Recent advances in pruritus – what we have learned and where are we headed
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Abstract
Chronic pruritus is an emerging health problem with a significant impact on quality of life. Recent advances in our understanding of newly discovered pathways and receptors for itch have been made. It is hoped that recent advancements will also drive the development of novel therapies for this often-neglected and bothersome symptom.

Introduction and context
Pruritus is a common symptom that has multifactorial etiologies that range from skin to neural and systemic diseases, and its pathophysiology has been, until recently, poorly understood. Epidemiological studies have shown that it is common in 8-12% of the general population [1]. Chronic pruritus has a profound impact on quality of life by disturbing sleep and affecting attention. A large study has shown that hemodialysis patients who itch have a higher mortality risk, which is related to their lack of sleep [2].

Recent advances
A specific separate pathway for histamine-induced itch was found more than a decade ago in a subset of C nerve fibers in humans and later in spinal projection neurons of cats [3,4]. In 2007, investigators discovered a separate parallel itch processing pathway activated by cowhage spicules (Mucuna pruriens), which revealed an activation of peripheral nerve fibers in humans as well as specific spinal projection neurons in primates [5-7]. However, these C fiber afferents are not itch-specific since they are also activated by heat stimuli that induce the sensation of pain. Cowhage is also known to induce a burning sensation along with itch. The active ingredient in cowhage has been isolated as a cysteine protease (mucunanin) that activates proteinase-activated receptor 2 (PAR2) and PAR4 [8] in nerve fibers and keratinocytes. PAR2 receptors and their ligands, serine proteases, have previously been demonstrated to have a significant role in the itch associated with atopic eczema [9]. Recently, cathepsin S, an endogenous cysteine protease secreted by keratinocytes, was found to induce itch [10]. This finding suggests that cathepsin S may have a role as an itch mediator in inflammatory skin diseases.

New evidence for a specific pathway for itch was generated by the findings of neurons expressing a gastrin-releasing peptide receptor (GRPR) gene that transmit only itch and not pain [11]. GRPR is a G protein-coupled receptor for gastrin-releasing peptide (GRP), a bombesin-like peptide that is widely distributed in the gastrointestinal tract and central nervous system. Moreover, in a model of chronic itch and atopic dermatitis-like skin lesions in mice, the mice pretreated with a GRPR antagonist presented no scratching [12]. The role of this receptor in humans and in atopic eczema remains to be defined.

The common view is that the epidermis may act as a receptor for itch, but a specific receptor has not yet been clearly identified. Recent studies provide evidence that, indeed, there are itch-specific receptors in the skin. A subset of C nerve fibers that contain MRGPR (Mas-related G protein-coupled receptor member A), a subfamily of G protein-coupled receptors, were found to...
mediate itch sensation induced by chloroquine [13]. Chloroquine is an antimalarial drug that is known to induce itch in humans, especially in those with dark skin color (Africans). These neurons did respond to histamine and capsaicin (these cells had also expressed GRP, the ligand for GRPR) as well as to histamine, providing evidence that these cells play an important role in pruritus. Another recent discovery of a possible itch receptor in humans was found in lichen amyloidosis, a localized form of severe itch common in Asians and Hispanics. A mutation in the oncostatin M receptor (OSMR) gene, which encodes OSMR-beta, an interleukin-31 (IL-31) cytokine receptor, was found in these patients [14]. IL-31 (a Th2 cell-derived cytokine) was previously found to elicit itch in atopic dermatitis and prurigo nodularis [15]. An IL-31 antibody effectively reduced scratching behavior in an atopic dermatitis-like murine model, suggesting the potential therapeutic role of IL-31 antibody in the treatment of chronic itch [16].

The concept of pruritic mediators that act centrally and peripherally is becoming more widely recognized. Among the long list of mediators, opioids have a major role in generalized pruritus. It has been known for decades that analgesia obtained with mu opioids induces itch, most probably via reduction of inhibition of pain fibers, whereas mu antagonists, such as naltrexone, inhibit itch. It has been suggested that chronic itch is associated with an imbalance between mu and kappa opioid systems [17]. This effect is not limited to the central nervous system but also occurs in the skin as demonstrated in keratinocytes of patients with atopic eczema [18]. This latter finding led to the development of a novel kappa opioid receptor agonist. Recent results of a phase III, double-blind study in chronic kidney disease-associated pruritus showed that orally taken nalfurafine effectively reduced itch [19]. Of note, nalfurafine was officially approved for clinical use as an antipruritic for chronic kidney disease-associated pruritus in Japan last year.

Chronic pruritus shares many similarities, including peripheral and central sensitization, with chronic pain [20]. Therefore, many endogenous inflammatory mediators that are involved in chronic pain via sensitization of nociceptive nerve fibers such as prostanoids, serotonin, nerve growth factor, and transient receptor potential vanilloids (TRPVs) also have a role in chronic pruritus [21]. TRPV1 and TRPV3 have recently been implicated in the pathogenesis of pruritus [22,23]. These observations taken together may suggest that TRPV1 is a relay through which capsaicin exerts its antipruritic effect. Beneficial effects of capsaicin have been reported in chronic, localized pruritic disorders, particularly those of neuropathic origin. Substance P is a neuropeptide widely distributed in peripheral nerve fibers and the central nervous system and is known to intensify itch perception. A recent study in rats demonstrated that the destruction of substance P receptor neurokinin 1-expressing neurons in the spinal dorsal horn significantly attenuated scratching response [24]. These results suggest that substance P and its neurokinin receptor 1 have a role as itch transmitters in the central nervous system [24].

The existence of central nerve sensitization is demonstrated by studies in chronic itch patients who perceive painful stimuli as itching [21]. Moreover, robust activation in the brain in areas involved in central sensitization has been noted in chronic itch [25]. This explains the rationale of using neuroleptics and antidepressants in the treatment of chronic pruritus [26]. The exact mechanisms, as well as the magnitude of their beneficial effects, remain largely unclear.

**Implications for clinical practice**

It is time to re-think the current itch treatment strategy that mainly includes topical corticosteroids and oral antihistamines that have limited effect in most types of chronic pruritus. At present, clinical management of chronic pruritus should include the use of drugs that reduce neuronal sensitization for pain (such as gabapentin) and pregabalin and selective serotonin and neuroepiphenrine antidepressants, either as monotherapies or in combination. Hopefully, in the future, we will see a wide range of topical and systemic therapies that target the various receptors and neural pathways that mediate itch of different types and lead to improved quality of life for millions of pruritic patients.

**Abbreviations**

GRP, gastrin-releasing peptide; GRPR, gastrin-releasing peptide receptor; IL-31, interleukin-31; OSMR, oncostatin M receptor; PAR, proteinase-activated receptor; TRPV, transient receptor potential vanilloid.

**Competing interest**

The author declares that he has no competing interests.

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**References**


