The neurobiology of itch

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Abstract | The neurobiology of itch, which is formally known as pruritus, and its interaction with pain have been illustrated by the complexity of specific mediators, itch-related neuronal pathways and the central processing of itch. Scratch-induced pain can abolish itch, and analgesic opioids can generate itch, which indicates an antagonistic interaction. However, recent data suggest that there is a broad overlap between pain- and itch-related peripheral mediators and/or receptors, and there are astonishingly similar mechanisms of neuronal sensitization in the PNS and the CNS. The antagonistic interaction between pain and itch is already exploited in pruritus therapy, and current research concentrates on the identification of common targets for future analgesic and antipruritic therapy.

Central sensitization
Plastic changes in the CNS (adaptive or pathological) that lead to enhanced responses and/or lower thresholds.

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Historically, the sensations of itch and pain have been regarded as closely related; weak activation of nociceptors has been proposed to mediate itch, and stronger activation results in weak pain — the 'intensity theory'[1]. Current data in rodents are still compatible with this idea[2]. However, the identification of primary afferent neurons in humans[3] and spinal projection neurons in cats[4] that respond to histamine application with a similar time course as the itch sensation clearly favours the 'specificity theory', which stipulates that separate sets of neurons mediate pruritus and pain. However, these histamine-sensitive neurons also respond to capsaicin, an algogen (a pain-producing substance), and could therefore be termed 'itch selective' rather than 'itch-specific'[5]. Research into itch has tried to identify specific pruritic mediators and mechanisms as opposed to algesic ones. In contrast to the separated neuronal pathways, the results have revealed that a broad overlap exists between pain and itch processing in terms of mediators, mechanisms and even therapeutic approaches: protease-activated receptor 2 (PAR_2) and members of the transient receptor potential (TRP) family have been implicated as targets for both algesic and pruritic mediators, and sensitization of peripheral nerve endings by nerve growth factor (NGF) is a known pathophysiological mechanism in both chronic itch and pain. There are strikingly similar patterns of central sensitization between allodynia and punctate hyperalgesia for pain, as well as between alloknesis and punctate hyperknesis for pruritus. These similarities are already being translated into similar therapeutic approaches, such as gabapentin treatment or the use of antidepressants against neuropathic pain and chronic itch.

In this review, we first introduce the definition and clinical classification of itch. We then focus on the interaction between itch and pain on a peripheral and central level. These interactions will be specified in terms of the mediators involved and their activity in pain and itch processing. Evolving similarities in the patterns of peripheral and central sensitization, and their therapeutic implications, are also highlighted. This functional approach is followed by a detailed analysis of the role of selected mediator systems, including PARs, TRP channels, opioids and cannabinoids in the modulation of itch, but also pain. Finally, the neuronal basis for the itch sensation is discussed, with a description of histamine-dependent and histamine-independent primary afferent fibres, spinal projection neurons and the central processing of itch. We also discuss results of central imaging experiments that visualize the similarities and differences between itch and pain processing.

For each aspect we not only focus on the particular relevance of mediators and mechanisms for itch, but also emphasize the complex interaction between pruritus and pain processing, including typical antagonistic modulation and unexpected similarities.

Itch: definition and classification

Itch was defined more than 340 years ago by the German physician Samuel Hafenreffer as an "unpleasant sensation that elicits the desire or reflex to scratch". This definition is still valid, but for many reasons we differentiate between acute and chronic pruritus, and it is understood that chronic itch is a complex, unpleasant sensory experience with many similarities to pain. Both sensations are multidimensional with sensory

Allodynia
The perception of a stimulus as painful when previously the same stimulus was reported to be non-painful.

Punctate hyperalgesia
Type of central sensitization for pain in which the pain elicited by punctate mechanical stimuli is more prolonged and stronger than normally experienced.

Alloknesis
Type of central sensitization for itch in which touch triggers the sensation of itch.

Punctate hyperknesis
Type of central sensitization for itch in which the itch evoked by punctate mechanical stimuli is more prolonged and stronger than normally experienced.

discriminative, cognitive, evaluative and motivational components. A mechanism-based definition of itch has been proposed[6] that separates itch that is induced in a healthy nervous system by peripheral (pruriceptive) and central (neurogenic) mechanisms from itch that is caused by diseased neurons (neuropathic). However, the pathophysiology of most clinical itch conditions is unclear, and therefore operational classifications are more appropriate for clinical use. Clinical relevance is obviously highest in chronic itch conditions that last longer than 3 months. In many cases such as dry skin, atopic eczema, psoriasis, urticaria, scabies and other inflammatory skin diseases, chronic itch comprises more complex skin-associated symptoms than are seen in, for example, acute insect bite reactions (TABLE 1). Other types of chronic itch include those that accompany diseases of organs other than the skin, such as chronic renal failure, chronic liver disease and lymphoma, and metabolic conditions such as hyperthyroidism. Neuropathic itch arises from diseases or disorders of the CNS or PNS, such as brain tumours, multiple sclerosis, peripheral neuropathy (for example, postherpetic itch) and nerve compression or irritation (for example, notalgia paresthetica and brachoradial pruritus). Such itches are often neuropathic in character, and the itch sensation could be combined with burning and stinging[7]. Other forms of itch are related to psychological or psychiatric disorders, such as itch that is associated with delusions of parasitosis or related to obsessive-compulsive disorders (for example, neurotic excoriations). Ideally, therapeutic approaches should be chosen according to a mechanism-based classification. However, as opposed to acute histamine-induced itch, specific pruritic mediators and therapeutic targets for most chronic itch conditions cannot be assigned.

Interactions between itch and pain

In addition to the well known antagonistic interaction between pain and itch, surprisingly similar patterns of peripheral and central sensitization have been characterized. Both antagonistic and parallel interactions are used therapeutically to combat itch.

Pain inhibits itch. It is common experience that the itch sensation can be reduced by the painful sensations caused by scratching. The inhibition of itch by painful stimuli has been shown experimentally using different types of stimulus (for example, heat, physical and chemical) to induce pain[8]. Painful electrical stimulation reduced histamine-induced itch for several hours at a distance of up to 10 cm from the stimulated site, which suggests a central mode of action[9]. Recent results suggest that noxious heat stimuli and scratching produce a stronger itch inhibition than noxious cold stimuli[10]. Consistent with these results, itch is suppressed inside the secondary zone of capsaicin-induced mechanical hyperalgesia[11]. Evidence for an antagonistic interaction between pain and itch also comes from a genetic approach: sensitivity in pain tests was inversely correlated to sensitivity in experimental pruritus in mice strains[12]. This finding also has implications for the current search for genes that control pain sensitivity[13], which might involve mechanisms that are relevant for itch modulation.

Itch can be reduced by painful stimuli; analgesia can reduce this inhibition and so enhance itch[14]. This phenomenon is particularly relevant to spinally administered μ-opioid receptor agonists, which induce segmental analgesia that is often combined with segmental pruritus[15]. Given that μ-opioids can induce itch, it is not surprising that μ-opioid receptor antagonists have antipruritic effects in experimental itch studies[16,17], and also in patients with cholestatic itch[18]. It is remarkable that, in some patients with cholestatic itch, the reduction of itch by naloxone is accompanied by the induction of pain[19] and withdrawal-like reactions[20] not seen in healthy controls, which suggests an upregulation of endogenous opioids in patients with cholestatic itch. Whereas the antipruritic potency of μ-opioid receptor antagonists is well established, κ-opioid antagonists enhanced itch in animal experiments[21]. In line with these results, κ-opioid receptor agonists have been shown to have antipruritic effects in animals[22,23], and also in patients with cholestatic itch[24]. However, the underlying mechanism for the antagonistic effects of μ- and κ-opioids on pruritus is unclear. This new therapeutic concept has already been successfully

Table 1 | **Clinical classification of itch**

Clinical classification	Mediators and mechanisms	Diagnosis	Therapy
Itch caused by skin disorders	Histamine, interleukins, prostaglandin and proteases	Inflammatory dermatoses (atopic dermatitis, psoriasis, drug reactions, mites and urticaria) and dry skin	Antihistamines, anti-inflammatory, immuno-modulatory topical and systemic therapy (cyclosporine A, pimecrolimus, tacrolimus and corticosteroids)
Itch caused by systemic disorders	Opiates, interleukins?	Chronic liver disease and chronic renal failure	Naltrexone, κ-opioid receptor agonists and gabapentin
Neuropathic itch	Damage to nerve fibres, neuropeptides (such as substance P) and proteases	Postherpetic pruritus, notalgia paresthetica and brachoradial pruritus, itch post-CVA	Gabapentin, pregabalin and capsaicin
Psychogenic itch	Serotonin, noradrenaline	Delusions of parasitosis, stress and depression	Olanzapine, pimozide and SSRI antidepressants
Overlapping and mixed			Central-acting itch inhibitors and topical anti-inflammatory drugs

CVA, cerebral vascular accident; SSRI, selective serotonin reuptake inhibitor.

tested in patients with chronic itch using a recently developed κ-opioid receptor agonist[25]. Buprenorphine, a substance combining μ-opioid antagonistic and κ-opioid agonistic effects, has recently been found to be effective in the treatment of chronic intractable itch[26].

Peripheral sensitization. In pain research, the sensitization of nociceptive nerve endings has been recognized as a major mechanism for inflammatory pain[27]. Classic inflammatory mediators such as bradykinin, serotonin (5-hydroxytryptamine; 5-HT) and prostaglandins, which are released in a wide range of painful and pruritic inflammatory conditions, have been shown to not only activate 'itch fibres' (pruriceptors)[12] but also acutely sensitize nociceptors[28]. In addition to acute sensitization[29], neurotrophins cause lasting structural changes (sprouting) of nociceptors. The expression of NGF is high in injured and inflamed tissues, and activation of the NGF receptor tyrosine kinase TrkA on nociceptive neurons triggers and potentiates pain signalling by multiple mechanisms[30].

The sprouting of epidermal nerve fibres that is initiated by increased NGF is not only found in combination with localized pain and hyperalgesia, such as vulvar dysesthesia[31], but also in atopic dermatitis[32]. In addition, remarkably increased serum levels of NGF and substance P have been found to correlate with the severity of the disease in atopic dermatitis[33]. The sources of NGF were mainly keratinocytes and mast cells[34]. Increased fibre density and higher local NGF concentrations were also found in patients with pruritic contact dermatitis[35], and increased NGF and TrkA immunoreactivity was detected in prurigo nodularis[36] and also in pruritic lesions of patients with psoriasis[37]. These similarities between localized painful and pruritic lesions might suggest that similar mechanisms of neuronal sprouting and sensitization exist for both pain and pruritus on a peripheral level. Anti-NGF strategies have already been used in animal pain models[38] and in patients with pains[39]. Therapeutic anti-NGF approaches against pruritus have been tested only in animal models of atopic dermatitis[40]. In NC/Nga mice (an atopic dermatitis mouse model), the role of increased epidermal NGF expression in abnormal itch perception has been validated[41].

NGF is known to upregulate neuropeptides, especially substance P and calcitonin-gene-related peptide (CGRP)[42]. Substance P has been found to have an important role in the induction of pain and hyperalgesia in rodents[43], although there is little evidence for the clinical analgesic efficacy of the antagonists of its receptor neurokinin 1 (NK_1)[44]. There is no confirmation that substance P is an acute pruritogen in humans[45], but it might contribute to itch by increasing neuronal sensitization and through its long-term interaction with mast cells[46]. A sensitizing effect on nociceptors has also been found for CGRP in rodents[13,47], but its role in pruritus is unclear[48]. Interestingly, in NC/Nga mice, substance P concentrations are elevated and CGRP levels are reduced compared with that in the controls[49]. Given that sensitivity to pain induced by heat correlates to CGRP concentrations[13], and pain sensitivity negatively correlates to itch sensitivity in animal models[12], it could be speculated that CGRP has a greater role in nociception and substance P has a greater role in itch.

Central sensitization. Noxious input to the spinal cord is known to provoke central sensitization[50], which consists of allodynia and punctate hyperalgesia. Two types of mechanical hyperalgesia can be differentiated. In allodynia, touch that is normally painless in the uninjured surroundings of a trauma can trigger painful sensations — a phenomenon also referred to as touch- or brush-evoked hyperalgesia. Although this sensation is mediated by myelinated mechanoreceptor units, it requires the ongoing activity of primary afferent C-nociceptors[51]. The second type of mechanical hyperalgesia results in slightly painful pin prick stimulation being perceived as more painful in the secondary zone around a focus of inflammation. This type has been called punctate hyperalgesia, and does not require ongoing activity of primary nociceptors for its maintenance. Punctate hyperalgesia can persist for hours after a trauma, usually much longer than touch- or brush-evoked hyperalgesia[52].

A strikingly similar pattern of central sensitization is observed in the itch pathway: touch- or brush-evoked pruritus around an itching site has been termed 'itchy skin'[53,54]. Like allodynia, it requires ongoing activity in primary afferents and is probably elicited by low threshold mechanoreceptors (A-fibres)[54,55]. Also, hyperknesis has been reported after histamine iontophoresis in healthy volunteers[14] (FIG. 1). The existence of central sensitization for itch can greatly improve our understanding of clinical itch. Under the conditions of central sensitization, normally painful stimuli are perceived as itching. This phenomenon has already been described in patients with atopic dermatitis, who perceive normally painful electrical stimuli as itching when the stimuli are applied inside their lesional skin[56]. Furthermore, acetylcholine provokes itch instead of pain in patients with atopic dermatitis[57], indicating that pain-induced inhibition of itch might be compromised in these patients.

The exact mechanisms and roles of central sensitization for itch in specific clinical conditions still need to be explored, whereas the importance of central sensitization in patients with chronic pain is generally accepted. It should be noted that, in addition to the parallels between experimentally induced secondary sensitization phenomena, there is also emerging evidence for corresponding phenomena in patients with chronic pain and chronic itch. It has recently been reported that, in patients with neuropathic pain, histamine iontophoresis resulted in burning pain instead of the pure itch that would be induced by this procedure in healthy volunteers[58,59]. This phenomenon is of special interest as it shows spinal hypersensitivity to C-fibre input in chronic pain. Conversely, normally painful electrical, chemical, mechanical and thermal stimulation is perceived as itching when applied in or close to lesional skin of patients with atopic dermatitis[60], which suggests that there is also spinal hypersensitivity to C-fibre input in chronic itch. Histamine prick tests in non-lesional skin of patients with atopic dermatitis provoked less intense

Iontophoresis
A non-invasive method of propelling high concentrations of a charged substance, normally medication or bioactive-agents, transdermally by repulsive electromotive force using a small electrical charge applied to an iontophoretic chamber containing a similarly charged active agent and its vehicle.

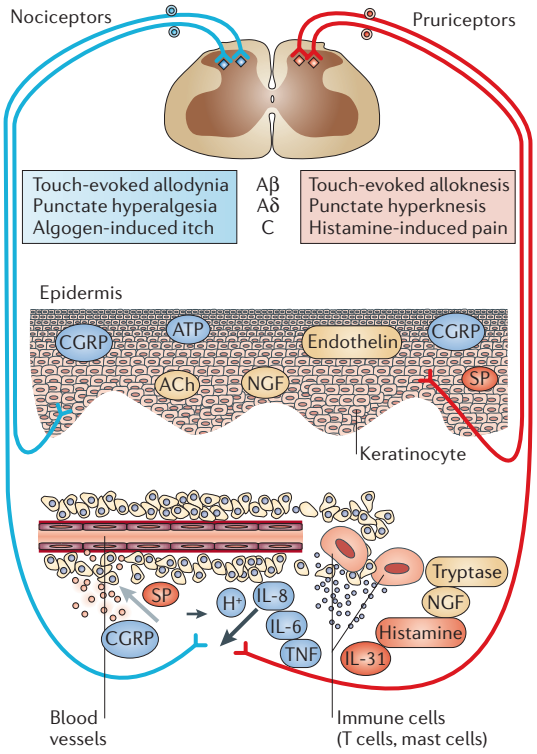

Figure 1 | **Mediators and the sensitization pattern of nociceptive and pruriceptive neurons.** Sensitizing and activating mediators in the skin are shown for primary afferent fibres involved itch (red) and pain processing (blue). Predominantly pruritic mediators are shown in red, algogenic mediators are shown in blue; mediators equally involved in pain and itch are shown in yellow. Note that different classes of fibres subserve pain (mechano-sensitive polymodal nociceptors and mechano-insensitive 'sleeping' nociceptors[200]) and itch (histamine-sensitive mechano-insensitive pruriceptors[3], and probably mechano-sensitive pruriceptors[158]). In the spinal cord, noxious input can induce central sensitization for pain and pruriceptive input can provoke central sensitization for itch. Of note is the corresponding pattern of central sensitization to touch by amyloid-β (Aβ) fibres (allodynia versus alloknesis), by Aδ fibres (punctate hyperalgesia versus punctate hyperknesis) and by C-fibres (histamine-induced pain versus algogen-induced itch). ACh, acetylcholine; CGRP, calcitonin-gene-related protein; H^+, hydrogen ion; IL, interleukin; NGF, nerve growth factor; SP, substance P; TNF, tumour necrosis factor.

itching compared with healthy controls. However, when the stimulus was applied inside their lesions, itch ratings were enhanced and lasted for an extended period of time, whereas the axon-reflex erythema was still smaller compared with the controls[55]. Therefore, in addition to peripheral sensitization, there is evidence for a central sensitization of itch in chronic pruritus.

Neuropathic pain medication for chronic itch. The similar patterns of central sensitization in itch and pain have led to antipruritic therapeutic approaches using drugs that are usually prescribed for neuropathic pain. So far, there have been no controlled studies; however, anecdotal reports show success with carbamazepine, gabapentin and the recently developed pregabalin[61]. Gabapentin and pregabalin inhibit the $\alpha_2\delta$-subunit of voltage-dependent Ca^{2+} channels[62]. Gabapentin has also proved to be effective for the treatment of neuropathic pruritus, particularly in the case of brachioradial pruritus and multiple sclerosis-related itch[63, 64]. Gabapentin seems to alter the sensation of itch, as well as pruritus associated with nerve damage in cutaneous and systemic diseases[65].

Antidepressants have been shown to reduce pruritus associated with some psychiatric diseases[66]. However, in a placebo-controlled trial, paroxetine also reduced itch in patients who did not have a psychiatric disorder[67]. Although selective serotonin reuptake inhibitors (SSRIs) are not commonly used against itch, third generation antidepressants might be more effective antipruritics. Mirtazapine is an antagonist of central presynaptic α_2-adrenergic inhibitory autoreceptors and heteroreceptors, and a potent antagonist of the 5-HT_2 and 5-HT_3 receptors, and of the histamine 1 (H_1) receptor[68]. It has been shown to be effective when used to treat pruritus associated with malignant cholestasis, lymphoma and uraemia, as well as itch related to inflammatory skin diseases that are resistant to high doses of sedating antihistamines[69,70]. It is interesting to note that a similar pattern of analgesic activity was found in animal experiments: amtryptiline and mirtazapine reduced mechanical hyperalgesia in a rat chronic constriction model, whereas the SSRI citalopram was ineffective[71]. The parallel occurrence of neuropathic pain and neuropathic postherpetic itch[72] provides further evidence for an intimate link between these two phenomena, although clinical data on the therapeutic implications are still rare.

Modulators for itch and pain

Instead of having a clear set of separate specific mediators for pain and itch, most receptor systems have a prominent role in both. This also includes the interaction between the keratinocytes and nerve endings that modulate pain and itch.

Histamine. Histamine is the best-known pruritogen and has been regarded as a main target for antipruritic therapies. Among histamine receptors, H_1 receptors have been presumed to be important in histamine-induced reactions. Indeed, histamine-induced itch, wheal and axon-reflex flare in human skin are almost completely suppressed by inhibitors of H_1 receptors, although local erythema remains[73]. However, inhibitors of H_1 receptors are successfully applied to only a few pruritic diseases (for example, certain subtypes of urticaria), and they are ineffective in many other diseases, such as atopic dermatitis[74]. Other histamine receptors such as H_4 receptors could have an independent role in pruritus, as has been shown for histamine-induced itch in mice[75]. However, as the species differences are large, the role of H_4 receptors in human pruritic diseases remains to be elucidated.

Interleukins. The crosstalk between immune cells and neurons has been in the focus of pain research during recent years[76]. However, until recently, no specific candidate could explain neuronal sensitization for itch.

Supernatants of mitogen-stimulated leukocytes, which were pruritic in patients with atopic dermatitis but not in controls, contained larger amounts of interleukin 2 (IL-2) and IL-6 (REF. 77). However, no correlation between IL-6-like content and itch intensity was found in atopic dermatitis[78]. IL-6 and IL-6 receptors are expressed in nerve and Schwann cells[79], and IL-6-like immunoreactivity was increased in nerve fibres of patients with positive epicutaneous patch tests and prurigo nodularis. This might indicate that IL-6 has a role in the pathophysiology of some types of itch. However, the discovery that IL-31 induces pruritic dermatitis in mice[47,80] has finally provided a candidate for itch-specific sensitization. Expression and protein content of IL-31 are increased in an atopic mouse model[81] and correlates to itch behaviour[82]. Moreover, this increase was already verified in patients with atopic dermatitis[83]. These results suggest a special role for IL-31 in pruritus. However, studies in pain models are still lacking and therefore a similar sensitizing role in pain induction cannot be ruled out.

Protease-activated receptors. The hypothesis that proteases are involved in pain and pruritic pathways is rather old[84]. Exogenous agents (for example, microbes or plants), as well as several inflammatory cells, can induce the production of sufficient amounts of proteases, which in turn activate protease-activated receptors (PARs). The expression and function of PARs vary among tissues and neuronal cells. PAR_2 has a role in the regulation of vascular tone, various pro- and anti-inflammatory effects, and is pronociceptive in models of somatic and visceral pain[85–87]. PAR_1 has been implicated in haemostasis and platelet signalling, has pro-inflammatory effects and can induce analgesia from either peripheral or spinal activation[88,89]. PAR_1 and PAR_2 are functional in primary afferent neurons and modulate nociception[90]. PAR_2 elicits hyperalgesia to both thermal and mechanical stimuli through an NK_1-receptor-dependent mechanism[85,87]. By contrast, PAR_1 mediates an analgesic response to both mechanical and thermal stimuli under normal and inflammatory conditions[88] — probably by modulating ascending nociceptive transmission in a fashion similar to that of opioid receptors — which results in analgesia.

The cloning of PARs, especially PAR_2, has shed new light on proteases as signalling molecules in nociception. Functional PAR_2 is mainly expressed in small-diameter sensory neurons and induces neurogenic inflammation[90], and dermal PAR_2 stimulation induces c-Fos expression in the superficial laminae of the dorsal horn[91]. PAR_2 is ultimately involved in inflammatory somatic[85] and visceral[87] hyperalgesia, thereby probably contributing to acute and chronic pain conditions[89]. With respect to pruritus, several proteases are upregulated during inflammation and can produce itching (for a review, see REF. 92). In humans, PAR_2 is upregulated in itchy dermatoses, and PAR_2 agonists induce pruritus in these patients. It is of note that concentrations of tryptase are enhanced in patients with atopic dermatitis, whereas histamine concentrations are unchanged, which suggests that PAR_2 — which is similar to histamine receptors — is a receptor for 'itchy' proteases in atopic dermatitis[93]. For PAR_1, both antihyperalgesic activity in peripheral inflammatory pain models[88] and hyperalgesic effects in neuropathic pain models[94] have been shown. A question that remains unanswered is that of the role of PAR_4, a receptor for leukocyte-derived cathepsin G, in inflammatory nociception[95]. So, proteases and PARs can directly activate both the itch and the pain pathway, and further *in vitro* and *in vivo* studies are required to finally determine their clinical role in nociception and pruritus.

Transient receptor potential receptors. TRP receptors that sense 'hot' and 'cold' represent another receptor family involved in itch and pain. The first and best-known is the capsaicin receptor TRP vanilloid receptor 1 (TRPV1). TRPV1 expression in humans has been described on primary afferent neurons, keratinocytes, dendritic cells and mast cells, although so far its functionality has not been verified in all cells[96–98]. Certain itch and pain mediators — such as capsaicin or eicosanoids, histamine, ATP and various neurotrophins[73,99–102] — activate or sensitize the non-selective, calcium-permeable TRPV1 (REFS 99,103–105). TRPV1 activation is related to action potential generation and neuropeptide release[105], but prolonged calcium influx can also desensitize the primary afferents[106]. Interestingly, TRPV1 acts synergistically with PAR_2 and the substance P receptor NK_1R, which might have implications for the sensitization to itch and pain. Moreover, TRPV1 can activate the release of cytokines, which are involved in pruritus[107,108].

Topical application of TRPV1 agonists has been proposed for pruritic lesions, but also for painful skin; for example, in postherpetic neuralgia[109]. On chronic stimulation, TRPV1 desensitizes in a Ca^{2+}-dependent manner and leaves the nociceptive and pruriceptive neurons inactive. Moreover, neuropeptides such as substance P are depleted from the sensory nerve fibres; the axonal transport of both neuropeptides and NGF in the periphery is slower. Clinically, the first days of the therapy are accompanied by a burning sensation and neurogenic inflammation, followed by a lasting depression of pain and itch. Also, other members of the TRP family that are activated in warm (TRPV2, TRPV3 and TRPV4) or cold (TRPM8 and TRPA1) temperature ranges might be involved in modulation of pruritus[110] (TABLE 2; FIG. 2). In particular, activation of neuronal 'cold receptors'[111,112] might be beneficial for the treatment of pruritus, as there is evidence for antipruritic effects of cold. TRPM8 can be activated by cold (that is, 8–28 °C) or by menthol and icilin[113] (for a review, see REF. 110), which might therefore be used therapeutically for cold-mediated suppression of itch[114]. TRPA1 is co-expressed with TRPV1 in rat dorsal root ganglion neurons[115] and can be activated by noxious cold (≤17 °C). It is responsive to mustard oil, cinnamon oils and raw garlic, and can be sensitized by camphor, endocannabinoids and bradykinin[112,116]. However, no direct link to the pruritus pathway has been described.

Recent findings have revealed that TRPV ion channels not only contribute to the thermal activation of sensory neurons, but are also thermosensory receptors for epithelial cells[117]. The important question of whether — and if so, how — TRPV1-activated keratinocytes communicate

Table 2 | **Involvement of some neuromediators in pruritus and pain**

Neuromediator	Receptor	Source	Role in itch	Role in pain
NGF	TrkA	Keratinocytes, mast cells, fibroblasts and eosinophils	Peripheral sensitization in atopic dermatitis[33,34,41]; Anti-NGF is antipruritic[40]	Peripheral and central sensitization[30,201]; Upregulation of TRPV1 (REF. 30); Upregulation of substance P and CGRP[42]; Anti-NGF analgesic[38,39]
Interleukin 31	gp130-like receptor	T-cells and macrophages	Pruritic in the skin[47,80]. Increased expression in atopic dermatitis[83]	Not clear
Opioids	μ-, κ-, δ-opioid receptors (partly receptor-independent T-cell activation)	Neurons and keratinocytes	Antipruritic in the skin (?). At the spinal level, μ-opioids are pruritic[15], κ-opioids are antipruritic[23,25]	Analgesic in the skin, and at the spinal and supraspinal level[15,123]
Endocannabinoids	Cannabinoid receptors	Neurons and keratinocytes	Antipruritic in the skin[145]	Analgesic in the skin[142,144,150], and at the spinal and supraspinal level[202]
Endothelins	Endothelin receptors (ET-A and ET-B)	Endothelium and mast cells	Direct pruritic (burning itch)[203]	Direct algogenic through ET-A Analgesic through ET-B[204]
Kallikreins, proteases	Partly by protease-activated receptors (PARs) and tryptic enzymes	Leukocytes, keratinocytes, mast cells, endothelial cells and platelets	Pruritic through PAR_2 (REFS 93,110,205)	Neurogenic inflammation through PAR_2 (REF. 90); Thermal and mechanical hyperalgesia through PAR_2; Analgesic effects of PAR_1; Thrombin enhances mechanical analgesia and stimulates heat hyperalgesia[85–87,89]
Substance P	Neurokinin 1 receptor	Sensory nerve fibres	Priming of mast cells[46] Pruritic in rodents only[45,206]	Increase of mast cell TNFα Central sensitization[43]
CGRP	CGRP receptors	Sensory nerve fibres	Not clear	Sensitization of primary afferents to heat[12,13,47]

CGRP, calcitonin-gene-related peptide; NGF, nerve growth factor; TNFα, tumour necrosis factor-α; TrkA, tyrosine receptor kinase A;TRPV1, transient receptor potential vanilloid receptor 1.

with sensory nerves is currently unanswered. Potential signalling molecule candidates are endothelin, ATP and endorphins[117] (FIG. 1; TABLE 2). Human epidermal and hair follicle keratinocytes express functional TRPV1 (REF. 98), and its stimulation leads to the release of prostaglandin E_2 (PGE_2) and IL-8, which suggests that TRPV1 is involved in skin inflammation following thermal injury[107]. It is also assumed that TRPV1 modulates keratinocyte proliferation, differentiation and apoptosis[98]. Camphor, which induces a warm sensation on topical application[118] and acts as an antipruritic agent, activates TRPV3 (REF. 119), but also TRPV1 (REF. 120). Together with TRPV4, TRPV3 is expressed on keratinocytes and mediates warm-induced currents[121,122]. Therefore, keratinocytes have the potential to participate in temperature transduction; however, their significance in this process still needs to be assessed.

Opioids and cannabinoids. Opioids are potent neurotransmitters, hormones and immunomodulators[123] and can be divided into three classes: endorphins, dynorphins and enkephalins. They exert their effects through the activation of μ-, κ-, and δ-opioid receptors, which are widely distributed in the CNS and PNS[124,125]. In the periphery, opioid receptor mRNA is associated with up to 90% of substance P-containing dorsal root ganglion cells, which indicates a role in nociception, as well as neurogenic inflammation[126]. Activation of opioid receptors reduces neuronal excitability through the inhibition of voltage-dependent Ca^{2+} channels and adenyl cyclase, and activation of K^+ channels[127]. Regarding the primary afferent neurons in the skin, this reduced excitability by the activation of opioid receptors would lead to an inhibition of pain and itch[123].

The psychotropic, but also analgesic, effects of cannabinoids have been recognized for centuries. They bind to two G-protein-coupled receptors, the cannabinoid receptors CB_1 and CB_2 (REFS 128–130). CB_1 receptors are mainly localized in the CNS, but they are also expressed in primary afferent neurons[131–134]. CB_2 receptors are predominantly found in the periphery; for example, on T lymphocytes and mast cells[135,136], but also on rat spinal cord and human sensory nerve fibres[137]. Endogenous cannabinoids belong to a group of fatty acid amines, the *N*-acetylethanolamines (NAEs), with *N*-arachidonoylethanolamine (anandamide) and *N*-palmitoylethanolamine (PEA, palmidrol, *N*-(2-hydroxyethyl) hexadecanamide) being the most abundant[138,139]. Biochemical evidence indicates that endogenous NAEs are produced and released by animal and human neurons[139], and by human epidermal keratinocytes[140,141]. On local application, cannabinoids have analgesic and antipruritic effects in acute pain and itch models[142–145]; moreover, there is growing evidence for the suppression of itch by topical cannabinoid receptor agonists under clinical conditions. Direct activation of CB_1 and CB_2 (but also activity at TRPV1), a new cannabinoid-receptor 'CB_2-like receptor'[146] and non-receptor-mediated effects are discussed as possible itch-suppressing mechanisms.

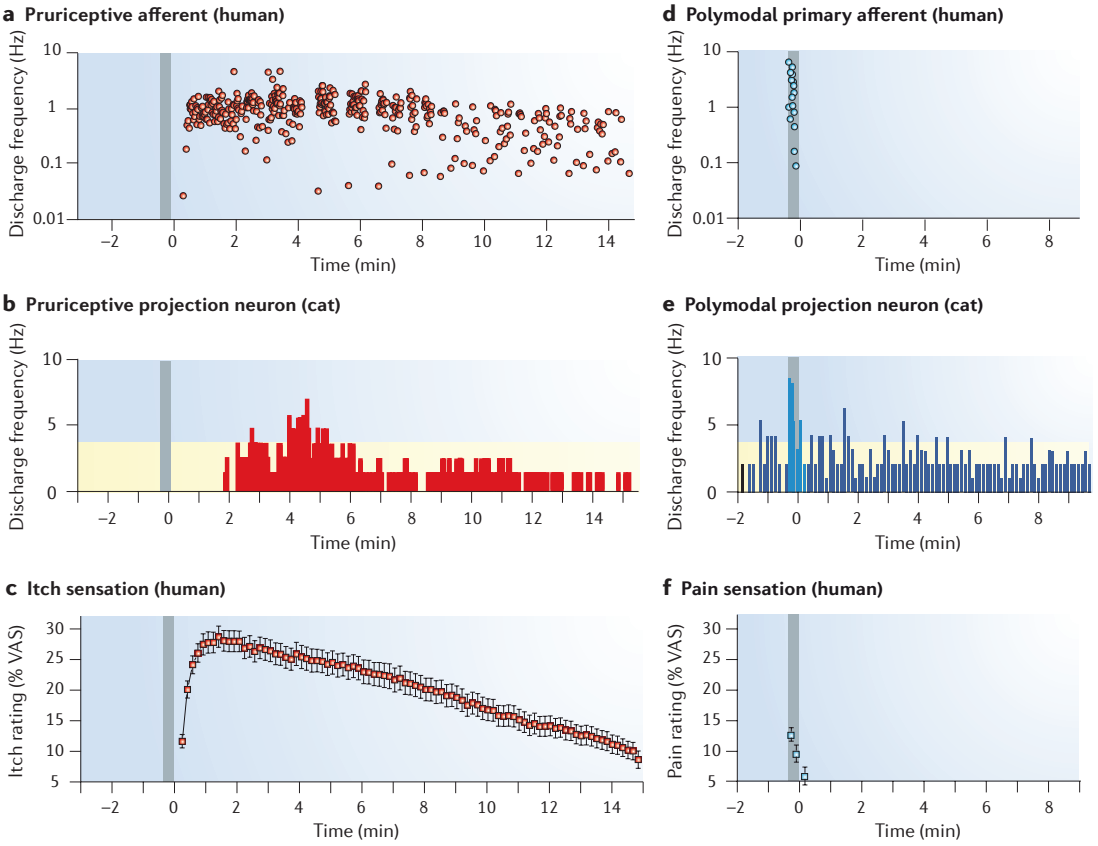

Figure 2 | **Activation patterns of primary afferent fibres and spinal projection neurons in response to itch or pain sensation evoked by iontophoresis of histamine.** Electrophysiological recordings of discharge frequency were carried out after application of histamine by iontophoresis at 20 milli Coulombs (the duration is indicated by the grey bar in all panels). The response pattern of a mechano-insensitive pruriceptive primary afferent fibre (**a**) matches the time course of activity in spinal pruriceptive projection neurons (**b**) and the time course of itch sensation reported by the participants (**c**), implicating a role in itch perception. By contrast, a primary afferent mechano-responsive polymodal nociceptor responds to the identical stimulus only during the iontophoretic current (**d**). The spinal polymodal projection neuron exhibits spontaneous activity before the application of the current (dark blue), but increases firing rate during activation by the iontophoretic current (light blue) (**e**). | The transient increase in firing rate correlates to the short lasting pain sensation evoked by this stimulus (**f**). There is an absence of spontaneous activity in the itch processing spinal projection neurons compared with the spontaneously active nociceptive neurons (shown as a yellow band). Ratings on a Visual Analogue Scale (VAS) with the end points 'no itch' – 'unbearable itch' or 'no pain' – 'unbearable pain'. Bars in panels **d** and **f** indicate standard error of means (data modified from REFS 5,23). Panels **a** and **c** modified, with permission, from REF. 3 © (1997) Society for Neuroscience. Panels **b** and **e** modified, with permission, from REF. 4 © (2001) Macmillan Publishers Ltd.

The cannabinoid and opioid systems share neuroanatomical, neurochemical and pharmacological features. There is growing evidence for a crosstalk between the endogenous cannabinoid and opioid systems, including induction of the release of opioid peptides by cannabinoids, or endocannabinoids by opioids[147–149]. Although this connection was first shown in the CNS, recent data suggest that the receptors and agonists interact on the cutaneous level. Neuronal- or immune cell-derived cannabinoids can stimulate the release of β-endorphin from keratinocytes through CB_2 activation, thereby allowing a combination of inhibitory cannabinoids and opioids to modulate the excitability of local nociceptive nerve endings[150]. It is of note that the nociceptive effects can be blocked by antibodies to β-endorphin, or in μ-opioid receptor-deficient mice[150]. These data clearly indicate a crucial role of keratinocyte-derived opioids in nociception.

Neuronal pathways for itch

The selective histamine-sensitive neuronal pathway can be correlated with histamine-induced itch, which supports the specificity theory of itch. However, additional histamine-independent itch pathways are crucially required to explain key aspects of clinical itch conditions.

Pruriceptive primary afferents. The primary afferent neurons responsible for histamine-induced itch in humans belong to the group of unmyelinated C-fibres, because they still conduct when myelinated fibres are blocked by a differential nerve compression block[151]. Among human C-nociceptors, two major classes have been identified — mechano-responsive (polymodal) nociceptors and mechano-insensitive (silent) nociceptors[152,153]. Data from studies in humans suggest that the mechano-insensitive class has a key role in the generation

of the axon-reflex erythema and in mechanical sensitization[154]. Histamine-sensitive C-fibres that respond in parallel to the itch sensation have been identified in the class of mechano-insensitive C-fibres in healthy volunteers[3] and in patients with itch[155] (FIG. 2). By contrast, the most common polymodal nociceptors only show spurious histamine responses and are related to pain processing[15,156]. The histamine-sensitive pruriceptors have large innervation territories in the skin of the foot and lower leg (with a maximum diameter of roughly 10 cm)[3], which fit to the poor two point-discrimination for histamine-induced itch[157].

New itch fibres. It is obvious that histamine-dependent itch, although of major importance as an experimental itch model, does not have the same role in clinical itch conditions. Mechanically induced itch or itch without accompanying flare reaction, which are both commonly observed clinically, cannot be explained by histamine-sensitive pruriceptors. Indeed, there is growing evidence for the existence of histamine-independent types of itch fibres, which could explain itch without accompanying axon-reflex erythma[158]. Itch can be generated without flare reaction by the cowhage spicules containing the protease mucunain[159], and also by papain[160]. Activation of mechano-sensitive C-fibres by cowhage has already been reported[161,162]. It can therefore be expected that pruriceptive nerve fibres also have different classes, similar to the C-nociceptors that can be differentiated in mechano-sensitive and mechano-insensitive units (FIG. 1). Different classes of pruriceptors could also account for the various submodalities of pruritus reported by patients[163,164], which are well known in the field of pain research[165].

Spinal projection neurons. Histamine-sensitive neurons have also been studied by recording dorsal horn neurons in the cat, and represent a small fraction (about 5%) of spinothalamic projection neurons in the cat[4]. These neurons are similar to the primary afferent fibres in that they are mechanically insensitive and respond to histamine with a typical prolonged activation[4]. Therefore, there is a distinct neuronal pathway for the processing of histamine-induced itch consisting of specialized primary afferent and spinal projection neurons. There is still an open question regarding the specificity of pruriceptors, because their responses to capsaicin or mustard oil do not support the theory of specificity for pruritus, and instead support the selectivity theory[5]. However, as capsaicin can also provoke itch on topical application[166] it is unclear whether the lack of specificity is to be attributed to capsaicin or to the pruriceptors. It might take some time to resolve this issue because of the elaborate techniques required to identify pruriceptive fibres and their low prevalence[4,167].

In contrast to spinothalamic projection neurons involved in pain processing, the pruriceptive projection neurons do not exhibit spontaneous activity (FIG. 2). It has been speculated that pain processing spinal neurons exert tonic inhibition to silence the pruriceptive neurons[168]. Thereby itch could be generated by downregulating the pain-induced inhibition of pruritic neurons in the spinal cord in the absence of activity in primary afferent pruriceptive neurons. The itch-selective spinal neurons form a distinct pathway projecting from lamina I of the spinal cord to the ventrocaudal part of the nucleus medialis dorsalis (MDvc); the MDvc has projections to the anterior cingulate and dorsal insular cortex[4,169].

Central processing. Itch and pain are complex sensations consisting of sensory discriminative, affective and motivational components. Brain imaging studies in the early 1990s have significantly widened our knowledge and understanding of the complexity of pain presentation in the brain, trying to correlate different aspects of the pain sensation to particular brain areas[170]. It is generally accepted that spatial, temporal and intensity aspects of pain perception are processed in the primary and secondary somatosensory cortex (S1 and S2, respectively), whereas the anterior cingulate cortex (ACC) and insular cortex are involved in the affective-motivational component[171,172]. Somatotopic representation of pain is reported for the S1[173], but might be much clearer in the dorsal posterior insula[174]. This would confirm a different central projection pathway for pain primary projections to the dorsal posterior insula as part of a basic interoceptive cortex with homeostatic function[175]. Moreover, the thalamus, prefrontal cortex, premotor areas[176,177] and cerebellum are most commonly activated by painful stimulation[178].

Some central imaging studies on itch have been carried out using positron emission tomography (PET) and functional MRI (fMRI). An early PET study[179] found significant activation in the prefrontal cortex, premotor areas and ACC in response to itch. More recent studies[180,181] using histamine pricks or injections showed similar activation of the premotor area, as well as the prefrontal area and S1. Also, with the less noxious iontophoresis of histamine, a similar dose-related activation pattern was induced in the ACC, premotor cortex and the posterior parietal cortex[182].

fMRI studies have provided further information on itch processing in the brain with improved temporal and spatial resolution[183,184]. In these studies, as above, the premotor areas, prefrontal cortex, ACC and cerebellum were activated. When comparing the brain areas involved in itch and pain processing (FIG. 3), a large overlap between the two sensations was identified, with no obvious itch-specific activation pattern. Differences mainly relate to the lack of S2 activation and the predominant activation of ipsilateral motor areas in pruritus. The activation of ipsilateral motor areas can be correlated to the planning of the scratch response directed to the stimulated limb, as opposed to the pain response in which contralateral motor activation is required to withdraw the stimulated limb.

However, this comparison is based on only a few studies and is to be regarded as preliminary. Some of the differences might also relate to variant experimental protocols involving either the prolonged time course of histamine-induced itch or acute pain responses

Positron emission tomography
(PET). *In vivo* imaging technique used for diagnostic examination that involves the acquisition of physiological images based on the detection of positrons, which are emitted from a radioactive substance previously administered to the patient.

Functional MRI
(fMRI). Technique that allows the spatial investigation of central neuronal activation by the measurement of the secondary increase of perfusion following neuronal activity.

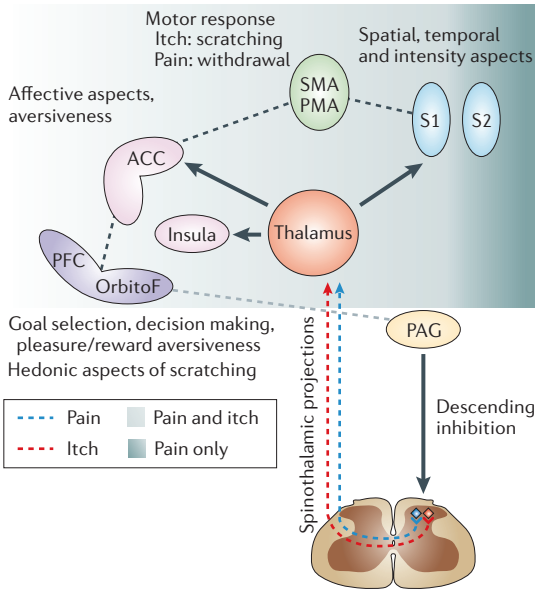

Figure 3 | **Activated brain areas in pain and itch as assessed by central imaging.** Areas activated by both algogenic and pruritic stimuli (light grey) include the thalamus, insular cortex (insula), anterior cingulated cortex (ACC), prefrontal cortex (PFC), orbitofrontal cortex (OrbitoF), supplementary motor area (SMA), premotor area (PMA), cerebellum and primary somatosensory cortex (S1). The effects of the activation of the particular areas common to pain and itch are indicated by black arrows. Differential responses (red, itch; blue, pain) are found mainly for the motor response and the lack of activation of the secondary somatosensory cortex (S2; dark grey). Activation of prefrontal areas and the orbitofrontal cortex can be associated with hedonic aspects of scratching. Activation of the periaqueductal grey (PAG) area is involved in the modulation of itch and pain.

following short-lasting mechanical or heat stimuli. Short-lasting itch responses evoked by electrical stimulation have recently been compared with electrically induced pain sensation in an fMRI setting. This study could not identify a specific itch-related activation site after subtracting the pain response[185]. A reduction of itch ratings after the painful stimulus was also evident in this study, but could not be correlated with a specific brain area. The first results of itch inhibition by painful cold stimuli, examined by functional PET (fPET), revealed activation of the periaqueductal grey when painful and itching stimuli were applied simultaneously[182]. This activation was combined with reduced activity in the ACC, dorsolateral prefrontal cortex and parietal cortex, suggesting that the periaqueductal grey, which is known for its role in endogenous pain inhibition, might also be involved in the central inhibition of itch by pain (FIG. 3). Scratching is an alternative and more common way to reduce itch[10]. In ongoing studies using fMRI in healthy control participants, it has been shown that repetitive scratching significantly inhibits itch-related brain activity in the ACC as induced by histamine (R. C. Coghill and G.Y., unpublished observations).

Hedonic sensations associated with scratching

Pain and itch can be easily separated, according to not only the sensation they evoke but also the reverse reflex pattern: whereas the withdrawal reflex triggered by pain leads to retraction, and therefore protection, of the endangered part of the body, the scratching reflex induced by itch aims to localize the affected skin site and draws attention to it. Obviously, withdrawal would be inadequate against a stimulus that has already invaded the skin[186]. In this situation, close inspection and scratching is a more promising way to, for example, remove insects from the skin. Independent of the teleological purpose of scratching, it should be noted that the scratching represents a potentially damaging noxious stimulus. Traditionally, reduction of the tormenting itch has been regarded as main reward of scratching, which the body receives in return for this self-inflicted noxious behaviour. However, this ignores the hedonic aspects of scratching an itch, which are well known in clinical experience[187] but have raised only a little scientific interest. The hedonic aspects would therefore 'compensate' the individual for the potentially noxious scratching, which in turn might be required to remove parasites from the skin.

As referred to by the definition of itch sensation, itch is accompanied by the desire to scratch, which in turn reduces the itch. In addition, a hedonic experience (algedonic pleasure[188]) can accompany the scratching of an itch: "At least it may be noted that scratching an itch with a violence that would cause pain elsewhere may be experienced as one of the most exquisite pleasures"[189]. The hedonic aspect of scratching can be problematic in chronic itch: patients with atopic dermatitis may report that they scratch until it no longer provokes pleasant sensations rather than until the itch has subsided[190]. However, albeit being a key factor in the vicious itch/scratch cycle, this clinically important aspect has gained only little scientific attention[187,191]. Itch-related activation of the prefrontal and orbitofrontal cortices[183,184] might provide some objective background to this topic. Rather than just indicating the motivational aspects of the itch sensation, including reward systems and decision making, these frontal brain areas are also involved in the hedonic experience[192]; their activation might therefore contribute to the compulsive component of itch and scratching. Should the hedonic experience be based on the release of endogenous opioids, as might be suggested from results in pain modulation[193], the antipruritic therapeutic approach with naloxone would have an additional central target.

'Contagious' itch. We regularly see cognitive factors in relation to scratching in the numerous anecdotal stories of physicians experiencing itch immediately after treating patients with scabies. In addition, events of 'contagious scratching' are common occurrences, and even discussion on the topic of itch can lead to a desire to scratch. Clearly, itch is more than a localized phenomenon in the region where we scratch. Results from a recent study[194] showed that itch and scratching were induced purely by visual stimuli in a public lecture on itching. It has previously been reported that 25% of the population

are conscious that scratching an itchy area can produce the sensation of itch elsewhere — the so-called 'referred itch'[195]. Infectious scratching has also been observed in monkeys[196], but the underlying mechanism is not clear. A possible neural substrate is 'mirror neurons'[197], which are active on executing a certain motor action, but also on viewing others performing the same action. They have been implicated in imitation and learning[198]. No data on central activation for contagious itching are available, but for a similar phenomenon, contagious yawning, a classical imitation pattern with activation of the human mirror neuron system has been proposed but not verified[199].

Conclusions and future perspectives

Itch and pain are different sensations that are processed by distinct sets of neurons. Histamine-sensitive pruriceptors have been characterized that can explain acute histamine-induced itch. However, they cannot account entirely for the clinically more relevant histamine-independent types of chronic itch. Therefore, additional classes of pruriceptors will have to be characterized.

Complex interactions exist between pain and itch, with itch inhibition by painful stimuli such as scratching being used in everyday life to combat itch. Another example of the antagonistic interaction is itch induced by analgesic opioids. More than just being a side effect of opioid therapy, this antagonistic interaction is therapeutically exploited by μ-opioid receptor antagonists acting as antipruritics under central itch conditions. In addition to the antagonistic interaction, there is a broad overlap between relevant mediator systems in pain and itch, including NGF, TRPV1 and PARs. Peripheral mechanisms of itch and pain are so closely related that even similar therapeutic strategies are being exploited, for example, anti-NGF.

Parallels between pain and itch processing are even more evident in the pattern of central sensitization. Touch- and pin prick-induced pain (allodynia and punctate hyperalgesia) correlate to touch- and pin prick-induced itch (alloknesis and punctate hyperknesis). The similarities of these symptoms have led researchers to successfully apply validated therapeutic approaches from the pain field — such as gabapentin for neuropathic pain — in itch therapy. Moreover, the knowledge about similar mechanisms of sensitization could also spark the interest of pain researchers in chronic pruritic diseases to study neuronal sensitization mechanisms. It remains to be established whether central processes leading to memory formation in chronic pain are also of clinical relevance for chronic itch.

Central imaging techniques like PET and fMRI have identified the pattern of central activation that correlates to acute itch. Central areas involved in itch processing include the dorsal posterior insula, ACC and PFC, thalamus and premotor areas. So, there is considerable similarity to areas involved in pain processing. More pronounced ipsilateral activation of motor areas in itch might relate to the planning of the scratch response, whereas so far the background for the lack of activation of the S2 in itch is not clear. Clinically important, itch not only has aversive dimensions but also has a hedonic component, which might be a major drive for compulsive scratching. Teleologically, this aspect is of considerable interest, as the reward of scratching could compensate the organism for its potentially damaging effects.

New candidates for itch-specific mediator systems have emerged and will be tested for clinical significance in humans. Although data on histamine H_4 receptors are currently restricted to mice, data on IL-31 are much broader and are highly promising. The interaction between inflammatory cells and neurons has gained major attention for peripheral, but also central, sensitization mechanisms. Recent work has highlighted the role of keratinocyte–neuron interactions in the generation of itch. In this interaction, keratinocytes can be the source and recipient of various sensitizing mediators, and might even be involved in the transduction process through their TRP receptors. Classical inflammatory signs (swelling, redness and warmth) can fail to appear after the release of keratinocyte-derived inflammatory mediators, because of the special environment in the vessel-free epidermis. Instead, disturbed barrier function, dry skin and itch can result. Therefore, the study of keratinocyte–neuron interactions is of considerable interest for further investigation of pruritic mechanisms in the skin. Central imaging techniques and experimental protocols for the study of itch have been developed. In the future, patient-based research in fMRI settings and interaction studies between itch and pain will further clarify the brain mechanisms of chronic itch and its inhibition. Finally, enormous progress has been achieved in the development of clinically relevant animal models for itch. Although no animal model exists so far for systemic itch (for example, hepatic or renal itch), the acute chemical stimulation models have been further refined. Now animal models for atopic dermatitis and dry skin are available, which will facilitate translational aspects to humans.

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Competing interests statement
The authors declare no competing financial interests.

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