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Central Mechanisms of Itch

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Abstract

This chapter summarizes recent findings regarding the central transmission of acute and chronic itch. Itch is transduced by cutaneous pruriceptors that transmit signals to neurons in the superficial spinal cord. Spinal itch-signaling circuits utilize several neuropeptides whose receptors represent novel targets to block itch transmission. Itch is relieved by scratching, which activates spinal interneurons to inhibit itch-transmitting neurons. Spinal itch transmission is also thought to be modulated by descending pathways. Itch is transmitted rostrally via ascending pathways to activate a variety of brain regions involved in sensory discrimination of affective and motor responses to itch. The pathophysiological mechanisms of chronic itch are poorly understood but likely involve sensitization of itch-signaling pathways and/or dysfunction of itch-inhibitory circuits. Improved understanding of central itch mechanisms has identified a number of novel targets for the development of antipruritic treatment strategies.

Itch is defined as an unpleasant sensation associated with the desire to scratch. Chronic itch decreases the quality of life [1] and imposes a high economic burden [2, 3]. This chapter reviews recent breakthroughs in our understanding of the central processing of itch and novel therapeutic approaches to block itch transmission or enhance the inhibition of itch at peripheral, spinal, and supraspinal sites. We also address the poorly understood pathophysiology of chronic itch and potential interventions.

Peripheral Encoding of Itch

Pruritic stimuli activate at least two distinct classes of itch-signaling nerve fibers (fig. 1). Histamine activates mechanically insensitive C-fibers [4, 5] via H_1/H_4 receptors and transient receptor potential cation channel V1 (TRPV1) [6], while non-histaminergic pruritogens activate polymodal nociceptors [7, 8] via TRPA1 [9]. Figure 1 provides a list of many pruritogens and their receptors. The participation of TRP channels in itch provides an avenue to allow the small local anesthetic QX-314 to enter into pruriceptive afferent fibers and block conduction, thereby silencing itch transmission [10]. Additional details

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concerning peripheral mechanisms of itch may be found in the chapter by Azimi et al. [this vol., pp. 18–23].

Spinal/Trigeminal Encoding of Itch

The central branches of pruriceptors terminate in superficial layers of the spinal or medullary dorsal horn to activate second-order neurons. Candidate neurotransmitters released from the central terminals of pruriceptors include glutamate [11] and the neuropeptides gastrin-releasing peptide (GRP), substance P, and brain natriuretic peptide (BNP) [12–15] (fig. 1). BNP is released from pruriceptors and is necessary for both histaminergic and nonhistaminergic itch [15]. MrgprA3-expressing pruriceptor terminals directly contact spinal neurons expressing the GRP receptor, implicating GRP as a neuropeptide released from pruriceptors [16]. GRP is also released from excitatory spinal interneurons. Neurotoxic ablation of neurons expressing neurokinin 1 (NK1), the receptor for substance P, also reduced itch behavior [14]. Nearly all spinal neurons with ascending axonal projections to the thalamus and parabrachial nucleus (see below) express NK1 [17]. These data suggest a spinal itch-signaling pathway in which BNP is released from pruriceptors to serially activate interneurons that release GRP, and then substance P, to activate NK1 receptor-expressing neurons that transmit itch signals to the brain (fig. 1). A cocktail of antagonists for NK1, GRP, and glutamate (AMPA; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors completely inhibited scratching behavior and activation of dorsal horn neurons elicited by chloroquine (MrgprA3 agonist), whereas individual or pairs of antagonists were less effective [11]. In contrast, the AMPA antagonist alone was sufficient to block histamine-evoked itch and excitation of dorsal horn neurons. These data implicate multiple spinal neuropeptides in mediating nonhistaminergic itch, and glutamate as the primary neurotransmitter for histamine-mediated itch. The use of combinations of antagonists for NK1, GRP, BNP, and glutamate (AMPA) receptors may prove useful to relieve itch.

Scratch Inhibition of Itch

It is well known that scratching relieves itch. Scratching within or adjacent to the receptive field area of spinal neurons inhibits their pruritogen-evoked activity [18, 19]. This effect is state dependent in that only pruritogen- but not algogen-evoked firing is suppressed by scratching. The inhibitory neurotransmitters GABA (γ-aminobutyric acid) and glycine mediate scratch inhibition [20], and mice lacking spinal glycine exhibited excessive scratching [21]. A specific class of inhibitory interneurons expressing the transcription factor Bhlhb5 (and co-expressing the somatostatin 2A receptor and galanin or neuronal nitric oxide synthase) is crucial for inhibition of itch. Genetic ablation of these inhibitory interneurons resulted in abnormally increased itch behavior [22]. The inhibitory interneurons are thought to release dynorphin, which acts at κ-opioid receptors presumably expressed by itch-signaling neurons [23]. Indeed, κ-opioid agonists such as nalfurafine suppressed itch behavior in mice [23, 24] and relieved itch from chronic kidney disease in human patients [25]. In mice lacking Bhlhb5, excessive scratching was significantly attenuated and skin lesions improved following spinal transplantation of GABAergic neurons [26]. These data thus indicate that GABA, glycine, and dynorphin modulate the spinal transmission of itch

signals and that agonists of these inhibitory neurotransmitters may prove useful in treating itch.

Ascending Transmission of Itch

Itch-signaling neurons send ascending axons to the contralateral ventrobasal thalamus (spinothalamic tract) and to the lateral parabrachial nucleus bilaterally (spinoparabrachial tract) (fig. 1). In primates, separate subpopulations of spinothalamic tract neurons responded to histamine versus cowhage [27], a bean plant whose seed pods have spicules containing proteases that elicit nonhistaminergic itch [28]. This distinction is less evident in rodents, whereby most spinal neurons respond to histamine as well as nonhistaminergic pruritogens (fig. 1). In rodents, many spinothalamic and spinoparabrachial neurons respond to multiple pruritogens [29–31]. Interestingly, most or all pruritogen-responsive neurons are also excited by the algogens capsaicin and mustard oil, as well as other pain-producing stimuli. This presents a problem in terms of understanding how the nervous system discriminates between itch and pain. One possibility is that pruritogen-responsive neurons signal itch (even though they can be activated by noxious stimuli), while pain is signaled by a larger population of nociceptive neurons that is insensitive to pruritogens. This is consistent with a report that capsaicin, which normally elicits pain behavior, instead elicits itch behavior in mice lacking the capsaicin-sensitive receptor TRPV1, in whom TRPV1 was genetically inserted selectively back into sensory neurons expressing MrgprA3 [16].

Descending Modulation of Itch

Spinal itch transmission is thought to be under descending modulation from the brain, although to date there is limited data. Depletion of spinal cord levels of norepinephrine increased itch behavior, indicating a role for noradrenergic pathways descending from locus coeruleus and adjacent regions to inhibit itch transmission, possibly by activating inhibitory interneurons [32] (fig. 1). Depletion of supraspinal serotonin reduced itch behavior, indicating that serotonergic pathways descending from the rostral ventromedial medulla may tonically facilitate itch [33] (fig. 1).

Supraspinal Processing of Itch

To date, little is known regarding the functional properties of neurons in the ventrobasal thalamus or parabrachial nuclei that receive direct ascending pruriceptive input. However, numerous functional imaging studies in humans have revealed a variety of brain regions that are activated during itch [34]. These include (1) the thalamus, primary and secondary somatosensory cortex, areas involved in recognition of and attention to itch, and localization and intensity rating of itch, (2) the cingulate and insular cortex, areas associated with cognition, motivation to act (scratch), and awareness of emotional state and body feeling, (3) the medial parietal cortex, posterior cingulate cortex, and precuneus, areas possibly associated with the subjective sensation of itch, and (4) motor-related areas, including the supplementary, premotor, and primary motor cortices, striatum and cerebellum, areas potentially involved in planning motor responses (e.g. scratching) to itch and affective aspects such as the desire to scratch.

Itch relief by scratching and the act of scratching itself have been suggested to be pleasurable. It is interesting that scratching during itch activates brain areas associated with reward including the midbrain striatum, medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex [34].

Humans often perceive itch and scratch themselves when observing other people scratching, a phenomenon called contagious itch [35]. Contagious scratching has also been observed in monkeys [36]. Interestingly, contagious itch is associated with activation of the same brain areas that are active during histamine-evoked itch [37].

Chronic Itch

Chronic itch arises from a variety of skin conditions, such as atopic dermatitis or psoriasis, from systemic kidney or liver disease, nerve damage, and many other sources, and is usually resistant to antihistamine treatment, implying dysfunction of the nonhistaminergic itch pathways. Chronic itch could be due to altered skin physiology or damage causing sensitization of pruriceptors, central sensitization of spinal/trigeminal transmission, disruption of spinal itch-inhibition, disruption of descending itch modulation, altered supraspinal processing of itch signals, or combinations thereof. Symptoms of chronic itch include ongoing (spontaneous) itch, increased itch to a normally pruritic stimulus (hyperknesis), and itch elicited by low-threshold tactile stimulation (alloknesis). In rodent models of atopic dermatitis, dry skin itch, and contact hypersensitivity, animals exhibited spontaneous scratching behavior, alloknesis, and enhanced scratching elicited by nonhistaminergic pruritogens (chloroquine, serotonin, proteases), but not histamine [38–40]. Primary and second-order sensory neurons with input from dry skin exhibited significantly enhanced responses to nonhistaminergic itch mediators, but not to histamine [38, 41], suggesting peripheral and possibly central sensitization of nonhistaminergic itch-signaling neurons in this dry skin model.

Mice lacking a subset of spinal inhibitory interneurons (see above) exhibited enhanced spontaneous scratching and hyperknesis [22], suggesting that dysfunction of spinal inhibition contributes to this genetic model of neuropathic itch.

Human patients suffering from itch of end-stage renal disease exhibited greater baseline activation in the anterior cingulate cortex, insula, claustrum, hippocampus, and nucleus accumbens, as well as reduced cowhage-evoked activation of primary somatosensory cortex and other areas, compared to healthy control subjects [42]. This suggests that chronic itch results in altered supraspinal processing of itch signaling.

Conclusions

Our understanding of the central transmission of itch has increased dramatically in recent years, revealing a number of attractive targets for future development of novel therapeutics to block itch transmission or enhance itch inhibition at peripheral, spinal, and supraspinal sites. Less is known regarding pathophysiological mechanisms underlying chronic itch. However, with the availability of animal models for many types of chronic itch, we can

expect dramatic advances to be made in our knowledge of the pathophysiology of chronic itch with the advent of new evidence-based treatment strategies.

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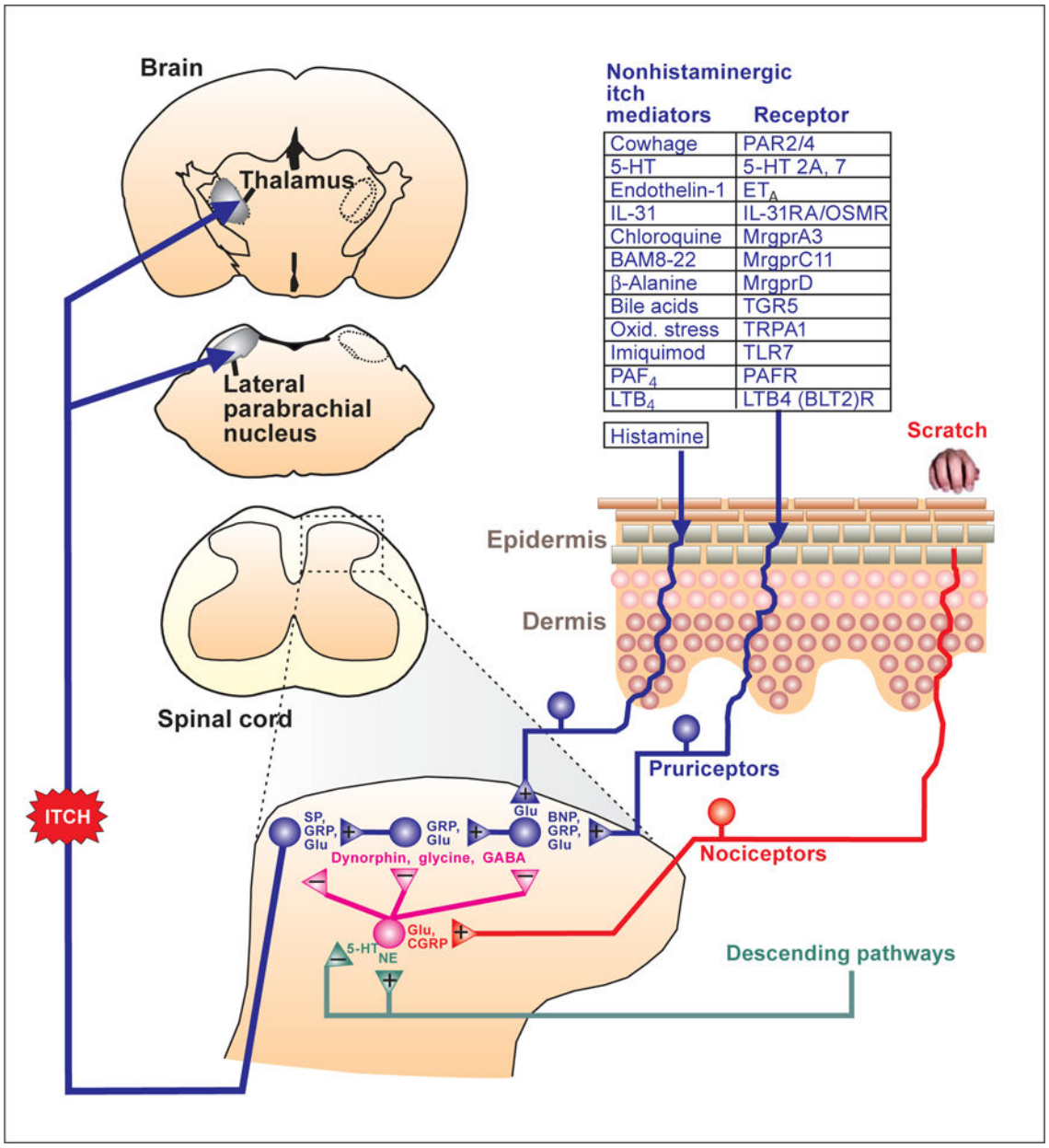

Fig. 1.

Schematic drawing of the neural pathway for itch. 5-HT = 5-Hydroxytryptamine (serotonin); CGRP = calcitonin gene-related peptide; ET_A = endothelin-A receptor; Glu = glutamate; IL = interleukin; LTB_4 = leukotriene B_4 ; Mrgpr = Mas-related G protein-coupled receptor; NE = norepinephrine; OSMR = oncostatin M receptor; Oxid. stress = oxidative stress; PAF = platelet-activating factor; PAR = protease-activated receptor; PAFR = platelet-activating factor receptor; SP = substance P; TGR5 = G protein-coupled bile acid receptor; TLR = Toll-like receptor.