Why do we itch and scratch?

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Introduction

Most of us experience itch, an unpleasant sensation associated with perceived disruption to the skin, multiple times a day and a quick scratch near the itchy area usually abolishes it[1]. This everyday itching and scratching is probably useful; itching can alert us to potentially harmful stimuli, such as insects, on the skin and scratching is a movement that can remove them[2]. Scratching can also have useful social functions: self-scratching is used by macaques to show others when they are stressed[3] and scratching others has been observed as a grooming behaviour in chimpanzees[4]. Many humans also enjoy scratching[5]. Therefore, much of our everyday itching and scratching is harmless and may be beneficial.

Unfortunately, itching and scratching can also represent debilitating problems for patients. This essay will explore the importance of itching and scratching in medical practice, before discussing the physiological mechanisms of itch and scratch and outlining examples of therapies for itching and scratching. It aims to show why we itch and scratch, how this can become chronic, and how we are using this information to develop therapies for problematic itch and scratch.

Itching and scratching are common and reduce quality of life

Chronic itching is common in dermatology, but also in general medicine and the wider population. For example, the prevalence of itch in a German dermatology practice

was found to be 36.2%[6], which highlights its frequency in skin disease. However, a similar percentage (39.9%) of patients in an outpatient general internal medicine clinic in the USA reported itch[7]. This highlights that itch is common and not restricted to dermatology: non-dermatological causes include neuropathy, cholestasis, uraemia and iron-deficiency anaemia, among others[8]. Finally, in a study of the general population of Oslo, itch was reported by 8.4% of participants and was the dominating skin complaint[9]. Therefore, itch has a significant presence in the general population, as well as general medicine and dermatology.

As well as being widespread, itching and scratching negatively affect quality of life[6,7]. The itch sensation feels irritating in itself, while cycles of itching and scratching can be experienced as a loss of control, and the associated skin lesions can lead to stigma and social isolation[10]. Itch has been associated with depressed mood and anhedonia; patients with atopic dermatitis (AD), a chronic itchy skin condition, have higher levels of anxiety, depression and suicidal ideation[7,11]. Therefore, as well as being common, itching and scratching can have a major impact on mental health.

The physiology of itch

Although itch is felt as a skin sensation, it is ultimately a product of the activity of the central nervous system (CNS). The events leading to itch involve signalling in the skin, activation of primary afferent neurons, transmission of a signal to the spinal cord, onward transmission to the brain, and the perception of itch by certain areas of the brain[12]. Therefore, although itch often originates from the skin, it can also originate from elsewhere. This overview will outline itch signalling, including some mechanisms underlying chronic itch.

Itch signalling in the skin

Itch signalling in the skin ultimately leads to stimulation of itch-sensitive nerve fibres. This can be accomplished in various ways, as many different signals cause nerve stimulation. Signals from outside the body include mucunain, which is produced by the plant cowhage and causes itchiness[13], while other chemical signals such as histamine are released by cells in the skin[14]. Itch can also be stimulated by very light touch, such as an insect on the skin surface[15]. Signalling pathways in the skin are not simply linear, but involve interactions between keratinocytes, immune cells and nerve cells to enhance the itch signal (**Error! Reference source not found.**).

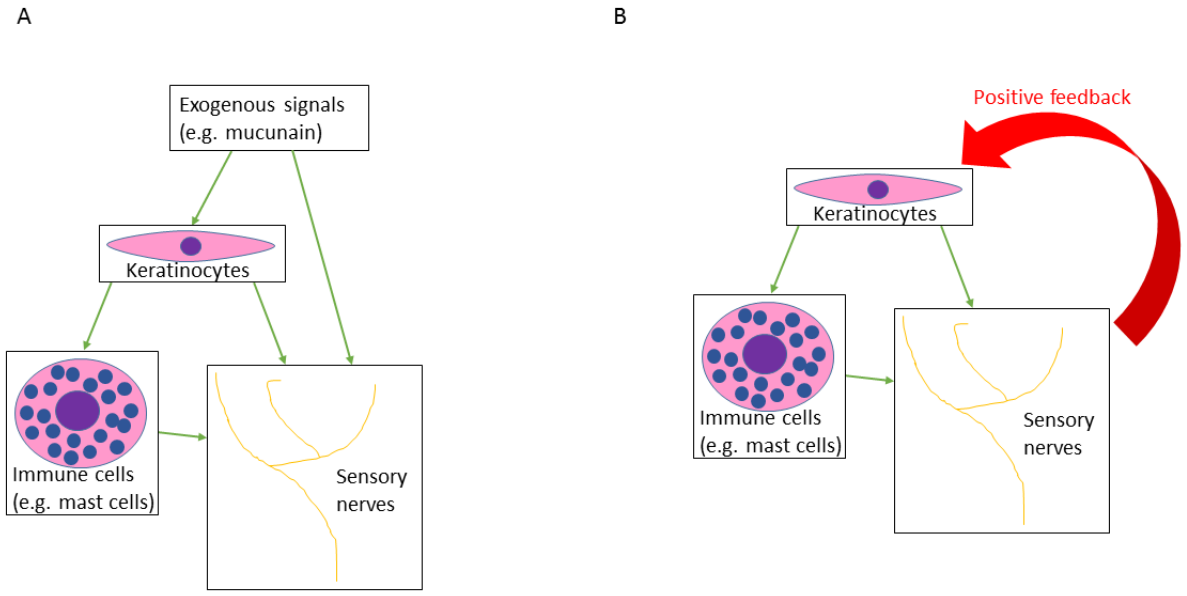

Figure 1 Skin itch signalling *(A)* Multiple signals can activate cutaneous sensory nerves, including exogenous signals and signals from keratinocytes and immune cells. *(B)* Sensory nerves are active participants in itch signalling and produce factors which activate other cell types.

Many signals and cell types are involved in activating sensory nerves (**Error! Reference source not found.**A). At the beginning of the pathway, external signals promote itch by multiple mechanisms. For example, mucunain can activate both sensory nerves and

keratinocytes via a receptor called proteinase-activated receptor 2 (PAR2)[16,17]. Activation of sensory nerves is a direct mechanism to promote itch, but stimulating keratinocytes accomplishes the same goal in an indirect way, as keratinocytes produce more itch signals. An example is thymic stromal lymphopoietin (TSLP), which again has multiple actions. TSLP acts directly on sensory nerves[18], but also activates immune cells, which release further signals to activate neurons[16,17]. Thus, itch signalling involves a complex pathway and chemicals at each stage can activate neurons to produce the itch sensation or promote production of more signalling factors. To add to this complexity, the pathways leading to nerve activation are not linear but involve feedback loops which up-regulate itch signalling (**Error! Reference source not found.**B). As an example, activated sensory nerves release neuropeptides (e.g. substance P), which act to induce skin inflammation by further activating keratinocytes[17,19]. Thus, activation of sensory nerves amplifies signalling, which causes more nerve activation and more itch.

Skin-derived chronic itch occurs when itch signalling processes continue long-term. For example, AD is linked to a defective epidermal barrier, which allows external compounds to enter the skin where they promote itch and inflammation[20]. Inflammation can further damage the epidermal barrier, exacerbating the problem; for example, interleukin-31 (IL-31), which is produced by immune cells, binds sensory nerves to induce itch but also represses keratinocyte differentiation so that the epidermal barrier is further impaired[21]. A positive feedback loop ensues in which itch signalling contributes to epidermal barrier dysfunction, which increases itch signalling; chronic itch is produced.

Itch signalling by sensory nerves

Itch-sensitive sensory neurons receive itch signals from the skin and transmit them to the spinal cord. Despite the variety of signals involved, itch-sensitive neurons share a basic activation mechanism, in which membrane receptors activate ion channels, followed by membrane depolarisation and action potential generation[14,22]. When the action potential arrives at the spinal cord, the neuron releases itch neurotransmitters (e.g. gastrin releasing peptide) to activate spinal neurons[14]. Thus, the itch signal is carried from the skin to the spinal cord.

Any changes in sensory neurons that increase the amount of signalling to the spinal cord could mediate chronic itch. One way this can occur is by reducing their activation threshold. For example, the type 2 cytokines IL-4 and IL-13 promote chronic itch but do not directly activate itch-sensitive neurons *in vivo*. Instead, they sensitise neurons to other itch-promoting signals[23]. This means that neurons fire in response to lower levels of other signals and so lower levels of skin itch signalling can produce neuronal itch signalling. Another mechanism by which neuronal signalling could be altered is widespread damage or dysfunction of sensory nerve axons, for example due to diabetes[24]. This causes an itch sensation which is unrelated to any skin pathology. Therefore, changes in sensory nerves can contribute to chronic itch, either by nerves responding more easily to skin signalling or by firing inappropriately due to neuropathy.

Itch signalling in the spinal cord

The neurons of the spinal cord have two distinct roles in itch signalling. Their simplest role is to act as a relay station, transmitting signals to the brain via the spinothalamic tract (STT). The importance of the STT in itch signalling is demonstrated by the observation that lesions in the anterolateral spinal cord of humans (where the STT is

found) ablate the sensation of itch below and contralateral to the lesion[16]. Thus, it is fundamental to the perception of itch. However, the spinal cord also has an important role in processing the itch signal via its interneurons. Some of these can inhibit itch; for example, mice lacking neurons which express the transcription factor Bhlhb5 develop skin lesions due to excessive licking and scratching, suggesting that Bhlhb5-expressing neurons act to inhibit itching in the spinal cord[25]. In contrast, itch is a common side effect of morphine and it is thought that morphine promotes itch by activating excitatory interneurons[14]. Therefore, spinal cord interneurons have the potential to both inhibit and amplify itch signals.

Due to its roles in relaying and processing the itch signal, the spinal cord can influence chronic itch. Regarding the relaying of the signal, damage to the spinal cord can produce itch, for example in multiple sclerosis[24]. The spinal cord is also implicated in aberrant itch processing. For example, an important problem in chronic itch is alloknesis, in which itch is evoked by stimuli which are normally non-itchy, such as light stroking. When a specific population of interneurons (expressing Y-Cre) is ablated, mice develop increased scratching behaviours in response to light touch[15]. This suggests that spinal processing is important in alloknesis. Therefore, the spinal cord can cause chronic itch due to damage or through abnormal processing patterns, which produce an itch sensation when there would normally be none.

Itch processing in the brain

The brain is the final processing centre of the itch sensation, where activation of specific areas leads to the perception of itch and discomfort[12]. Numerous brain regions are activated in itch and the pattern of activation is different to other sensations such as pain[26]. These include areas involved in the recognition of and attention to itch, such as the

thalamus and somatosensory cortex, but also areas associated with emotion and motivation, such as the cingulate cortex and insula, and motor-related areas for planning actions (e.g. scratching), such as the motor cortex[27].

Processing in the brain can underlie chronic itch. One demonstration of this is the psychiatric disorder of delusional parasitosis, in which a patient believes they are infested with parasites in the absence of medical evidence[28]. Brain processing is also altered in other chronic itchy diseases. For example, there are significant differences in brain processing of histamine-evoked itch in AD patients compared to healthy subjects, which may produce differences in how patients perceive and respond to itch[29]. AD patients also have an increased susceptibility to experience contagious itch when watching others scratch[30]. This supports the idea that changes in brain processing can contribute to chronic itch, by causing itch to be perceived differently or by generating itch more easily in response to visual cues.

The physiology of scratch

Itching and scratching may have evolved together, allowing itching to sense and scratching to remove harmful stimuli from the skin[2]. Consistent with this idea, scratching is considered a reflex. Physiological studies support this by showing that animals with transected spinal cords rub their limbs against body sites that receive cutaneous mechanical stimulation[31]. However, neuroimaging shows that brain areas involved in movement are active during itch sensation and involved in planning scratching[26]. To link these observations, it may be that the spinal reflex initiates scratch, while brain activity carries out further planning and modulation of scratching.

As well as being a reflex response to itch, scratching is defined as a movement that counteracts itch using slightly painful stimuli (one of many links between itch and pain)[1,12].

This inhibition of itch by scratch might be useful as a signal that the itchy area of skin has been attended to, for example cleared of a parasite. Scratching can reduce itching even when it takes place centimetres away from the itchy site, suggesting that this inhibition occurs in the CNS[32]. Within the CNS, STT neurons responding to skin histamine application have a reduced rate of firing after scratching[32]. Thus, scratching must act before stimulation of the STT, and this localises the inhibition of itch by scratch to interneuron circuits in the spinal cord. Indeed, the interneuron circuitry for a painful (scratch) stimulus to inhibit itch is present; stimulation of C fibres (which carry pain as well as itch) can activate inhibitory interneurons in the dorsal horn, which are able to suppress itch[1].

In acute itch, scratching thus acts in the spinal cord to inhibit further itch. However, cycles of itching and scratching can become chronic. Firstly, repetitive or vigorous scratching can cause skin damage, which leads to inflammation of the skin and further itch[21]. In addition, neural processing of itching and scratching can exacerbate the problem. For example, the pain of scratching likely increases serotonin in the spinal cord, which facilitates itch transmission; thus, scratching ultimately increases itch sensation[33]. Finally, the activity of brain reward circuits in chronic itching suggests that scratching becomes perceived as pleasurable and so the itch-scratch cycle becomes addictive and difficult to break[26,29]. Therefore, scratching is common in chronic itching and can make patients' conditions worse.

Therapeutic approaches for chronic itching and scratching

The sequence of events leading to chronic itch and its associated scratching can involve the skin, sensory nerves, spinal cord and brain. Therapies to reduce chronic itching and scratching can theoretically target processes in all of these areas. As itch has many aetiologies and involves complex signalling pathways, there is no single universal anti-itch

treatment available[34]. Therapies can target cutaneous or neural mechanisms, treating important aspects of specific diseases (for example, corticosteroids in inflammatory skin conditions or gabapentin in neuropathic disorders)[34]. Table 1 gives examples of how therapies can target distinct levels in the itch pathway and includes some recent developments.

Level of the pathway	**Example of an anti-itch intervention**
Skin barrier	Regular emollient use reduces the risk of AD relapse[35]. In addition, daily emollient use in high-risk infants might prevent AD developing at all[36].
Immune signalling in the skin	Nemolizumab (an antibody against an IL-31 receptor) inhibits IL-31 signalling and treatment leads to dose-dependent reduction in itch[37].
Sensory nerve sensitivity	Type 2 cytokines signal through Janus kinase (JAK) to sensitise sensory neurons; itch improves during treatment with the JAK inhibitor tofacitinib[23].
Spinal cord processing	Designer drug technology can reduce scratching in mice by stimulating inhibitory interneurons, suggesting that a future treatment to stimulate these interneurons may relieve itch in humans[38].
Brain processing	Habit reversal training and cognitive behavioural therapy can reduce scratching behaviour and change how patients respond to their symptoms[39].

Table 1 Examples of therapies which target itching and scratching at different points in the pathway

Conclusion

Understanding why we itch and scratch deserves attention because itching and scratching are important medical problems which reduce quality of life. Chronic itch is a sensation that can be generated anywhere in a complex sensory pathway between the skin and the brain and the scratching which exacerbates it can seem unavoidable, both because

scratching is a spinal reflex and also because it can become addictive. This complexity represents a challenge, as an important step towards treatment is identifying the parts of the pathway which are contributing to a patient's symptoms. However, understanding the processes which occur at each stage of itching and scratching also demonstrates that there are multiple ways in which we can intervene. Currently, therapies which target specific parts of the pathway are improving the range of treatment options and combining these will allow us to tackle the debilitating problems of itching and scratching from multiple directions.

Word count: 2491

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