Itch and pain

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ABSTRACT: The discovery of a specialized neuronal pathway for itch has markedly improved our understanding of itch processing under physiological conditions. However, the complex interactions of pain and itch are only partly understood. This review focuses on the neurophysiological mechanisms involved in clinical and experimental itch conditions. There is emerging evidence that similar patterns of peripheral and central sensitization occur in chronic pain and chronic itch conditions. It will be of major interest to reveal whether the underlying mechanism for sensitization in the itch and pain pathways are also similar, as this might have major implications for therapy.

KEYWORDS: alloknesis, opioids, sensitization

Introduction

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 experimentally demonstrated by use of various painful thermal, mechanical, and chemical stimuli. Recently, electrical stimulation via an array of pointed electrodes (“cutaneous field stimulation”) has also been successfully used to inhibit histamine-induced itch for several hours in an area around a stimulated site 20 cm in diameter. The large area of inhibition suggests a central mode of action (1). Consistent with these results, itch is suppressed inside the secondary zone of capsaicin-induced mechanical hyperalgesia (2). This central effect of nociceptor excitation by capsaicin should be clearly distinguished from the neurotoxic effect of higher concentrations of capsaicin that destroy most C-fiber terminals, including fibers that mediate itch (3). The latter mechanism therefore also abolishes itch (3). The latter mechanism therefore also abolishes itch locally until the nerve terminals have regenerated.

Inhibition of pain may enhance pruritus

Not only is itch inhibited by enhanced input of pain stimuli, but vice versa inhibition of pain processing also may reduce its inhibitory effect, thus enhancing itch (4). This phenomenon is particularly relevant to spinally administered µ-opioid receptor agonists (FIG. 1), which induce segmental analgesia often combined with segmental pruritus (5). This mechanism might well account for the antipruritic effect of µ-opioid antagonists observed in experimental itch (6) and also in patients with cholestatic itch. It is remarkable that in some of the cholestatic patients, the reduction of itch by naloxone is accompanied by the induction of pain.

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FIG. 1. Simplified schematic view of central interaction between pain and itch under physiological conditions. While having a similar inhibitory effect on the pain processing, µ and kappa opioids differentially modify the spinal itch processing. DRG: dorsal root ganglion; CNS: central nervous system.
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Itch and pain (7) and withdrawal-like reactions (8). Conversely, in animal experiments κ-opioid antagonists enhanced itch (9). In line with these results, the κ-opioid agonist nalbuphine has been shown to reduce µ-opioid-induced pruritus in a meta-analysis (10). This new therapeutical concept has already been tested successfully in chronic itch patients using a newly developed κ-opioid agonist (11).

Central inhibition of itch can also be achieved by cold stimulation. In addition, cooling has a peripheral inhibitory effect: histamine-induced activation of nociceptors can be reduced by cooling (12). Also, in humans cooling of a histamine-treated skin site reduced the activity of the primary afferents and decreased the area of “itchy skin” or “hyperkinesis” around the application site (13) (see following discussion). Conversely, warming the skin led to an exacerbation of itch. However, as soon as the heating becomes painful, central inhibition of pruritus will counteract this effect (14).

Sensitization to itch

Classical inflammatory mediators such as bradykinin, serotonin, prostanoids, and low pH have been shown to sensitize nociceptors. In addition, acute sensitization can also be achieved by inflammatory cell mediators, such as interleukins. It has become clear that acute effects of inflammatory mediators cannot explain the prolonged changes of neuronal sensitivity observed in inflammatory processes. Regulation of gene expression induced by trophic factors, such as nerve growth factor (NGF), has been shown to play a major role in persistently increased neuronal sensitivity. NGF is released in the periphery and specifically binds to TRK-A receptors located on nociceptive nerve endings. It is then conveyed via retrograde axonal transport to the dorsal root ganglion, where gene expression of neuropeptides and receptor molecules, such as the vanilloid receptor (TRPV1), is increased. Trophic factors also initiate nerve fiber sprouting and thus change the morphology of sensory neurons. Sprouting of epidermal nerve fibers in combination with localized pain and hypersensitivity has been reported before (15). Similar mechanisms may be at work in chronic itching, as shown in the next section.

Peripheral sensitization

Increased intradermal nerve fiber density has been found in patients with chronic pruritus (16). In addition, increased epidermal levels of neurotrophin 4 (NT4) have been found in patients with atopic dermatitis (17), and massively increased serum levels of NGF and SP have been found to correlate with the severity of the disease in such patients (18). Increased fiber density and higher local NGF concentrations were also found in patients with contact dermatitis (19). It is known that NGF and NT4 can sensitize nociceptors. These similarities between localized painful and pruritic lesions might suggest that on a peripheral level, similar mechanisms of nociceptor sprouting and sensitization exist. It has not yet been possible to morphologically differentiate nociceptors from pruriceptors. Thus, there is no way at present to test for a specific sprouting of pruriceptors that would spare the nociceptors. Apart from this obvious lack of knowledge, it is very unlikely that peripheral mechanisms alone account for the obvious differences between patients with localized chronic itch and pain.

Central sensitization

There is a remarkable similarity between the phenomena associated with central sensitization to pain and to itch. Activity in chemonociceptors leads not only to acute pain but also can sensitize second-order neurons in the dorsal horn, thereby leading to increased sensitivity to pain (hyperalgesia). Two types of mechanical hyperalgesia can be differentiated. Normally painless touch sensations in the uninjured surroundings of a trauma are felt as painful “touch or brush-evoked hyperalgesia,” or allodynia. Although this sensation is mediated by myelinated mechanoreceptor units, it requires ongoing activity of primary afferent C nociceptors (20). The second type of mechanical hyperalgesia results in slightly painful pinprick stimulation being perceived as being more painful in the secondary zone around a focus of inflammation. This type has been called “punctuate hyperalgesia.” The latter does not require ongoing activity of primary nociceptors for its maintenance. It can persist for hours following a trauma, usually much longer than touch or brush-evoked hyper-algesia (21).

In itch processing, similar phenomena have been described: touch or brush-evoked pruritus around an itching site has been termed “itchy skin” (22,23). Like allodynia, it requires ongoing activity in primary afferents and is most probably elicited by low-threshold mechanoreceptors (A-β fibers).
(FIG. 2) (13,23). Also more intense prick-induced itch sensations in the surroundings, hyperkinesis, have been reported following histamine iontophoresis in healthy volunteers (4).

The existence of central sensitization for itch can greatly improve our understanding of clinical itch. Under the conditions of central sensitization leading to punctuate hyperkinesis, normally painful stimuli are perceived as itching. This phenomenon has already been described in patients suffering from atopic dermatitis, who perceive normally painful electrical stimuli as itching when applied inside their lesional skin (24). Furthermore, acetylcholine provokes itch instead of pain in patients with atopic dermatitis (25), 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 have still to be explored, whereas a major role 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 a corresponding phenomena in patients with chronic pain and chronic itch. In patients with neuropathic pain it has recently been reported that histamine iontophoresis resulted in burning pain instead of pure itch, which would be induced by this procedure in healthy volunteers (26,27). This phenomenon is of special interest as it demonstrates spinal hypersensitivity to C-fiber input. Conversely, normally painful electrical, chemical, mechanical, and thermal stimulation is perceived as itching when applied in or close to lesional skin of atopic dermatitis patients (13,28). The combination of reduced peripheral activation and increased perception of itch might be explained by a lowered central “itch perception threshold.”

Long-lasting activation of pruriceptors by histamine has been shown to experimentally induce central sensitization for itch in healthy volunteers (28): following the application of histamine via dermal microdialysis fibers, low pH stimulation of the skin close to the histamine site was perceived as itch instead of pain. Ongoing activity of pruriceptors, which might underly the development of central sensitization for itch, has already been confirmed microneurographically in a patient with chronic pruritus (29). Thus, there is emerging evidence for a role of central sensitization for itch in chronic pruritus. As there are many mediators and mechanisms that are potentially algogenic in inflamed skin, many of them could provoke itch in a sensitized patient. Thus, a therapeutic approach targeting only a single pruritic mediator does not appear to be promising for patients with chronic itching diseases, e.g., atopic dermatitis. In contrast, the main therapeutic implication of this phenomenon is that a combination of centrally acting drugs counteracting the sensitization and topically acting drugs counteracting the inflammation should be more promising in ameliorating pruritus in those cases.

**Conclusion**

Beyond direct activation of the itch pathway by mediators such as histamine, two major mechanisms can contribute to pruritus under pathological conditions, i.e., peripheral and central sensitization. Although there is obviously an antagonistic interaction between pain and itch under normal conditions, the patterns of peripheral and central sensitization phenomena for pain and itch are surprisingly similar. In the periphery, anti-inflammatory therapy will reduce both sensitization for pain and for itch. It remains to be established whether this similarity will also include the underlying mechanism that would also implicate similar therapeutic approaches for the treatment of centrally mediated itch such as gabapentin (30) or clonidine (31).
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References


