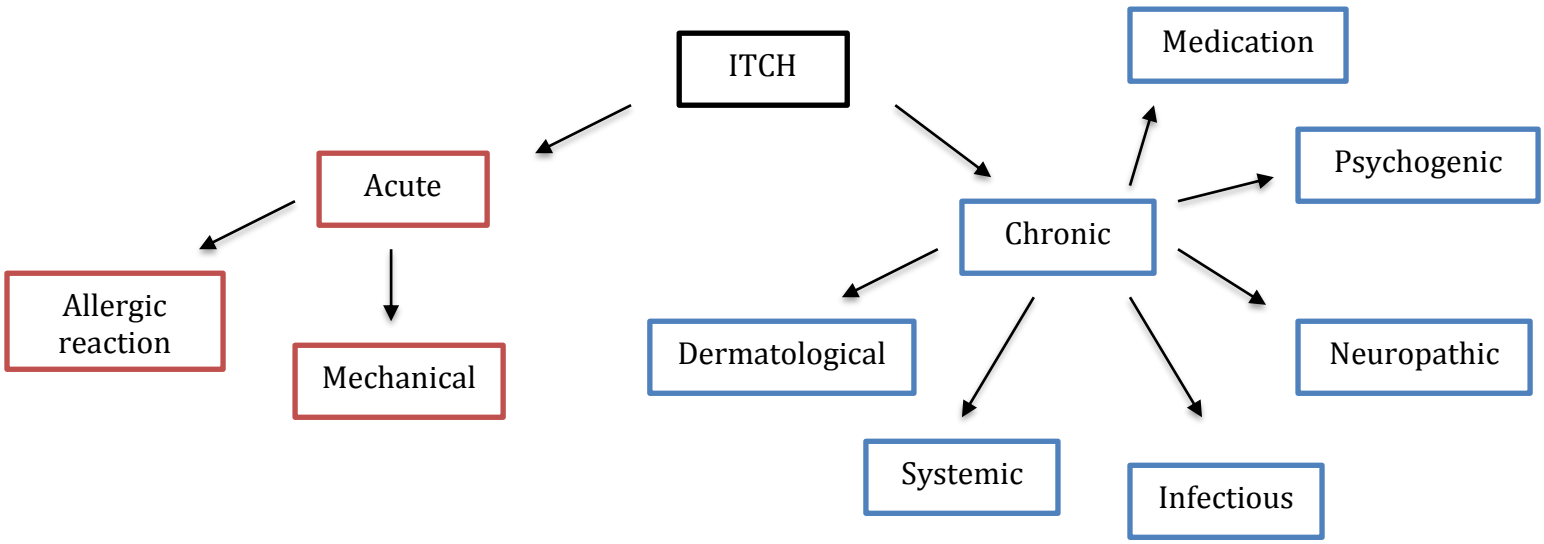

Figure.1: Causes of itch, grouped by clinical time-course.

Acute itch

Acute pruritus may be defined as itch that is directly stimulated by a pruritogen but relieved by scratching[6]. It may also be considered in terms of the duration of symptoms, whereby acute itch persists no longer than six weeks[14]. Allergic reactions employ the use of the most well characterised pruritogen: histamine. In allergy, itch is provoked as part of a type I hypersensitivity reaction to an allergen. This evokes an IgE response with histamine-mediated release from mast cells, stimulation of histamine receptors and downstream activation of TRPV1[15].

Mechanically induced itch can be easily appreciated in daily life, for example following the contact of cotton wool on skin. It may be classified as acute as removal of the stimulus terminates the itch sensation. The first experiments demonstrating light mechanical stimulation as a cause of itch were performed using an electrically controlled wire loop to vibrate vellus hairs on human skin. An intense itch was elicited independently of histamine[16].

Chronic itch

Dermatological

Itch in dermatological conditions is often associated with inflammation, dryness and dysfunction of the protective skin barrier. Common inflammatory dermatoses include atopic dermatitis (AD) and psoriasis. The cause of AD remains poorly defined, both in terms of molecular pathophysiology of AD as well as the temporal relationship between itch and eczema. The immune response is strongly implicated, possibly triggered by hypersensitivity to environmental allergens or microorganisms, such as *Staphylococcus aureus*. Th2 responses are specifically implicated, associated with increased levels of IL-4, 5 and 13[17]. Genetic factors also contribute to AD, with evidence of an association with variants in the IL-13 coding region and the α-subunit of the IL-4 receptor[18]. Psoriasis is characterised by hyper-proliferation of keratinocytes and a Th1 immune response. There are also genetic factors implicated in psoriasis, with some genetic loci shared with AD. Although the inflammatory response is clearly important in itch associated with AD and psoriasis, there may also be a neuropathic component. Variations in neuropeptide distribution and nerve fibre

density are well categorised in psoriasis[19,20]. Furthermore, failure of resolution of pruritus in response to antihistamines suggests that histamine is not implicated in activation of peripheral pruriceptors[21].

Systemic

Pruritus may also be associated with systemic diseases and may in fact be the primary manifestation. Although it is also a recognised symptom of haematological malignancies, such as lymphoma, the focus here will centre on renal and hepatic causes.

Uraemic pruritus is a significant complication of chronic renal disease and may affect up to 90% of dialysis patients[22]. Gradual resolution of pruritus occurs post renal transplantation, suggesting that a causative factor normally removed by the kidney is not efficiently filtered by dialysis[23]. The underlying cause is unknown. However, increased activity of μ-opioid receptors have been implicated[24] as well as abnormalities in calcium metabolism, with precipitation of calcium phosphate crystals causing stimulation of pruriceptors[23].

Cholestatic pruritus is also clinically important. Impaired bile secretion results in accumulation of bile acids. Direct application of bile acids on human skin elicits itch[25] and cholestyramine, a drug which sequesters bile acids, effectively relieves pruritus[26]. At a molecular level, TGR5 is the receptor directly targeted by bile acids. Scratching behaviour is abolished in TGR5 knockout mice and injection of a TGR5 agonist stimulated a scratch response[11]. Lysophosphaditic acid and autotaxin are other mediators hypothesised to contribute to cholestatic pruritus.

Comparative analysis of the serum of patients with pruritus and controls revealed a significant relationship between autotaxin activity and the severity of pruritus[27].

Infectious

Itch can also be associated with infectious diseases, most notably HIV and parasitoses. Pruritus may be a primary symptom of HIV infection or may be related to disorders that are associated with states of immunosuppression. Eosinophilic folliculitis is the most common pruritic papular eruption in HIV and is associated with CD4 counts around 200 cells/μL[28]. The molecular basis of HIV-associated pruritus remains unclear, however the HIV-1 viral protein Gp120 has exhibited direct excitatory action on nociceptive neurons[29]. Further research is required to investigate the effect of Gp120 on itch pathways.

Parasitoses can cause intense pruritus. In fact, the simultaneous intense itching in family members is almost pathognomonic of scabies. Infestation of mites elicits an immune response to the mite, eggs or faeces manifesting as burrows, associated with severe itching, often worse at night.

Neuropathic

Encoding of itch requires faithful communication of the stimulus by a complex neuronal network. Damage to any part of the neuronal circuitry can result in neuropathic itch. Postherpetic itch, inflammatory transverse myelitis and ischaemic stroke-related itch are examples of conditions associated with damage

to the periphery, cord and brain respectively. The varied clinical pattern observed post zoster infection hints at the complexity of the pathological basis of neuropathic itch. Following resolution of shingles, some patients develop localised itch, others develop neuralgia and some develop both. This suggests that a combination of factors may be involved: a specific stimulus, nerve damage and individual susceptibility[30].

Psychogenic

Until now, itch has been considered the result of successful neuronal circuitry. However, this rigid neuroanatomical pathway does not consider the role of behavioural or emotional contributions. 36-42% of psychiatric inpatients are affected by idiopathic pruritus[31,32]. Anxiety and depression share strong associations with pruritic skin disease, most notably AD and psoriasis[33,34], often with reciprocal causality. Pruritus can also be associated with psychotic disorders. Delusional parasitosis is a well-established monodelusion where individuals who otherwise function normally develop an irrational fixed belief that they are infested by parasites. Another psychiatric cause of chronic itch is impulse control disorders. Neurotic excoriations result in inability to resist the urge to scratch, despite awareness of the damage this is inflicting on the skin[35].

3. Why we scratch

Scratching is a conscious and voluntary response to itch, aiming to terminate the sensation and provide relief. The mechanism employs the concept of surround inhibition. Scratching excites low threshold mechanoreceptors which activate

myelinated A fibres. This results in stimulation of presynaptic and postsynaptic neurons and causes inhibition of interneurons in the grey matter of the spinal cord[36]. The scratch response also activates nociceptors and utilises the inhibitory action of pain on itching that acts at the level of the cord[37].

It must be noted that scratching does not always neatly terminate itching. This is well demonstrated by the perpetual itch-scratch cycle **(Figure.2)**, which is well known to burden inflammatory dermatoses.

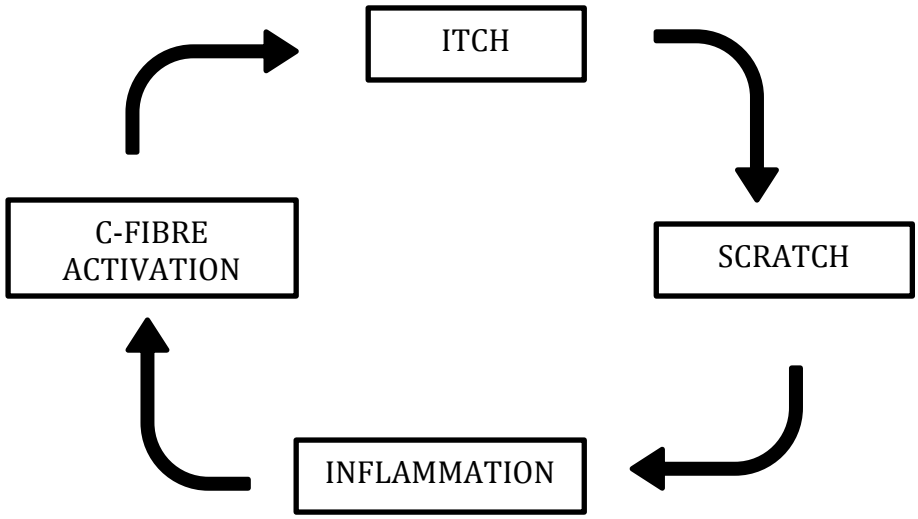

Figure.2: The itch-scratch cycle

At a molecular level, central serotonin signally has been implicated in potentiation of itch. This has been demonstrated experimentally, where scratch behaviours were attenuated in mice lacking brainstem serotonergic neurons[38]. Scratching has also been shown to stimulate reward centres in the brain. An fMRI study observed a relationship between reported pleasure derived from self-scratching subjects and increased deactivation of the anterior cingulate cortex and insula[39].

4. Does it serve any purpose?

It is important to consider the purpose of itch and to reason whether it served any evolutionary benefit. The ability to sense itch may offer a protective advantage. Previously, it may have been useful to alert organisms to the presence of parasites or contact with toxic substances. In modern medicine, itch associated with anaphylactic reactions can be an informative symptom, which may offer protection by stimulating immediate termination of exposure to the allergen. Furthermore, although pruritus may be a vague symptom, it can provide useful clues to the astute clinician regarding diagnosis or progression of systemic conditions, ultimately facilitating timely intervention.

However, itch may also prove burdensome and even harmful. Persistent scratching, as observed in AD, results in a physical breach of the protective barrier of the skin and secondary infection by *Staphylococcal* species. Pruritus may also prove problematic when normal control mechanisms are deregulated, by means of peripheral and central sensitisation[40]. Hypersensitivity to itch is well documented in patients with inflammatory dermatoses compared with healthy individuals[41,42]. Hyperinnervation in both animal models[43] and humans with AD[44] has been demonstrated and may provide one explanation. Increased expression of the pruritogen TLR3[45] and the pruriceptor PAR2[46] have also been implicated as well as enhanced levels of endogenous nerve growth factor (NGF). It is likely that NGF contributes to sensitisation via its neurotrophic effect on nerve growth and survival[47]. A combination of peripheral and central sensitisation can be appreciated by the phenomenon of alloknesis. This occurs when stimuli that are not usually pruritogenic evoke an itch response, likely due

to a decreased activation threshold of primary sensory neurons. A mouse model has demonstrated scratching behaviour elicited by light mechanical stimulation to skin near a site of pruritogen injection[48].

The psychological burden of living with a chronic itch condition exemplifies an important harmful consequence. One study revealed 70% of dermatology inpatients suffering with chronic pruritus were diagnosed with up to six psychosomatic conditions[49]. This suggests the need for liaison between dermatology and psychiatric services in order to provide holistic care. Chronic pruritus can have debilitating implications on quality of life. Studies have reported impairment of sleep[50], appetite and concentration as well as increased feelings of stigmatisation[51].

Itching may serve an indeterminate purpose which is neither beneficial or particularly harmful, as demonstrated by the ability of itch-related visual stimuli alone to evoke an itch sensation and scratch response in healthy participants[52]. This observation supports the association of contagious itch with a mirror neuron system.

Conclusion

The skin is constantly bombarded by an array of stimuli, some of which activate pruriceptors and initiate itch signalling. Although the development of this sensation may have originally conferred some evolutionary advantage, overall the harms associated with chronic pruritus outweigh the protective benefits.

The ultimate aim of understanding of the mechanisms underlying itching and scratching is to facilitate development of targeted therapeutic interventions. These may function at a molecular level, for example with use of receptor antagonists, or a behavioural level. The diversity of underlying causes evoking production of pruritogenic stimuli emphasises the fascinatingly broad differential diagnoses that the clinician may consider when faced with an itchy patient.

Word count: 2444

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