

Review

Itch

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Itch is a common skin sensation, with substantial effects on behaviour. Neurophysiological research has permitted accurate definition of neural pathways of itch, and has confirmed the distinctiveness of itch pathways in comparison with pain. A clinical classification of itch, based on such improved understanding, describes the difference between peripheral (pruritoceptive) and central (neurogenic or neuropathic) itch. New specific and sensitive investigational methods in people and animals enable us to better understand this bothersome symptom, and have important clinical implications. We describe the clinical classification of itch, new findings on neuropathophysiology of itch, methods for assessment, and improved treatments.

Itch, along with pain, is a major part of nociception and an important symptom of systemic problems, as well as skin diseases. Progress in understanding of its neuropathophysiology and molecular basis has been hampered by absence of specific and sensitive investigational methodology in man, and unsuitability of animal models. Since the last update in *The Lancet* more than 5 years ago on itch pathophysiology,¹ research has begun to overcome these difficulties, with important clinical implications.

Definitions, types, and clinical classification

Itch has many similarities to pain.² Both are unpleasant sensory experiences, but the behavioural response patterns differ—pain elicits a reflex withdrawal, whereas itch leads to a scratch reflex. However, both can lead to serious impairment of quality of life.

A stimulus causing itch leads to two distinct responses:³ first, a well localised itch at the site of the stimulus, which persists only briefly after the stimulus has been removed; and second, a subsequent diffuse poorly localised area surrounding the site, which responds with intense itch when exposed to gentle touch or other minor stimuli. This sensation of itchy skin is also called *alloknesis*.

Twycross⁴ has proposed a clinical classification of four categories of itch, on the basis of advances in understanding of the peripheral and central origins of itch.

Pruritoceptive itch

Itch originating in the skin, due to inflammation, dryness, or other skin damage, is termed *pruritoceptive* and is transmitted by C nerve fibres. Examples are itch due to scabies, urticaria, and reactions to insect bite.

Neuropathic itch

Itch that arises because of disease located at any point along the afferent pathway is called *neuropathic itch*.⁵ Post-herpes zoster neuropathy and the itch occasionally associated with multiple sclerosis and brain tumours are in this category.

Neurogenic itch

Neurogenic itch is defined as that which originates centrally but without evidence of neural pathology, such as the itch of cholestasis, which is due to the action of opioid neuropeptides on μ -opioid receptors.

Psychogenic itch

The fourth type of itch is *psychogenic*, as in the delusional state of *parasitophobia*.

This classification is both clinically relevant and informative as to the pathomechanisms of *pruritus*. Of course there is no reason why one type of itch cannot coexist with another—for example, in the itch of atopic eczema, neurogenic as well as *pruritoceptive* itches seem to arise in the same patients.⁶

Neurophysiology

Neuronal pathways

Findings of investigations with direct nerve recordings in awake individuals have shown that itch is transmitted by dedicated C neurons, which are distinct from the polymodal nociceptors that are implicated in pain processing. These itch neurons can be identified by their lasting response to histamine application, and are characterised by their slow conduction velocities and extensive terminal branching.⁷ The idea of dedicated itch neurons has now been complemented and extended by studies of recordings from the cat spinal cord. A specific class of dorsal horn neurons projecting to the thalamus was noted, which responded selectively to histamine iontophoretically applied to skin.⁸ The time course of these responses was similar to that of itch sensation in man, and matched the responses of the distinct peripheral C fibres that transmit itch (figure 1).⁹ These important observations obviate recourse to alternative, mainly theoretical,

Search strategy

We searched Medline in July, 2002, with the key words itch and pruritus, and obtained data from reports in peer reviewed journals, book reference lists, and findings presented at the International Workshop for the Study of Itch in Singapore (2001).

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explanations of itch, such as itch-specific patterns of firing, absence of surround inhibition, or variations in stimulus intensities.²

However, there is no specialised itch receptor on peripheral nerve endings. The specificity of itch neurons is therefore based on their spinal connections to the itch pathway, rather than on unique peripheral receptors.

Does the brain have an itch centre?

The supraspinal processing of itch and its corresponding scratch response have been investigated in man with functional positron emission tomography (PET). Induction of itch by intradermal injection of histamine and histamine skin-prick elicits coactivation of the anterior cingulate cortex, supplementary motor area, and inferior parietal lobe, with a left-hemisphere predominance.^{10–12} The substantial coactivation of the motor area lends support to the clinical observation that itch is inherently linked to a desire to scratch. The activation of multiple sites in the brain after itch induction suggests that there is not a sole itch centre, and shows the multidimensionality of the itch sensation. The pattern of activation is very similar for the pain sensation; indeed, a broad overlap of activated brain areas is evident for pain and itch.¹² However, subtle differences in the activation pattern between itch and pain have been described, such as absence of detectable activation of thalamic and somatosensory cortex on parietal brain in itch.

By use of functional MRI with histamine iontophoresis to provoke itch in volunteers, McGlone and colleagues¹³ showed activation of several forebrain regions by itch (Brodmann areas 10, 21, 22, and 40, and the cerebellum). The increased availability of functional MRI and technical development of central imaging techniques will lead to further insights into the central control of itch, such that recordings in patients with itch become realistic, as exemplified in pain imaging.¹⁴

Scratching and rubbing

Scratching and rubbing the skin inhibits itch (surround inhibition).¹⁵ These activities stimulate myelinated A neurons via low threshold mechanoreceptors, which excite presynaptic and postsynaptic mechanisms to inhibit neuronal circuits in the grey matter of the spinal cord, and lead to temporary suppression of itching. Scratching also activates nociceptors, which also reduces itch via the spine, since pain inhibits itch. There have been several practical applications of this observation, such as the development of transcutaneous nerve stimulation for persistent localised pain and itch, and a new technique called cutaneous field stimulation. This technique electrically stimulates the afferent nerve fibres to inhibit histamine-induced itch in healthy volunteers.¹⁶ Vagus nerve stimulation, which is known to relieve pain by central inhibition, has been shown to suppress histamine induced pruritus in man.¹⁷ These procedures might act through endogenous central inhibitory mechanisms that are usually activated by scratching the skin. Notably, in some patients with chronic itch these central inhibitory mechanisms might not be functional (neurogenic itch), and consequently cutaneous field stimulation might even aggravate itch during application.¹⁸

Protease-activated receptors and the action of capsaicin

The proximity of dermal mast cells to afferent C neuron terminals in skin suggests a functional relation between these two cell types. Human dermal mast cells express two proteases: tryptase and chymase. Steinhoff and colleagues¹⁹

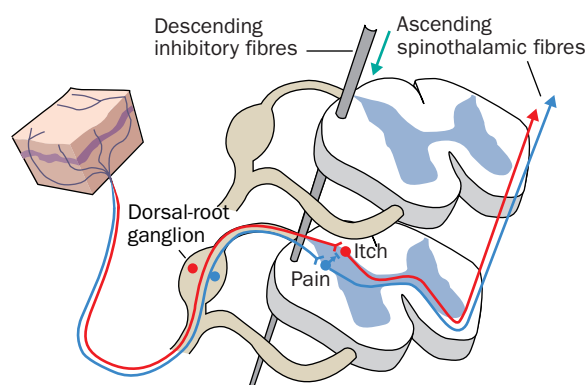


Figure 1: Neurophysiology of itch

Unmyelinated C fibres subserving the itch sensation and those subserving pain originate in the skin. Information on itch and pain is conveyed centrally in two separate systems that both use the lateral spinothalamic tract.

have proposed a link between mast cell tryptase and excitation of nociceptors in rat skin. Activation of the mast cell releases tryptase, which in turn activates proteinase activated receptor-2 (PAR-2) localised on C fibre nerve terminals. The activated C fibres will transmit this information to the central nervous system, where it might cause the sensation of itch. Additionally, activation will lead to a local release of neuropeptides including substance P. Although endogenously released substance P does not degranulate mast cells in healthy human skin²⁰ or cause any sensation at physiological concentrations,²¹ direct communication between nerve fibres and mast cells through substance P has been verified.²² Rather than causing immediate mast cell degranulation, for which high concentrations of this substance are needed (figure 2), low concentrations of substance P can specifically activate NK1 receptors on mast cells, leading to sensitisation of these cells and increased production of tumour necrosis factor (TNF) α .²³ TNF α in turn is known to sensitise nociceptive nerve endings—further evidence of the extensive crosstalk between nerve and mast cells (figure 2). Topical application of capsaicin desensitises C neuron terminals through the vanilloid VR1 receptors and thereby can alleviate itching.²⁴ Additionally, progressive depletion of substance P might enhance the antipruritic action of capsaicin²⁵ by inhibition of the crosstalk between nerves and mast cells.

Animal models

The main obstacle for development of animal models of itch is that scratching behaviour in animals is a regular occurrence and might not be a true indicator of itch. Behavioural data suggest that intradermal injection of substances that induce itch in man lead to dose-related hindlimb scratching in rodents, which could be distinguished from responses to pain.^{26,27} This model is of potential benefit for studies of itch physiology. However, in view of the large differences in skin sensitivity between patients with chronic itch and healthy individuals, experimental itch models of diseased skin^{28,29} might prove more relevant for the assessment of new antipruritics.

Itch in skin and systemic diseases

Itch is a common and important symptom of systemic disease, but is frequently difficult to control. It is often multifactorial, involving pruritoceptive components such as skin dryness, as well as neurogenic factors. However, advances in understanding of pathophysiology and molecular mechanisms have in some instances improved treatment.

Chronic renal disease and cholestasis

Although troublesome and sometimes severe in 25–85% of patients with renal failure, distressing itch is becoming less prevalent because of improved dialysis techniques.³⁰ Patients who are dialysed with less permeable and less biocompatible membranes are more likely to have pruritus than those using more permeable polysulphone types.³¹ Unfortunately, the long list of unsubstantiated suggestions for underlying mechanisms is proof of the ineffectiveness of treatment for such conditions.^{31,32} A role for opioid peptides has been proposed on the basis of results of a placebo-controlled trial,³³ suggesting that the oral opioid antagonist naltrexone was effective in renal pruritus. However, these findings were not confirmed.³⁰ κ -opioid agonists have been shown to be antipruritic in the mouse,³⁴ whereas a κ -opioid antagonist induced pruritus,³⁵ and early results in uraemic patients have confirmed the antipruritic effect of κ -opioid agonists.³⁶ From this antagonistic activity of μ -opioids and κ -opioids, we would assume that a combination of these two agents might be the optimum antipruritic. Thus, antagonism between itch and pain via the spine might be bidirectional: pain inhibits itch, whereas inhibition of pain can cause itch.

Pruritus in cholestasis can be severe and debilitating, especially in patients with chronic hepatitis C infection.³⁷ It can even be an indication for liver transplantation. Since no peripheral causes of cholestatic itch have been identified, pruritus of both renal and hepatic origin can be classified as neurogenic, but there is convincing evidence that opioid peptides play a part in the itch of chronic liver disease.³⁸ Accordingly, opioid antagonists including naloxone, naltrexone, or nalmefene have proven useful, either alone or in combination with cholestyramine.

HIV disease

Itch is an early symptom of HIV-1 and HIV-2 disease, and can be associated with several pruritic skin diseases

(including scabies, eczema, xerosis, and psoriasis) or with systemic causes (including chronic hepatic or renal disease and lymphoma). However, itch can also be an early primary symptom of HIV infection.³⁹ Eosinophilic folliculitis is an intensely pruritic eruption that arises in HIV-positive patients with a CD4 count of less than 300/ μ L.⁴⁰ Clinically, it presents with follicular or non-follicular urticarial papules or plaques, which sometimes become pustular, on the upper trunk, limbs, and face. Eosinophilic folliculitis is associated with raised serum IgE, and flares up after administration of retroviral treatment. Although the exact pathomechanism of itch in HIV is still unclear, there is evidence for a direct excitatory effect of the HIV-1 coat protein gp120 on nociceptive neurons.⁴¹ Additionally, gp120 is also linked to inflammatory axonal damage;⁴² thus, the itch in HIV-1 could be classified as pruritoceptive and neuropathic.

Neuropathic itch

Postherpetic neuralgia, one of the most common causes of neuropathic itch, can occur simultaneously with pain.⁴³ Central neuropathic itch has been reported in multiple sclerosis; its most distinctive features are a paroxysmal abrupt onset of itch and duration from seconds to minutes.⁴⁴ Attacks often awaken the patient from sleep. Features of the pruritic attack are similar to the well known Lhermitte's sign of multiple sclerosis. Impaired synaptic conductivity, rather than demyelination, might be responsible for these symptoms.⁴⁵

Atopic eczema

The molecular basis of pruritus in atopic eczema remains largely unexplained, and whether the itch precedes the eczema, or the other way round is also unresolved. Certainly, an itch-scratch vicious cycle exists in atopic patients, in which scratch damage enhances itch. Itching is especially acute in response to punctate stimuli such as wool fibres. Rubbing or scratching elicits surround inhibition. Alloknesis is a prominent feature of the itch of atopic eczema⁴⁶ and explains the bouts of intense itching associated with sweating, sudden changes in temperature, dressing, and undressing.

A central (neurogenic) component to the itch of atopic eczema is suggested, in view of the usually good response to sedative antihistamines, relative to the usually disappointing response to low sedation antihistamines.⁶ This effect also suggests that histamine is not a major peripheral mediator of atopic eczema;⁴⁷ alternative candidates include cytokines or proteases. Opioid peptides might serve as central mediators, since opioid antagonists are effective in some patients.⁴⁸ Nocturnal scratching is a major problem in atopic eczema, which arises during sleep stages 1 and 2 (superficial sleep)⁴⁹ and occupies 10–20% of total sleeping time, leading to tiredness and irritability. Treatment should be directed first at management of dryness and infection—two important and remediable causes of itch. Sedative antihistamines could also be useful.⁶

Topical steroids allay itching caused by inflamed skin, but the lowest effective concentration should be used. Phototherapy (UVB) and photochemotherapy (8-methoxypsoralen-UVA, PUVA) might be effective in some patients. Oral azathioprine or cyclosporin can be given to some treatment-resistant patients with severe handicap.^{50,51} Tacrolimus, a topically applied macrolide immunosuppressive with an action resembling that of oral cyclosporin, can also relieve the pruritus of atopic eczema;⁵² however, it has no primary antipruritic action.

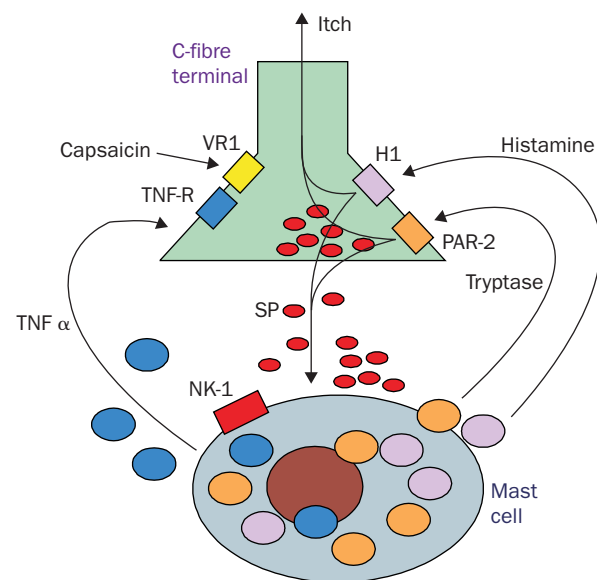


Figure 2: Cross-talk between cutaneous afferent C neuron terminals and dermal mast cells

Mast cell activation releases tryptase, one site of action for which is PAR-2, a receptor located on adjacent C neurone terminals and causes them to release substance P. Substance P activates dermal mast cells via NK1 receptors, resulting in increased release of TNF- α , which in turn sensitises nociceptor nerve terminals, and enhances their responsiveness. The antipruritic capsaicin desensitises C neurones and depletes substance P from terminals via VR-1 receptors. TNF=tumour necrosis factor; TNF-R=TNF receptor; H1=histamine H1 receptor; PAR=proteinase activated receptor; NK1=neurokinin receptor 1; SP=substance P; VR1=vanilloid receptor 1.

Psoriasis

Itch is a symptom reported in 80% of patients with psoriasis.⁵³ Findings of a study in psoriatic patients with widespread disease showed that itching had a daily cycle and occurred mainly at night.⁵⁴ Itch arose in all areas of the body, had a long duration, and was not restricted to the psoriatic plaque. It was unresponsive to most antipruritics and caused substantial impairment of quality of life. The local inflammation in psoriasis would favour a classification as pruriceptive pruritus. However, changes in epidermal nerve fibre density and neuropeptide distribution are well documented in psoriasis,^{55,56} thus such itch could also be neuropathic.

Evaluation of symptoms

A detailed conventional history and thorough examination are all important, but a detailed description of the qualitative, temporal, and spatial characteristics of itch symptoms should also be obtained from the patient. Two itch questionnaires^{57,58} to help to assess these components have been validated, both based on the well recognised McGill pain questionnaire. One is based on the long form of the McGill questionnaire, and covers in detail sensory descriptors of itch; the other resembles the short form and includes measures of the effect of itch on quality of life and daily activities. Information from a well constructed questionnaire is valuable in diagnosis and in finding the best treatment.

In research, indirect objective correlates are often used, with the assumption that scratch equals itch. Such methods include use of an infrared camera to take time-lapse exposures of nocturnal itching,⁵⁹ piezoelectric transducer devices attached to fingernails,⁶⁰ and limb movement meters.^{61,62} These do not seem to be more valuable than the traditional visual analogue scale, which allows the patient to quantify itch subjectively and quite accurately.⁶³

Treatment

Improved understanding of the pathophysiology of itch has led to modest advances in treatment. No doubt in time this progress will lead to selective topical antipruritics. Topical corticosteroids are not direct antipruritics and should not be used as such, although they effectively relieve itching secondary to inflammatory skin disease. Antipruritic strategies could be assigned according to proposed classification of itch. Therapeutics mainly targeting pruritoceptive itch consist of topical modalities like capsaicin cream, doxepin, and aspirin.

The active ingredient of chilli, capsaicin, owes its antipruritic properties to desensitisation of nociceptive nerve endings (figure 2). It is especially useful at concentrations of 0.025–0.075% in localised intractable pruritus. It is also effective in pruritus of atopic eczema, but its value is limited by production of irritation at the site of application. Although this irritation diminishes after repeated use, it reduces patient compliance.⁶⁴ Such irritation can be reduced by the topical anaesthetic EMLA (eutectic mixture of local anaesthetics).⁶⁵

Because of its exceptionally high potency as an antihistamine, the tricyclic compound doxepin has been formulated as a topical medication. Findings in placebo-controlled double-blind trials have confirmed the effectiveness of doxepin in relief of the itch of atopic eczema.⁶⁶ However, this substance causes sedation by percutaneous absorption, and is therefore not very useful.

Prostaglandins contribute to pruritus induced by histamine by lowering the skin threshold for itch.⁶⁷ Although oral administration of aspirin seems to have little or no effect on clinical itch,⁶⁸ topical aspirin has an

antipruritic effect in experimentally induced itch.⁶⁹ Controlled double-blind crossover trial confirmed the effect of aspirin in patients with severe lichen simplex chronicus, a form of localised itch.⁷⁰

A new topically active antipruritic has been derived from the Amazonian medicine *sangre de grado*.⁷¹ The reported antipruritic effect on itch induced by insect bites was convincing. But further clinical studies are needed to assess the role of this drug in patients with chronic itch.

Therapeutic options for neurogenic itch are mainly based on the antagonistic interaction between itch and pain via the spine. The inhibition of itch by pain has been successfully used to suppress experimental itch. Clinically, μ -opioid receptor antagonists mainly have proven effective.^{32,33,72-74} The antipruritic effect of κ -opioid agonists³⁵ in uraemic patients seems promising, but requires further confirmation. Therapeutic options for neuropathic itch are few. Successful anecdotal treatments have used drugs proven to be effective in neuropathic pain, such as low dose lidocaine⁷⁵ and oral gabapentin.⁷⁶

Understanding of the pathomechanisms of itch in common pruritic disorders such as atopic eczema and cholestasis has improved. Assessment of new treatments is dependent on appreciating the multidimensional nature of itch as a symptom, and use of quantitative methods to give results that can be statistically analysed. Although evidence-based improved treatment modalities are emerging, the development of an ideal antipruritic drug is some way off.

Conflict of interest statement

None declared.

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