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Targeted treatment of pruritus - a look into the future

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Abstract

Recent advances in pruritus research have elucidated mediators and neuronal pathways involved in itch transmission and this fast-emerging knowledge may possibly be translated into new therapies in the near future. In the skin and peripheral nerves, potential mediator and receptor therapeutic targets include the H4 histamine receptor, proteinase-activated receptor 2, serine proteases, Cathepsin S, peripheral mu- and kappa-opioid receptors, interleukin-31, transient receptor potential vanilloid 1 and 3, fatty acid amide hydrolase, nerve growth factor and its receptor, acetylcholine, and the Mas-related G-protein-coupled receptor. In the spinal cord, gastrin-related peptide and its receptor, as well as substance P and its receptor neurokinin receptor-1 serve as potential therapeutic targets. In the brain, reduction of itch perception and modulation of emotions may possibly be achieved through drugs acting on the anterior cingulate cortex. Clinically, management of pruritus should be instituted early and address the skin pathology, peripheral neuropathy, central sensitisation, and the cognito-affective aspects of the disease.

Keywords

Target; Itch; Pruritus; Management; therapy

Introduction

Pruritus is a common symptom and a source of significant morbidity.1 However, research in itch, unlike pain, has not received much interest until the current decade and management of pruritic conditions has been hampered by our inadequate understanding of the pathophysiology of itch. Recent advances have elucidated the mediators and neuronal pathways involved in itch transmission (Fig. 1), and it may be that this fast emerging knowledge will be translated into new therapeutics in the near future. In addition to reviewing promising new agents, this article highlights important recent findings in pathogenesis of itch and explores how the mediators and receptors involved can serve as potential targets for the development of novel anti-pruritic drugs in various diseases (Tables 1 and 2).

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Anti-histamines

Histamine has been the prototypic pruritogen for decades2 but robust evidence for its role and the efficacy of histamine H1 receptor antagonists is limited to only a few diseases (namely urticaria, mastocytosis, allergic drug reactions, and insect bite reactions). The role of histamine in most forms of chronic pruritus (defined as more than 6 weeks by the International Forum for the Study of Itch)3 is minimal and H1 anti-histamines are frequently ineffective in these conditions. The recent discovery of H3 and H4 histamine receptors and their involvement in pruritus and inflammation4,5,7 has, however, rekindled interest in histamine. In particular, the H4 receptor, first cloned in 2000,8 has been found to be involved in allergic inflammation and the functioning of mast cells, eosinophils, monocytes, dendritic cells and T cells.8,9,10,11

In mice, H4 histamine receptor agonists have been shown to induce pruritus that was independent of mast cells or other haematopoietic cells; this suggests that the H4 receptor-mediated itch results from a direct action on peripheral nerves.6 The H4 receptor antagonist, JNJ-7777120 (Johnson & Johnson Pharmaceutical Research & Development), has been demonstrated to be efficacious in models of pruritus, asthma, and allergic rhinitis.12,13,14 Antagonism of the H4 receptor was also able to inhibit substance P-induced pruritus,15 which was resistant to H1 receptor antagonists15,16. The effect of H4 receptor antagonism on both pruritus and Th2-cell-mediated inflammation highlights its therapeutic potential in atopic dermatitis (AD).17 Clinical studies are currently ongoing and this novel form of anti-pruritic treatment is expected to be available in the near future.18

Protease Pathway

A distinct itch transmission pathway mediated by the pruritogen cowhage has been elucidated in recent years.19 Cowhage is a tropical plant and the spicules on its pods contain a cysteine protease, known as *mucunain*, which binds to protease-activated receptors (PAR) 2 and 420 to stimulate cutaneous mechanical-sensitive C-fibers.21 The secondary neurons of these peripheral nerves were also found to be distinct from the neuronal pathway transmitting histamine-induced itch in primates,22 although findings of a study in mice suggested a functional overlap between these two pathways in the spinal cord.23 The protease-PAR-2 pathway appears to be a suitable model for the study of itch in AD. Cowhage-induced itch, similar to that of AD, does not have accompanying axonal reflex flare, is associated with burning and/or pricking sensations24, and can be induced mechanically19. PAR-2 receptors, which cowhage binds to, were found to be increased in AD lesions.25 We have also recently found that cowhage induces a far more intense sensation compared to histamine and that the protease pathway is likely the main determinant of itch perception when both histamine and protease pathways are activated together (unpublished data). The protease pathway therefore plays an important role in itch transmission in AD and probably also in other chronic pruritic conditions.

One approach in the management of pruritus is to target the specific components in the protease pathway, which consists of PAR-2 and endogenous proteases. These endogenous proteases includes serine proteases, such as mast cell tryptase26,27 and kallikreins28, and cysteine proteases, such as Cathepsin S29. In addition to pruritus, serine proteases signalling through PAR-2 have been shown to play a regulatory role in epidermal barrier function30 and skin inflammation28. Serine proteases and PAR-2 may therefore be therapeutic targets in AD, which consists of all these 3 features, and in other conditions such as pruritus of the elderly and ichthyosis.

Nafamostat mesilate and camostat mesilate are synthesized serine protease inhibitors that inactivate tryptase and kallikrein. Nafamostat mesilate, which has been used as an anti-

coagulant, has also been shown to also inhibit mast cell activation and the production of inflammatory cytokines.31,32 The successful treatment of two patients suffering from refractory chronic urticaria with nafamostat mesilate and camostat mesilate has recently been reported.33 Nafamostat mesilate was also found to effectively inhibit scratching in mice, mainly via its action on tryptase26,27.

Another group of drugs that target the protease pathway are the tetracyclines. Tetracycline and its derivatives, doxycycline and minocycline, were found to reduce PAR-2-mediated production of interleukin-8 in keratinocytes.34 Tetracyclines can potentially be useful in inflammatory diseases which are pruritic, such as subsets of acne vulgaris and bullous pemphigoid, by reducing both inflammation and pruritus through its antagonistic effect on PAR-2. PAR-2 antibodies [such as SAM-11 (Santa Cruz) and P2pal-2135] and antagonists [such as FSLLRY (Peptides International), ENMD-106836] have been used in mice to inhibit itch induced by tryptase and itch occurring in AD and chronic dry skin.26,27,37 Another potential therapeutic target is cysteine protease, and an inhibitor targeting Cathepsin S (E-6438) has been used in laboratory studies to inhibit itch signaling20,29.

Opioid system

It is well known that the opioid system has a role in itch processing in the central nervous system. There is growing evidence, however, that opioid receptors and endogenous opioid agonists are also functional in the skin and they have been found on peripheral nerve fibres, keratinocytes, melanocytes, hair follicles and immune cells.39 It is believed that an excess of mu-opioid receptor activity in comparison to kappa-opioid receptor activity results in pruritus40 and stimulation of the kappa-opioid receptor was found to inhibit mu-receptor effects both centrally and peripherally41,42. Mu-opioid receptor antagonists, such as naloxone, naltrexone and nalmefene, have been shown in controlled clinical trials to be effective in treating pruritus associated with cholestasis, uraemia and dermatologic diseases.43–46 Nalfurafine, a kappa-opioid receptor agonist, has been shown to significantly reduce uraemic itch,47 and was approved for use for this purpose in Japan in 2009. Its efficacy in the pruritus of chronic liver disease has also been investigated in a phase II trial,48 but the results are currently unavailable. Two other kappa-opioid receptor agonists, bremazocine and GR 89696,49,50 have been shown in monkeys models to inhibit itch induced by intrathecal morphine. Butorphanol is both a kappa-receptor agonist and a mu-receptor antagonist; the epidural form was found to be effective in relieving pruritus associated with epidural morphine51 and the intranasal form has been reported to be effective in patients with severe and intractable pruritus secondary to systemic and inflammatory skin diseases52.

Nausea and analgesia withdrawal are significant problems associated with opioid antagonists, and central nervous system depression and addiction are important side effects with opioid agonists. Peripherally-acting opioid receptor agonists and antagonists, which do not cross the blood-brain barrier, are devoid of such central effects and provide an alternative to circumvent these problems.

Subcutaneous methylnaltrexone is a peripherally-active mu-opioid receptor antagonist approved in the United States for use in patients under palliative care who do not respond sufficiently to laxative therapy. The drug has also been approved for use by Health Canada and the European Medicines Agency. In a double-blind randomised controlled trial involving 10 healthy volunteers, oral methylnaltrexone at a dose of 19.2mg/kg significantly improved itch induced by intravenous morphine.53 Methylnaltrexone has also been used by anaesthesiologists for short-term management of pruritus in patients receiving intraspinal and epidural analgesia.54 These results support the role of peripheral opioid receptors in

mediating itch, but more studies are required to evaluate the efficacy of methylnaltrexone in pruritic conditions. Alvimopan is an orally administered peripherally-acting mu-opioid receptor antagonist that has been approved in the United States for acceleration of gut function after bowel resection and primary anastomosis. Its efficacy as an anti-pruritic agent remains to be explored.

Preliminary data on peripherally-acting kappa-opioid receptor agonists suggest that they may be useful in the treatment of itch. ICI 204,448 (Tocris Bioscience) has previously been shown to prevent chloroquine-induced itch in mice.55 Asimadoline (EMD-61753), which is being developed for the treatment of irritable bowel syndrome56, has been reported to inhibit itch induced by compound 48/80 (which degranulates mast cells to release histamine) and a kappa-receptor antagonist57. SA14867 (Santen Pharmaceutical Co.) has been shown to inhibit itch induced by substance P and 5-hydroperoxyeicosatetraenoic acid (HPETE) in mice and attenuate morphine-induced scratching in monkeys.58

Topical preparations of opioid receptor agonist/antagonist, which would be useful in localised pruritic conditions, have been developed but are currently not commercially available. 1% naltrexone cream has been used in patients with AD in an open study in which more than 70% of the 18 subjects experienced significant reduction in pruritus.59 Subsequently, a placebo-controlled, cross-over trial involving 40 AD patients demonstrated that the cream was effective in reducing pruritus. 59 Lim *et al.* formulated a topical liposomal butorphanol preparation and showed that the formulation is able to release a consistent amount of butorphanol into the systemic circulation over 24 hours.60 This formulation, however, has not been tested in humans. Further trials involving the abovementioned topical agents will be required to demonstrate their clinical utility.

Interleukin-31

Interleukin-31 (IL-31) is a cytokine that has been found to play an important role in pruritus. 61 Over-expression of IL-31 in lymphocytes in mice induced scratching and dermatitis,62 and higher levels of IL-31 have been found in the lesions of patients with AD and prurigo nodularis63. A common IL-31 haplotype was found to be significantly associated with the non-atopic type of eczema (defined as the absence of specific IgE against common allergens), and this suggests that altered regulation of IL-31 gene expression is a risk factor for development of the disease.64 A genetic mutation in the IL-31 receptor has also been recently implicated in the pathogenesis of familial primary cutaneous amyloidosis, a form of localised pruritic disease.65,66

IL-31 is produced predominantly by Th2 lymphocytes,62 which are the main inflammatory cells in acute AD. Th1 lymphocytes, the predominant component of the inflammatory infiltrate in chronic AD, produce lesser amounts of IL-31.62 IL-31 receptors were found to have a much higher expression in the dorsal root ganglia compared to other tissues63 and IL-31 may exert its pruritogenic effect by directly binding to its receptors on cutaneous nerve fibres. IL-31 antibody has been demonstrated to reduce scratching during the onset of skin manifestations in a murine AD model,67 and this result further supports the role of IL-31 as an important mediator of pruritus. IL-31 antibody may well serve as a new therapeutic approach in AD and other pruritic inflammatory skin diseases.

Vanilloids

Vanilloids are endogenous and exogenous agents that possess the ability to activate transient receptor potential vanilloid (TRPV) ion channels either directly or indirectly. The best known member is TRPV1, a non-selective cation channel expressed on both sensory neurons and non-neuronal cells (such as epidermal and hair follicular keratinocytes, mast

cells, dendritic cells, and endothelial cells).[68–70] Activation of TRPV1 results in excitation and subsequent desensitisation of C-fibres through depletion of neuropeptides, a mechanism which has been utilised to alleviate pain and itch.[71–72] TRPV1 was also found to be required in histamine- and serotonin-induced itch,[73] and has been shown to mediate histamine-induced itch via activation of phospholipase A2 and 12-lipoxygenase[74]. Endogenous vanilloids consist of a heterogenous group of mediators that include histamine, prostaglandins, bradykinin, eicosanoids, adenosine triphosphate, and various neurotrophins.[75–77]

Topical capsaicin, the active compound in chilli pepper, is an exogenous vanilloid. It has been shown to be useful in localised, chronic pruritic diseases, particularly those of neuropathic origin, such as post-herpetic itch, brachioradial pruritus, and notalgia paresthetica.[78] It has also been used in pruritus associated with haemodialysis[79], psoriasis[80], and AD[81]. Capsaicin is available over the counter in concentrations of 0.025% to 0.1%, and the main problem with its use is the initial burning sensation which usually lasts several days. Patients can be advised to apply a topical anaesthetic, such as lignocaine or eutectic mixture of local anaesthetic (EMLA), before application of capsaicin in the first 2 weeks of treatment in order to reduce the discomfort. The topical anaesthetic, in addition, serves as an anti-pruritic treatment in itself. Pre-treatment with an anaesthetic agent has been shown to effectively reduce burning sensation and attenuate heat hyperalgesia during capsaicin treatment.[82] A new high-potency transdermal formulation containing 8% capsaicin (Qutenza, formerly NGX4010) has recently been approved in Europe and the United States for the treatment of post-herpetic neuralgia. It was shown to be superior to a low-concentration formulation in the treatment of various types of neuropathic pain[83] and a single 30- or 60-minute application may provide up to 3 months of localised pain relief with minimal adverse effects. Although there is no data on its efficacy in neuropathic itch, this formulation is likely to be effective in these conditions and can be helpful in more resistant cases.

Tacrolimus is a calcineurin inhibitor that may inhibit pruritus through its effects on TRPV1. In addition to its anti-inflammatory action, tacrolimus has been reported to have direct anti-pruritic effects in AD and other diseases.[84–86] It was found to induce the release of substance P from neurons, probably by favouring phosphorylation of TRPV1 and depleting phosphatidylinositol 4,5-bisphosphate, which in turn results in inactivation of calcium channels and desensitisation of neurons.[87] Unlike capsaicin, it does not bind to TRPV1 directly.

TRPV3 channel is another member of the TRPV family, and has a role in thermosensation[88] and hair growth[89]. A study showed that TRPV3 transgenic mice with a Gly573Ser gain-of-function mutation developed allergic dermatitis and spontaneous scratching (which was un related to the dermatitis)[90]. Like TRPV1, TRPV3 channels were found to be similarly expressed on keratinocytes and peripheral nerves. Modulation of these channels may potentially inhibit pruritus both at the epidermis (by inhibiting the production of itch mediators by keratinocytes) and in the peripheral nerves.[91] In addition, certain agents such as camphor may act on both TRPV1 and TRPV3,[92] and this creates the opportunity for using a single agent to target multiple receptors at multiple points in the itch signalling pathway.

Cannabinoids

The efficacy of cannabinoids in pruritus has been demonstrated in a few studies. Pre-treatment with topical cannabinoid receptor agonists has been found to significantly reduce histamine-induced itch and vasodilatation in healthy volunteers.[93,94] In mice, cannabinoid

receptor antagonists, such as rimonabant, have been shown to elicit a dose-dependent increase in scratching behaviour.95

In a large industry-sponsored trial, a cream containing N-palmitoylethanolamine (PEA) was found to significantly reduce pruritus and improve disease severity in AD.96 PEA was found to exhibit little affinity for cannabinoid receptors, but may act by enhancing the effect of anandamide, an endocannabinoid, through inhibition of the enzyme fatty acid amide hydrolase (FAAH).97 Anandamide was found to reduce the activity of TRPV1 in primary sensory neurons, probably by reduction of protein kinase A-mediated phosphorylation of TRPV1.98 The role of anandamide in itch has also been demonstrated in an acute allergenic murine model in which suppression of neuronal FAAH [using FAAH inhibitor URB597 (KDS-4103) (Cayman Chemical)] reduced scratching response.99 Direct-acting cannabinoid agonists also exert an anti-pruritic effect; however, unlike FAAH inhibitors, they have prominent central side effects such motor suppression, dependence, and psychomimesis.99,100 In contrast to the centrally-active URB597, a peripherally-restricted FAAH inhibitor has also been recently developed. This inhibitor is known as URB937 and was shown to be effective in inhibiting pain in mice.101 Research has been ongoing to examine drugs that prevent the catabolism of endogenous cannabinoids and enzymes such as FAAH serve as targets for the development of new therapies for itch.99,100

Neurotrophins

Neurotrophins are neuropeptides that regulate the growth and function of nerve cells. The prototypic neurotrophin is nerve growth factor (NGF), whose main sources are keratinocytes and mast cells.102 NGF has been shown to result in proliferation of nerve fibres103 and up-regulation of neuropeptides, such as substance P104. In AD lesions, higher levels of NGF have been found in keratinocytes in the epidermal basal and spinous layers, and increased density of NGF receptors, known as tropomyosin-related kinase A (Trk A), have been noted in the epidermis and upper dermis105. The level of NGF in the stratum corneum also correlated with the severity of itching and eruptions in AD106. Increased NGF and TrkA immunoreactivities have been detected in prurigo nodularis107 and pruritic psoriatic lesions,108 and higher local NGF concentrations and increased fibre density have also been found in the pruritic lesions of contact dermatitis109.

Anti-NGF strategies have been tested in the murine AD model. Anti-NGF antibodies were shown to significantly inhibit the development and proliferation of AD lesions and to prevent proliferation of epidermal nerves.110 TrkA inhibitors [K252a (Calbiochem) and AG879 (Alomone Labs)] were also demonstrated to significantly improve established dermatitis and scratching behaviour, together with decreasing nerve fibre density in the epidermis.111 Of note, anti-NGF antibodies have been used to treat pain in patients,112–114 and Tanezumab is a monoclonal antibody115 that has been investigated for the treatment of osteoarthritis and diabetic polyneuropathy in clinical trials116,117. Anti-NGF strategies therefore provide another possible avenue for the management of chronic pruritus.

Other members of the neurotrophin family include neurotrophins 3, 4 and 5 and brain-derived neurotrophic factor (BDNF). Neurotrophin 4 was found to be increased in the prurigo lesions of AD patients,118 and serum levels of BDNF correlated with the degree of nocturnal scratching, disease severity, and quality of life in patients with AD119. More studies will be required to clarify the roles of neutrophin 4 and BDNF in pruritus and AD.

Acetylcholine

Acetylcholine is the main neurotransmitter in the autonomic nervous system, and may have a role in mediating pruritus. Elevated expression of acetylcholine has been found in the skin

of AD patients.120 Intradermal injection of acetylcholine induced pain but itch was produced when the injection was performed in lesional AD skin.121–123 This phenomenon, however, may also be explained by the central sensitisation to itch that occurs in chronic AD.

Botulinum toxin inhibits the release of acetylcholine from presynaptic nerve terminals. It has been shown to reduce neurogenic inflammation (inflammation secondary to the release of neuropeptides from afferent neurons) induced by histamine, capsaicin, and transcutaneous electrical stimulation.124–127 The usefulness of subcutaneous botulinum toxin in localised pruritus has been reported in cases of notalgia paraesthetica, lichen simplex chronicus, and neuropathic itch128–130; however, botulinum toxin has also been reported to be inefficacious for neuropathic itch in a case series.131 The role of acetylcholine in pruritus and the benefits of targeting its action in therapeutics remain to be evaluated.

Toll-like receptor 7

In a recent study in mice, functional Toll-like receptor 7 (TLR7) was found to be expressed in C-fibre sensory neurons and was important in mediating itch induced by non-histaminergic pruritogens.132 Although TLR7 appears to be functionally conserved across mice and human species, studies are required to determine its role in pruritus in humans. The effectiveness of antagonising TRL7 to inhibit itch at the cutaneous level awaits evaluation.

Gastrin-releasing peptide and its receptor

The recent discovery of a specific group of inter-neurons in the dorsal horn of the spinal cord of mice provides evidence for a specific itch-transmitting central pathway that is distinct from pain signalling.133,134 The presence of such a pathway has long been a topic of debate. Gastrin-releasing peptide (GRP), a peptide initially discovered to play several roles in the regulation of gastrointestinal physiology, binds to gastrin-releasing peptide receptor (GRPR), a G protein-coupled receptor. In the study by Sun *et al.*, GRP was found to be specifically expressed in a small subset of peptidergic neurons in the dorsal root ganglia and expression of GRPR was found to be restricted to lamina I of the dorsal horn of the spinal cord.133 Mice with mutant GRPR and mice with a GRPR antagonist injected into their spinal cerebrospinal fluid demonstrated significantly less scratching behaviour when compound 40/80, a PAR-2 agonist, and chloroquine were applied. The GRPR-mutant mice, however, demonstrated normal response to pain stimuli. Provided that a similar mechanism of itch transmission is present in humans, GRP and GRPR may be central targets that can be used to inhibit itch induced by different pruritogens.

Mas-related G-protein-coupled receptors

A recent study in mice revealed that Mas-related G-protein-coupled receptors (Mrgprs), a family of G protein-coupled receptors expressed exclusively in peripheral sensory neurons, function as receptors in chloroquine-induced itch.135 Although Mrgprs do not seem to mediate histamine-induced itch, Mrgprs are activated by neuropeptides and it is possible that they may play a role in transmission of itch induced by other substances.136 Interestingly, the peripheral sensory neurons expressing Mrgprs also expressed GRP. This gives further support to the presence of a group of peripheral C-fibres specifically transmitting itch. A molecular model for the transmission of itch induced by chloroquine and possibly other pruritogens can also be derived from this information: the pruritogen activates Mrgprs on peripheral nerves and stimulates release of GRP in the spinal cord, which in turn activates GRPR on spinal inter-neurons and subsequently activates the secondary itch neurons in the spinothalamic tract. Therefore, in addition to GRP and GRPR, Mrgprs provide molecular access to itch-selective neurons, and may serve as a potential target in itch therapeutics.

Substance P-Neurokinin Receptor

Substance P is an important neuropeptide mediating itch and neurogenic inflammation.[137,138] It is a tachykinin that binds to neurokinin receptors (NKR) 1 to 3,[139] but has the highest affinity for NKR-1. NKR-1 is expressed in the central nervous system and the skin and NKR-1-expressing neurons in the superficial dorsal horn of the spinal cord were found to be involved in itch transmission in rats.[140]

Aprepitant is a selective high-affinity NKR1-antagonist which has been approved for the prevention of chemotherapy-induced emesis.[141] It has been reported to be effective in cases of Sezary syndrome, erythrodermic cutaneous T-cell lymphoma, metastatic sarcoma and breast carcinoma, erlotinib-induced itch, and chronic refractory pruritus from various causes.[142–146] The drug has generally been well-tolerated, and side effects were mild. However, it is extremely expensive and its efficacy as an anti-pruritic agent requires verification in randomised controlled trials. Besides aprepitant, other NKR-1 antagonists are available, and some are under development. These drugs include fosaprepitant (intravenously administered pro-drug of aprepitant), casopitant, vestipitant, orvepitant, lanepitant, dapitant, and L-733,060 (Merck, Sharpe & Dohme). They possess anti-depressant, anxiolytic, and anti-emetic properties and their utility in pruritic diseases remains to be explored.

Lysophosphatidic acid

A recent study showed that lysophosphatidic acid (LPA) functioned as a pruritogen in the sera of patients with cholestatic liver disease.[147] LPA is a phospholipid derivative synthesized by the enzyme autotaxin, and acts as a signalling molecule. In addition, the study found that the activity of autotaxin in patients' sera correlated with the presence and intensity of pruritus. LPA and autotaxin may therefore be potential targets in the treatment of cholestatic pruritus.

Cerebral processes

There is increasing evidence to support the phenomenon of central sensitisation in chronic pruritus, a process analogous to central sensitisation in chronic pain.[148,149] This process is thought to occur in the spinal cord in both instances. The latter has been attributed to a defective descending pain-inhibitory system arising from various areas in the brainstem,[150] and the cortical connections of these regions are unknown. From the management point of view, treatment of pruritus should be instituted early to avoid development of central sensitisation.

Little is known about the supraspinal processing of itch, and it is only in recent years that positron emission tomography and functional magnetic resonance imaging have been used to study the brains of healthy subjects and patients with AD. Induction of itch was found to activate various areas of the brain that are involved in sensory, motor, and emotional functions and these areas include the somatosensory areas I and II, supramarginal gyrus, inferior parietal lobe, anterior and posterior cingulate cortex, precuneus, and insula-claustrum complex. The areas of brain activation occurring in itch are similar to those of pain, except for the precuneus, which is involved in episodic memory retrieval and may be associated with the affective components of itch.[151,152] Among the areas activated in itch, the cingulate cortex appears to be an important region involved in the processing of pruritus. Compared to controls, the cingulate cortex was found to be significantly activated in patients with AD after histamine was administered, and the degree of activation correlated with disease severity.[151] The cingulate cortex was also found to be deactivated after scratching in healthy subjects.[153]

In addition to somatosensory input, the perception and interpretation of pruritus are very much influenced by cognitive and affective processes. Anti-depressants [selective serotonin reuptake inhibitors (SSRI) and mirtazapine] and gamma-aminobutyric acid (GABA)-ergic drugs (namely gabapentin and pregabalin) have been found to be effective in treating itch; their mechanisms of actions are unknown but they may work by modulating itch perception. Serotonin and GABA were found to inhibit the cingulate cortex in mice,154 and activity in the cingulate cortex may be a mechanism by which these serotoninergic and GABA-ergic drugs exert their effects. The anterior cingulate cortex is known to be involved in emotional and cognitive functions (such as reward anticipation),155 and with the recent findings of its role in pruritus, it appears to be an important target in the development of centrally-active anti-pruritic agents.

Mirtazapine is a noradrenergic and specific serotonergic anti-depressant that has been used to treat nocturnal itch156 and malignancy-associated pruritus157,158. Esmirtazapine (ORG-50,081), the (*S*)-(+)-enantiomer of mirtazapine, has a shorter half-life and is currently under development for the treatment of insomnia.159,160 Esmirtazapine would be a promising alternative for patients who benefit from mirtazapine but experience prolonged drowsiness following its use.

Serotonin–norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressants which has been used in the treatment of anxiety disorders, chronic neuropathic pain, and fibromyalgia.161 Among them, venlafaxine, desvenlafaxine (the synthetic active metabolite of venlafaxine), duloxetine, and bicifadine have been used to treat neuropathic pain, while duloxetine, milnacipran, and levomilnacipran (levo- isomer of milnacipran) have been used to treat fibromyalgia. The efficacy of SNRIs in itch has not been assessed, but they may potentially be useful in neuropathic itch and chronic itch associated with depression and/or anxiety.

In addition to the SSRIs, mirtazapine, and the SNRIs, NKR-1 antagonists may also possess concurrent anti-depressive, anxiolytic, and anti-pruritic properties. Vestipitant is under clinical evaluation as an anxiolytic and a potential anti-depressant162,163, and L-733,060 has been shown in animal studies to have antidepressive164,165 and anxiolytic166 effects. Aprepitant, however, was found in clinical trials to be ineffective for major depressive disorder167 and plans to market it as an anti-depressant have since been abandoned. The efficacy of NKR-1 antagonists in pruritus through antagonism of substance P activity and modulation of emotions awaits further elucidation.

Brain imaging has enabled identification of the various cerebral areas activated by itch. It should be noted, however, that the central mechanisms in different types of itch may differ. An example is seen in the use of gabapentin - it was shown to be efficacious in haemodialysis-associated pruritus168,169 but it caused worsening of pruritus of cholestasis170. Treatment of pruritus should therefore be tailored to target the different pathological mechanisms in various diseases and also individualised according to the medical co-morbidities and requirements of each patient.

From the clinical point of view, management of chronic pruritus must address not only the skin pathology, but also peripheral neuropathy (if present), central sensitisation, and the cognito-affective aspects. Targeting the brain is also of particular relevance in skin diseases in which there are many different types of mediators and triggers involved in causing itch, such as AD. Attempts to inhibit multiple peripheral receptors and mediators with multiple agents will conceivably incur many unwanted side effects, and mediating the cerebral processing of itch may be a more fruitful approach. Besides pharmacotherapy, psychotherapy can be used in management of the affective dimension, and the approaches

include psychoanalysis, psychodynamic therapy, guided affective imagery171, and hypnosis172,173. Management of the cognitive processes include providing education, support, and cognitive-behavioural therapy.174,175

Conclusion

With a better understanding of the pathological mechanisms of itch processing, targeting specific mediators and neuronal pathways offers a promising approach to more effective management of pruritus. In particular, the PAR-2 and H4 histamine receptor pathways, the opioid system, IL-31, and TRPV1 serve as targets for the development of novel anti-pruritic therapies. Clinically, management of pruritus should be instituted early and address the skin pathology, peripheral neuropathy, central sensitisation, and the cognito-affective aspects of the disease.

What is already known about this topic?

- Research interest in pruritus has spurred a tremendous increase in knowledge over the last few years.
- Management options for pruritus, however, are still limited and treatment is suboptimal.

What does this study add?

- Provides a review of the current knowledge and new discoveries regarding the pathogenesis of pruritus.
- Introduces promising drugs and identifies potential targets for the development of novel anti-pruritic therapies.

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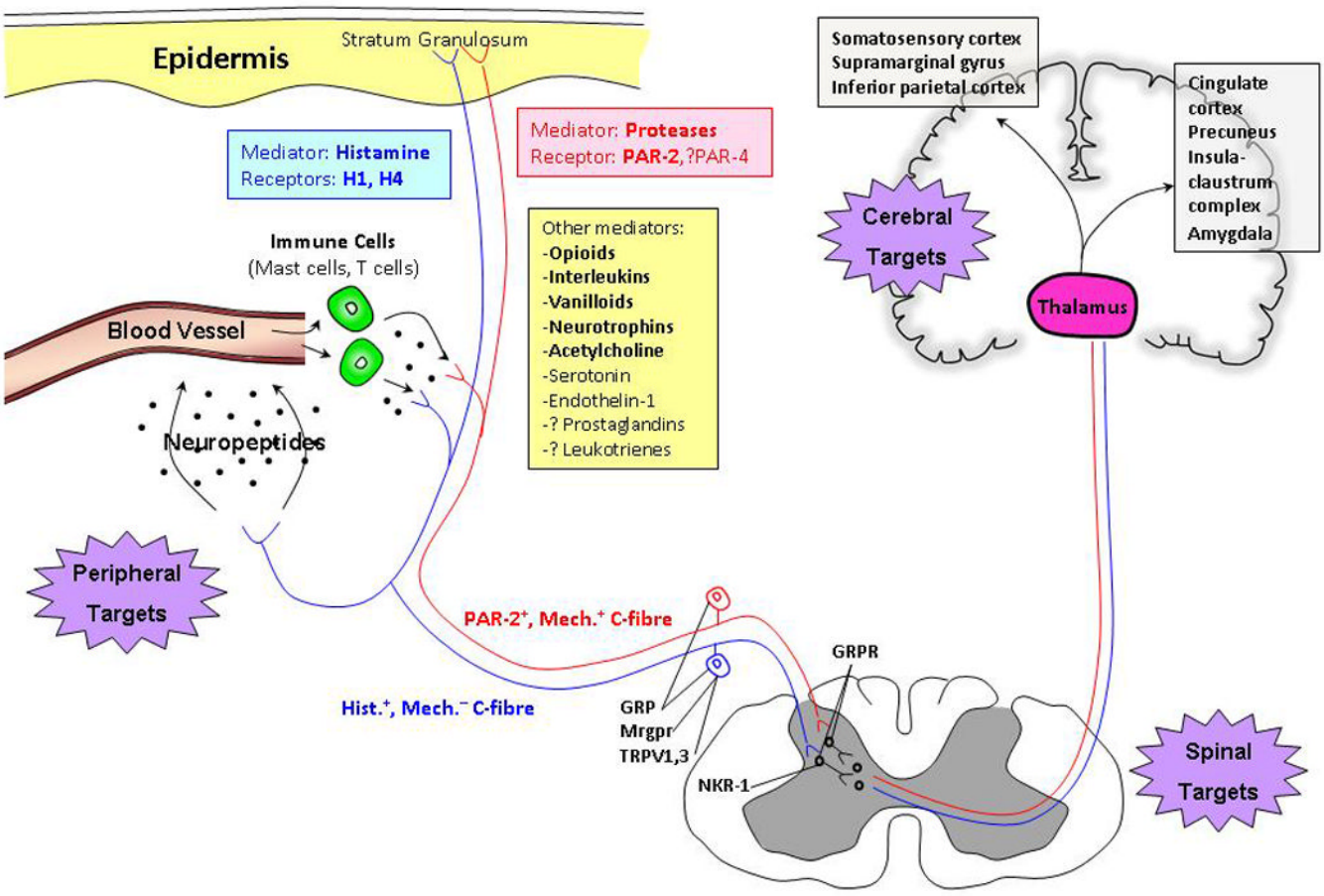

Fig. 1.

Current understanding of the pathological mechanisms of itch and the potential targets for itch therapeutics in the periphery, spinal cord, and brain. Histamine-induced itch is transmitted via histamine-sensitive and mechanical-insensitive C-fibres and protease-induced itch is transmitted via PAR-2 and mechanical positive C-fibres. Free nerve endings reach the stratum granulosum. Neurogenic inflammation is mediated by the axonal reflex, releasing neuropeptides (substance P in particular) which cause vasodilation and further inflammatory changes. *PAR*, proteinase-activated receptor; *Mech.*, Mechanical; *Hist.*, Histamine; *GRP*, gastrin-releasing peptide; *GRPR*, gastrin-releasing peptide receptor; *Mrgpr*, Mas-related G-protein-coupled receptor; *NKR-1*, neurokinin receptor-1.

Table I

Emerging and potential targeted anti-pruritic agents.

Site of action	Mechanism of action	Promising drugs / research molecules
Skin and peripheral nerves	H4 histamine receptor antagonism	JNJ-7777120
	Proteinase-activated receptor-2 inhibition	Antibodies: - SAM-11 - P2pal-2135
		Antagonists: - Tetracyclines - FSLLRY - ENMD-106836
	Serine proteases inhibition	Nafamostat mesilateCamostat mesilate
	Cathepsin S inhibition	E-6438
	Interleukin-31 (IL-31) inhibition	IL-31 antibody
	Mu-opioid receptor antagonism	Peripherally active antagonists: - Methylnaltrexone - Alvimopan
	Kappa-opioid receptor agonism	Peripherally active agonists: - Asimadoline - SA14867 - ICI 204,448
	Transient receptor potential vanilloid 1 activation	Transdermal 8% capsaicin (Qutenza) Tacrolimus ointment
	Transient receptor potential vanilloid 3 inhibition	-
	Cannabinoid receptor activation	Fatty acid amide hydrolase inhibitors: - URB597 (KDS-4103) (centrally active) - URB937 (peripherally-restricted)
	Nerve growth factor inhibition	Tanezumab
	Tropomyosin-related kinase A inhibition	K252a AG879
	Acetylcholine inhibition	Botulinum toxin (subcutaneous and topical)
	Mas-related G-protein-coupled receptor antagonism	-
	Lysophosphatidic acid and autotaxin inhibition	-
Periphery and central nervous system	Mu-opioid receptor antagonism	Topical antagonist: - 1% Naltrexone cream
	Kappa-opioid receptor antagonism	Systemic agonists: - Bremazocine - GR 8969649

Site of action	Mechanism of action	Promising drugs / research molecules
		Topical agonist: - Butorphanol (liposomal formulation)
Spinal cord	Substance P inhibition / Neurokinin receptor-1 (NKR-1) antagonism	NKR-1 antagonists: - Aprepitant - Fosaprepitant - Casopitant - Vestipitant - Orvepitant - Ezlopitant - Lanepitant - Dapitant - L-733,060
	Gastrin-related peptide (GRP) inhibition / GRP receptor antagonism	-
Cerebrum	Modulation of itch perception	Esmirtazapine Serotonin–norepinephrine reuptake inhibitors: - Venlafaxine/desvanlafaxine - Duloxetine - Milnacipran/levomilnacipran - Bicifadine NKR-1 antagonists: - Vestipitant - L-733,060

Table 2

Potential new therapies in various pruritic diseases

Pruritic diseases	Targets	Potential new therapies
Atopic dermatitis	Histaminergic pathway	▪ H4 histamine receptor antagonists
	Protease pathway	▪ Serine protease inhibitors ▪ Cysteine protease inhibitors ▪ PAR-2 antagonists and antibodies
	Opioid system	▪ Topical naltrexone ▪ Topical butorphanol ▪ Kappa-receptor agonists (centrally and peripherally acting agents)
	IL-31	▪ IL-31 Antibody
	Cannabinoids	▪ FAAH inhibitors (centrally and peripherally acting agents)
	Neurotrophins	▪ Anti-NGF antibodies ▪ TrkA inhibitors
	Cerebral processes	▪ Esmirtazapine
Pruritus of chronic liver disease	Opioid system	▪ Kappa-receptor agonists (centrally and peripherally acting agents) ▪ Peripherally-acting mu-receptor antagonists
	Pruritogens in blood	▪ LPA and autotaxin inhibitors (in cholestatic liver disease)
Malignancy associated itch (especially cutaneous T cell lymphoma)	Substance P – NKR-1	▪ NKR-1 antagonists
	Cerebral processes	▪ Esmirtazapine
Prurigo nodularis and lichen simplex chronicus	Opioid system	▪ Topical naltrexone ▪ Topical butorphanol ▪ Kappa-receptor agonists (centrally and peripherally acting agents)
	TRPV1	▪ 8% Capsaicin
	IL-31	▪ IL-31 Antibody
	Neurotrophins	▪ Anti-NGF antibodies ▪ TrkA inhibitors
Neuropathic itch	TRPV1	▪ 8% Capsaicin

Pruritic diseases	Targets	Potential new therapies
	Neurotrophins	▪ Anti-NGF antibodies ▪ TrkA inhibitors
	Cerebral processes	▪ SNRIs
Pruritus of the elderly	Protease pathway	▪ Serine protease inhibitors ▪ Cysteine protease inhibitors ▪ PAR-2 antagonists and antibodies
Chronic itch associated with mood disorders	Cerebral processes	▪ Esmirtazapine ▪ SNRIs
	Substance P – NKR-1	▪ NKR-1 antagonists
Morphine-induced itch	Opioid system	▪ Kappa-receptor agonists (centrally and peripherally acting agents) ▪ Peripherally acting mu-receptor antagonists
Chloroquine-induced itch	Opioid system	▪ Kappa-receptor agonists
	Mrgprs	▪ Mrgpr inhibitor
	GRP-GRPR	▪ GRP inhibitor ▪ GRPR antagonist

PAR, protease-activated receptor; *IL*, interleukin; *FAAH*, fatty acid amid hydrolase; *NGF*, nerve-growth factor; *Trk*, tropomyosin-related kinase A; *LPA*, lysophosphatidic acid; *NKR-1*, neurokinin receptor-1; *TRPV1*, transient receptor potential vanilloid 1; *SNRIs*, serotonin-norepinephrine reuptake inhibitors; *Mrgrps*, Mas-related G-protein-coupled receptors; *GRP*, gastrin-releasing peptide; *GRPR*, gastrin-releasing peptide receptor.