Review Article

Recent Advances in Pathophysiology and Current Management of Itch

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Abstract

The neurophysiology of itch, the dominant symptom of skin disease, has previously received scant attention. Recent advances in the neurophysiology and molecular basis of itch include the use of microneurography to demonstrate the existence of a subset of itch-dedicated afferent C neurons distinct from neurons which transmit pain; use of functional positron emission tomography (PET) and magnetic resonance imaging (MRI) of the brain to reveal an itch-specific activation matrix, and new evidence of a functional "dialogue" between C neuron terminals and dermal mast cells in which recently described proteinase-activated receptor type 2 (PAR2) and transient receptor potential vanilloid 1 (TRPV1) receptors, proteases and endovanilloids play a major role. As a necessary prerequisite to diagnosis and management, a pathophysiologically based classification of itch is proposed. Recent advances in understanding of the pathomechanisms of itch of cholestasis include the role of opioids and opioid antagonists. Focusing on neurogenic itch (itch without visible rash), common causes are reviewed and guidelines for laboratory and radiological investigation are proposed. A stepwise approach to management of generalised itch is recommended, including broadband or narrow band ultraviolet (UV), tricyclics such as doxepin, opioid antagonists including naltrexone and selective serotonin reuptake inhibitors (SSRIs) such as paroxetine. For troublesome localised itches such as insect bite reactions, physical urticaria, lichen simplex chronicus or, less commonly, notalgia paraesthetica, brachioradial pruritus, local cooling devices which rely on the cooling action of dimethyl ethers on thermosensitive TRP voltage-sensitive ion channels are now commercially available for short-term relief.

Ann Acad Med Singapore 2007;36:788-92

Key words: Antipruritics, Neurophysiology, Pruritus

Introduction

Itch is the principal symptom of skin disease and is an important skin manifestation of systemic disease. Nevertheless, little was known about the pathophysiology and neurobiology of itch until relatively recently. Previously, the understanding of itch had been essentially conjectural and based upon classical 19th-century concepts of the skin sensorium. It is therefore unsurprising that anti-itch therapy is currently crude, the choice of therapeutic agents being limited. However, new advances over the past 10 years have provided insights into the neurophysiology of pruritus and are opening up exciting possibilities for improved treatments.[1-3]

Neurobiology of Itch

Efficient management of the pruritic patient is greatly enhanced by awareness of the pathophysiology of itch.

Itch Receptors

Previously, it was believed that itch was received in the skin by unspecialised free unmyelinated nerve endings located in and around the dermoepidermal junction as well as intra-epidermally, there being no specialised itch receptors. However, recent work suggests that the epidermis itself, especially the keratinocytes which form the bulk of the epidermis, constitute the itch receptor.[4] Keratinocytes express a range of neuropeptide mediators and receptors

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which appear to be involved in pruritus, including opioids, nerve growth factors (NGF), substance P and receptors including vanilloid receptors and proteinase activated receptor type 2 (PAR 2) and voltage-gated ATP channels – all characteristic of neuronal cells. Thus, the epidermis and its associated ramifications of fine intraepidermal C-neuron filaments can be looked upon as the "itch receptor".

Neural Pathways for Itch

The advent of the microneurography technique, in which action potentials in individual C neurons can be recorded in human volunteers using ultra-fine glass electrodes, has established the existence of dedicated slow-conducting unmyelinated C neurons which only transmit itch (and temperature changes) in response to histamine – thus disproving the notion that itch is merely a mild version of pain.[5] These neurons, which represent only about 5% of the total, have also been shown to be selectively activated in chronic pruritic skin disease.[6] Microneurography has also established that the contralateral transmission neurones which convey itch to the thalamus consist of an itch-specific subclass of lamina 1 spinothalamic tract neurons,[7] thus establishing that dedicated neurons transmit itch not only peripherally but also centrally.

Is There an "Itch Centre" in the Brain?

The application of modern imaging techniques to brain function has enabled this question to be addressed.[8,9] Induction of localised itch, usually by histamine iontophoresesis, followed by imaging using positron emission tomography or nuclear magnetic resonance, has not revealed any evidence of an itch centre in the brain. However, multiple characteristic focal functional changes constituting an "itch matrix" have been observed, and these are distinct from similar responses following pain elicitation – the itch matrix is qualitatively different from the pain matrix. For example, itch but not pain shows left hemispheric dominance.

Regulation and Modulation of Itch

Inhibitory neuronal circuits located in the substantia gelatinosa of the posterior horns of the grey matter of the spinal cord appear to constitute a gated mechanism whereby afferent itch traffic can be regulated.[1,10] In this scheme, increased tone in descending pathways originating in the reticular formation of the periaqueductal grey results from visual, auditory and other stimuli. The result is the activation of inhibitory neuronal circuits leading to closure of the gated mechanism and diminished itch traffic. Thus, patients frequently point out that their itch is less troublesome during daytime working hours – when engagement of these stimuli is maximised, than in the evening when sensory input is diminished. Pruritus is also the result of an imbalance between opioid actions on central μ- and κ-receptors, the former increasing and the latter diminishing itch – probably due to their respective inhibitory and activating actions on the gated mechanism.[11]

How Does Scratching Temporarily Relieve Itch?

Scratching activates thickly myelinated fast-conducting A β neurons. These volleys cause widespread surround inhibition due to activation of the inhibitory neuronal circuits in the substantia gelatinosa. This view receives support from experimental evidence and is the basis of transepidermal electrical stimulation as a treatment of itch.[1,10,12] Alloknesis occurs when normally non-pruritic stimuli applied to skin (e.g., fine touch, temperature change) are perceived as causing pruritus. This phenomenon is believed to be due to central sensitisation, is comparable with the better known allodynia and explains the intense pruritus experienced by patients with atopic eczema in response to sweating or sudden changes in ambient temperature.

Mediators of Itch

Cross-talk between C neuron terminals and the spatially closely related dermal mast cells is increasingly being recognised as important in the pathophysiology of itch. Histamine, which ligates H1 receptors associated with C neurons, and a variety of other mast cell mediators including eicosanoids, tumour necrosis factor-α and other cytokines are important mediators of itching in inflammatory skin diseases.[13] Recently, a new class of histamine receptor, H4, which operates as a transducer of itch, has been recognised in mice and may revive interest in this amine as a major mediator of pruritus.[14] Mast cells produce 2 proteinases, chymase and tryptase. Tryptase has recently been shown to activate PAR 2 expressed on afferent C neuron terminals.[15] This stimulates the sensation of itch and also triggers release of the neuropeptide substance P which, apart from causing pruritus, also evokes further mast cell activation via TRK receptors.

Neurotrophins (prototype: NGF) are also key molecular players in the pathogenesis of itch. NGF causes the proliferation of unmyelinated afferent nerve terminals, sensitisation of afferent nerve terminals and increased expression of neuropeptides. Keratinocytes express high levels of NGF and its receptor TRKA and high urinary and plasma levels of NGF are to be found in patients with atopic eczema.[16]

Transient receptor potential V1 (TRPV1) channels are expressed on nociceptor sensory neurons and many other cell types and respond to changes in temperature and osmotic variations. Capsaicin, an active constituent of chili pepper, possesses antipruritic activity when applied topically

due to its ability to behave as an endovanilloid and ligate TRPV1, leading to depletion of substance P in nociceptor afferent nerve terminals.[17] TRP receptors are also expressed on keratinocytes and ligation of TRPV1 results in the release of proinflammatory and pruritic mediators from these cells.[18] The temperature sensitivity of these receptors may also explain the cooling antipruritic action of topical menthol.[19]

Classification of Itch

When faced with a pruritic patient it is useful to classify itch as an aid to diagnosis and treatment. Following a workshop on itch at Oxford in 2000, Yosipovitch et al[2] and Twycross et al[20] reported a pathophysiologically based classification of pruritus into 4 categories:

- *pruritoceptive* – generated in the skin usually by an inflammatory or other visible pathological process, e.g., scabies, urticaria;
- *neurogenic* – generated in the central nervous system in response to circulating pruritogens as in cholestasis or in response to intraspinal morphine;
- *neuropathic* – due to anatomical lesions of the central or peripheral nervous systems, e.g., nerve entrapment, tumours; and
- *psychogenic*, including delusional parasitosis.

Of course, these categories are not mutually exclusive in a given patient.

Itch of Cholestasis – A Neurogenic Itch

Opioids cause intense pruritus when injected both intraspinally and intracutaneously.[21,22] Biliary obstruction leads to increased intrahepatic synthesis of opioid peptides,[23] which spill over into the circulation and cause pruritus by acting on μ-opioid receptors in the central nervous system and skin. This pruritus can be partially relieved by opioid m-antagonists such as naloxone.[3,24] Evidence for the involvement of opioid peptides in the skin comes from demonstration of immunoreactive met-enkephalin and other opioids in skin of patients with cholestasis.[3] However, it is likely that other pruritogens, including bile salts, also play a role and rifampicin has been proven effective in well-controlled double-blind trials.[25]

Pruritus of End-stage Renal Failure

Although still a common complication of chronic renal failure, occurring in 40% to 50% of patients, persistent itching is less frequent than in previous years – possibly due to improved dialysis procedures. It is approximately equal in frequency in patients on haemodialysis and those receiving CAPD (continuous ambulatory peritoneal dialysis), and for reasons which remain unclear, it is very rare in children with renal failure and in acute renal failure at any age.

The aetiology is unclear and there have been numerous hypotheses, including increased numbers of cutaneous mast cells, increased histamine levels and secondary hyperparathyroidism. It has also been proposed that pruritus of end-stage renal failure is associated with the presence of dystrophic neuropathic changes in cutaneous nociceptor nerve endings.[26] That circulating mononuclear cells show increased expression of TH1 markers, chemokines (CCR4, CXCR3) and IL-6 has also recently been reported and dubbed "microinflammation" in end-stage renal failure.[27] The latter findings are of interest, given that topical calcineurin inhibitors have recently been found effective in relieving itching of renal failure in placebo-controlled studies.[28]

Treatments that do, or do not work in pruritus of renal failure are shown in Table 1.

Table 1. Treatments That Work or Do Not Work in Treatment of Itching in End-stage Renal Failure

Do not work (usually)	Do work (usually)
Antihistamines	Emollients
Corticosteroids	UVB phototherapy
Opioid antagonists (controversial)	Gabapentin[29]
Serotonin antagonists	Doxepin
Topical capsaicin	Topical calcineurin inhibitors

History, Physical Examination and Investigations in Patients with Neurogenic Itching

Careful history-taking and thorough physical examination are crucial in the effective management of itching in the absence of causative skin disease (pruritoceptive itch) and should in turn lead to appropriate investigation and successful treatment.

History-taking should include a detailed drug history, including morphine-like drugs such as tramadol, hydroxychloroquine and the recently described biological response-modifying agents used to treat severe psoriasis (infliximab, etanercept, efalizumab). Constitutional symptoms (fever, night sweats, weight loss) may denote an underlying lymphoma. Weight loss or gain should also prompt consideration of hyper- or hypothyroidism respectively. A history of promiscuity, substance or alcohol abuse raises the possibility of HIV infection or viral hepatitis. An accurate history of the timing (e.g., predominantly nocturnal or diurnal) of itching helps fine-tune the timing of antipruritic treatment.

Physical examination of the skin, mucosae, regional lymph nodes and abdomen should be performed. Eczematous changes secondary to itching, often with

superadded infection leading to impetiginisation, can easily cause confusion since, to the untrained eye, it may be difficult to distinguish them from primary eczematous skin disease causing pruritoceptive itching, leading to failure to recognise neurogenic itch. Other signs to look out for include jaundice, anaemia, and those pertaining to thyroid disease.

Investigations which should be routinely performed are listed in Table 2.

Table 2. Routine Investigations in a Patient with Extensive Itching and No Causative Skin Disease

Investigation	Comment
Renal function	
Full blood count and differential	
Plasma thyroid stimulating hormone assay	
Liver function tests	
Chest X-ray	Imaging may also be useful in localised neuropathic itch, e.g., due to a spinal cord tumour, nerve entrapment due to degenerative spinal disease, etc.
Cancer screening	If indicated by history (weight loss, change in bowel habit, etc.)
HIV testing	If indicated by history (weight loss, substance abuse, sexual promiscuity, etc.)

Treatment of Itch

General Measures

The patient with a generalised itch should be advised to keep the body cool since the intensity of itching is usually enhanced if the skin is warm.[30] Patients should be advised to avoid spicy foods and alcoholic drinks. Topical menthol in calamine cream is also appreciated by most patients, since it causes a cooling sensation via TPR afferent nociceptor receptor channels.[31,32] Dry skin is invariably itchy and should be corrected by moisturisation and avoidance of soaps. This is especially important in the xerosis of chronic renal failure. For troublesome localised itches, topical capsaicin, and in recalcitrant cases, trans-epidermal electrical nerve stimulation (TENS) or cutaneous field stimulation (CFS) is often very effective.[12,33]

Specific Measures Including Drugs

Antihistamines are usually poorly effective unless the pruritus is principally mediated by histamine, e.g., urticaria, although the sedative action of the first-generation H1 antihistamines may be useful in other cases of chronic pruritus. Corticosteroids either topically or systemically are not intrinsically antipruritic and are only effective in relieving pruritus occurring as a consequence of inflammatory changes in the skin.

Narrow band ultraviolet B phototherapy (311 nanometres) is beneficial in generalised itching due to most causes, and is especially useful in pruritus of end-stage renal failure.[34] Oral doxepin, a tricyclic compound, is a non-specific inhibitor of post-synaptic re-uptake of adrenaline and noradrenaline and is a powerful antipruritic, possessing greater potency as an H1 antihistamine than any other available H1 antagonist as well as being widely used as an antidepressant.[35] It should be prescribed in low dosage initially, and be used with extreme caution in patients with liver or cardiovascular disease. It should not be withdrawn abruptly or prescribed concurrently with other anti-depressants. It is not contraindicated in the presence of renal failure and is thus very useful in these patients. It is metabolised via the liver cytochrome P450 3A pathway and therefore should not be administered concurrently with macrolide antibiotics or imidazole antifungals.

Opioid antagonists, including oral naltrexone, are effective in some patients, especially in patients with cholestatic itching.[24] However, claims for effectiveness have been made for a variety of other pruritic disorders.[36] This class of drug is contraindicated in patients with severe liver disease, patients addicted to opioids and patients receiving opioid analgesia. Opioid antagonists seem to cause withdrawal symptoms and signs in patients with itching due to cholestasis and dosage should start low and be increased gradually to avoid this complication. Butorphanol, a combined μ-receptor antagonist and κ-receptor agonist, administered as a nasal spray, has showed considerable promise in the management of intractable pruritus.[37]

Gabapentin, a structural analogue of γ-amino butyric acid and an anticonvulsant, has been advocated as a potent antipruritic and has received support from at least 1 double-blind placebo-controlled trial in haemodialysis patients.[29] Other drugs that can be tried include mirtazepine, a serotonin type 3 receptor antagonist,[38] paroxetine, a selective serotonin reuptake inhibitor (SSRI)[39] and thalidomide.[40]

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