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Review

Itch and pain

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ABSTRACT

Decades of pain research have succeeded in elucidating complex mechanisms of acute activation and chronic sensitization of nociceptors leading to pain. In contrast, itch conditions have received less attention and even basic mechanisms for the induction of itch are still unclear. In this review we describe itch-specific pathways, but also evidence for a modified pattern theory of pruritus offering independent mechanisms for the itch induction. Traditionally pain and itch have been regarded as antagonistic as painful stimuli such as scratching suppress itch and opioids suppress pain, but generate itch. However, concerning mechanisms of sensitization to itch or pain, surprisingly similar patterns have been observed lately in both inflamed tissue and in the spinal cord. These similarities open up two highly interesting perspectives: the role of well established analgesic therapeutic concepts can be validated in chronic itch conditions and on the other hand investigations of sensitization in easily accessible pruritic skin may help to validate concepts of nociception in humans. These perspectives illustrate that itch and pain research no longer follows separate paths, but can be advantageously interconnected.

Contents

1. Primary afferent nerve fibers for itch and pain

Over the last decades several concurrent and mutually exclusive theories for the neurophysiological basis of itch have been formulated: the main concepts were the transition from itch to pain according to increased discharge frequency of nociceptors (intensity theory (v.Frey, 1922)), encoding of itch and pain by different discharge pattern composed in the central nervous system (pattern theory) and specific separate pathways for itch and pain (specificity theory) for reviews see (Craig, 2003; Greaves and Wall, 1996; McMahon and Koltzenburg, 1992). When C-fibers responding to histamine stimulation in parallel to the itch sensation of the subjects were found in 1997 (Schmelz et al., 1997) the specificity theory appeared to be proven as a distinct subgroup of C-fibres was found preferentially excited by pruritic compounds. In contrast, the most common type of C-fibres, mechano-heat nociceptors (CMH or polymodal nociceptors) are either insensitive to histamine or only weakly activated by it (Handwerker et al., 1991; Schmelz et al., 2003).

Only a few mediators can induce histamine-independent pruritus, such as prostaglandins (Woodward et al., 1995), serotonin (Hägermark, 1992) or acetyl choline (Vogelsang et al., 1995). Prostaglandin E2 was the only mediator that also selectively activated histamine positive fibers supporting the concept of separate and specific population of neurons for the itch sensation (Schmelz et al., 2003).

In the light of the pruritogenic effects of PgE_2, activation of histamine-responsive chemoreceptors by this mediator provides a strong argument for a dedicated neuronal system for itch, separate from the pain pathway. Even more substantial evidence for a 'labeled

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line' for itch was generated by the discovery of histamine-sensitive central projection neurons (Craig and Andrew, 2002): they found mechano-insensitive spinothalamic projection neurons responding to histamine iontophoresis in the peripheral receptive field with lasting discharge paralleling itch ratings in humans and differed from other pain processing neurons in their central thalamic projection and their resting activity (Craig and Andrew, 2002).

However, the histamine-responsive fibres are also excited by at least one algogen, namely capsaicin. In this situation one might either doubt specificity of the fibers (McMahon and Koltzenburg, 1992) or specificity of the mediator (Green and Shaffer, 1993; Namer et al., 2008). More fundamental criticism arose from recent data in the monkey, which question the existence of specific histamine-sensitive spinal projection neurons, but nevertheless propose two separate itch processing pathways, one being activated by histamine, the other being activated by cowhage (Davidson et al., 2007; Simone et al., 2004).

Confirming the existence of different itch processing pathway, in an early study using papain, itch was induced in the absence of an axon reflex flare (Hagermark, 1973). The axon reflex flare is a neurogenic vasodilation that characteristically surrounds a histamine stimulation site. It is induced by neuropeptide release from mechano-insensitive C-fibers (Schmelz et al., 2000). The absence of an axon reflex flare therefore suggests that the itch is independent of histamine-sensitive C-fibers. Itch without axon reflex flare can also be elicited by weak electrical stimulation (Ikoma et al., 2005; Shelley and Arthur, 1957), providing further evidence that the sensation of itch can be dissociated from cutaneous vasodilation (Ikoma et al., 2005). Therefore, C fiber afferents with electrical thresholds lower than those of mechano-insensitive C-fibers (Weidner et al., 1999) can likely convey itch sensation, but are not able to produce an axon reflex flare.

Cowhage spicules inserted into human skin produce itch comparable to that following histamine application. Mechano-responsive "polymodal" C-fiber afferents, usually assumed to be pure nociceptors, can be activated by cowhage in the cat (Tuckett and Wei, 1987) and according to recent studies also in non-human primates (Johanek et al., 2007, 2008) and in human volunteers (Namer et al., 2008). The active compound, the cysteine protease muconain, has been identified lately and shown to activate proteinase activated receptor 2 (PAR 2) and even more PAR 4 (Reddy et al., 2008). Polymodal C-fibers are the most frequent type of afferent C-fibers in human skin nerves (Schmidt et al., 1995) and they are not involved in sustained axon reflex flare reactions (Schmelz et al., 2000). This is consistent with the observation that cowhage induced itch is not accompanied by a widespread axon reflex flare (Johanek et al., 2007; Shelley and Arthur, 1955, 1957).

Given that cowhage spicules can activate a large proportion of polymodal nociceptors, we face a major problem to explain why activation of these fibers by heat or by scratching actually inhibits itch whereas activation by cowhage produces it.

2. Specificity for itch?

Cowhage induced itch is mediated most probably by mechanisms involving classical nociceptors. There are no results which would indicate a certain subpopulation of C-fibers to be responsible for cowhage induced itch. It is still unclear how the neuronal circuits manage to separate out the itch signal when it is at least partly generated by those fibers which would normally suppress the itch sensation (i.e. scratch-activated polymodal nociceptors). The cowhage results can be summarized by stating there is no evidence for specificity of cowhage-induced itch (Davidson et al., 2007; Simone et al., 2004).

It is an interesting development, that following the discovery of histamine-sensitive primary afferents and spinal projection neurons (Andrew and Craig, 2001; Schmelz et al., 1997) the specificity of itch was over-emphasized. Recently, the lack of histamine-specific projection neurons in the monkey and responses of histamine-sensitive neurons to the algogen capsaicin have led researchers to deny the specificity for itch (Davidson et al., 2007; Simone et al., 2004). In this discussion, it should be kept in mind, that specificity of neurons can only be tested with specific test agents: as noted above, capsaicin application can induce the sensation of itch upon topical application in about 50% of the volunteers (Green and Shaffer, 1993). Conversely, histamine injection provokes not only itch, but also pain: the pain upon histamine injection appears to inhibit the ensuing histamine induced itch as local anesthetics can abolish injection pain, but enhance the ensuing itch sensation (Atanassoff et al., 1999).

Most interestingly, capsaicin induces itch when applied on the tip of an inactivated cowhage spicule (Sikand et al., 2008) indicating, that the spatial characteristics of the application may be crucial and convert an algogenic mediator into a pruritic mediator: the highly localized stimulation in the epidermis strongly activates some of the local nociceptors while others – albeit being close by – remain silent resulting in a mismatch signal of activation and absence of activation from this site. It has thus been hypothesized, that this mismatch might be perceived by the central nervous system as itch (Namer et al., 2008)—interestingly scratching in this condition would activate all the mechanosensitive nociceptors in the stimulated area and thus end the mismatch.

The discovery of the role of gastrin-releasing peptide receptor (GRPR) as marker for spinal pruriceptive neurons in the mouse has recently provided new evidence for a separate set of itch processing neurons (Sun and Chen, 2007). Anyway, there are conflicting results concerning the specificity of the neuronal pathway for histamine-induced itch: the primary afferent fibers can be identified by their unique histamine response and their unique activation to PgE2, and thus can be regarded as specific. However, the specific spinothalamic projection neurons in the cat contrast the non-specific projection neurons in the monkey (Davidson et al., 2007; Simone et al., 2004).

The discussion on specificity might appear as purely academic and interesting mainly for neuroscientists, however, it is crucial to identify those neurons in the skin that are mediating the itch sensation, especially in chronic itch patients. Therefore, studies investigating structures and staining patterns of different primary afferent nerve fiber classes in the epidermis as already being established in the mouse (Dussor et al., 2008; Zylka et al., 2005) are required for humans to understand how painful and pruritic stimuli are processed in the epidermis.

3. Itch modulation by painful and non-painful stimuli

It is a 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 (Ward et al., 1996). Painful electrical stimulation reduced histamine-induced itch for hours in an area 10 cm around the stimulated site suggesting an interaction on the spinal level (Nilsson et al., 1997). Recent results suggest that noxious heat stimuli and scratching produce a stronger itch inhibition than noxious cold stimuli (Yosipovitch et al., 2005). Consistent with these results, itch is suppressed inside the area of secondary capsaicin-induced mechanical hyperalgesia (Brull et al., 1999). This central effect of nociceptor excitation by capsaicin should be clearly distinguished from the neurotoxic effect of higher concentrations of capsaicin which destroy most C-fiber terminals, including fibers that mediate itch (Simone et al., 1998). The latter

mechanism, therefore, also abolishes pruritus locally, until the nerve terminals have regenerated.

Itch can be reduced by painful stimuli, but vice versa analgesia may reduce this inhibition and thus enhance itch (Atanassoff et al., 1999). This phenomenon is particularly relevant to spinally administered μ-opioid receptor agonists, which induce segmental analgesia often combined with segmental pruritus (Andrew et al., 2003). Given that μ-opioids can induce itch it is not surprising that μ-opioid antagonists have antipruritic effects in experimental itch (Heyer et al., 1997) 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 (McRae et al., 2003) and withdrawal-like reactions (Jones et al., 2002), suggesting an upregulation of endogenous opioids in these patients (Marzioni et al., 2007). Both, μ-, but also κ-opioid agonists are used clinically as analgesics. Thus, it is surprising, that κ-opioid antagonists enhanced itch in animal experiments (Kamei and Nagase, 2001). In line with these results, κ-opioid agonists have been shown to reduce experimental cholestatic itch (Inan and Cowan, 2006), but also μ-opioid induced pruritus in man (Kjellberg and Tramer, 2001) and primates (Lee et al., 2007). This new therapeutic concept has already been tested successfully in chronic itch patients (Delmez, 2006).

While the effects of opioids in the spinal cord and central nervous system have been investigated for decades, local production of opioids in the skin is a recent finding.

When *peripheral* opioid receptors in the skin were first discovered, research focused on peripheral analgesic effects (Stein et al., 2003) whereas opioid effects other than analgesia were of minor interest (Braz et al., 2001). But finally discovery of endogenous opioid production in the skin, such as β-endorphin, promoted studies on multiple different functions (e.g. control of hair growth and pigmentation (Schmelz and Paus, 2007) including wound healing and differentiation (Bigliardi-Qi et al., 2007). We are just beginning to understand which stimuli induce epidermal opioid release such as cannabinoid receptor (CB2) activation (Ibrahim et al., 2005) and how they may contribute to control growth and differentiation, but also the inflammation and modulation of neuronal excitability.

4. Peripheral sensitization

Numerous endogenous inflammatory mediators have been identified that can activate and sensitize nociceptive nerve endings (Reeh and Kress, 1995). It is interesting to note that many of the classic inflammatory mediators like bradykinin, serotonin, histamine and prostaglandins, which are released in a wide range during inflammation, have been demonstrated to acutely sensitise nociceptors (Kidd and Urban, 2001), but also to activate pruriceptors (Schmelz et al., 2003).

The complex effects of inflammatory mediators are also complicated by their interactions: supra-additive effects are known for various combinations such as between prostaglandin E2 and histamine (Nicolson et al., 2007). Moreover, sensitization of the Capsaicin receptor TRPV1 by various mediators – among them proteinase-activated receptor 2 (PAR-2) (Amadesi et al., 2006) – provide evidence for possible underlying mechanisms of cross-sensitization.

Acute sensitization and activation of primary afferent nerve fibers can be readily explained by combinations of inflammatory mediators. However, the chemical stimulation underlies strong adaptation and tachyphylaxis in the primary afferent nerve endings leading to desensitization (Liang et al., 2001). Despite the expected desensitization many patients suffer from long-lasting hypersensitivity for months and years.

Thus, in addition to acute sensitization long lasting structural changes are required to mediate clinical states of hypersensitivity. Neurotrophins can induce acute sensitization (Zhang et al., 2005), but also cause lasting structural changes (sprouting) of nociceptors. The expression of nerve growth factor (NGF) is high in injured and inflamed tissues and activation of the NGF receptor, tyrosine kinase trkA, on nociceptive neurons triggers and potentiates pain-signaling by multiple mechanisms (Hefti et al., 2006).

Sprouting of epidermal nerve fibers initiated by increased NGF is not only found in combination of localized pain and hyperalgesia like vulvar dysesthesia (Bohm-Starke et al., 1998), but also in atopic dermatitis (Urashima and Mihara, 1998). 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 (Toyoda et al., 2002). The sources of NGF were mainly keratinocytes and mast cells (Groneberg et al., 2005). Increased fiber density and higher local NGF concentrations were also found clinically in pruritic contact dermatitis (Kinkelin et al., 2000), while increased NGF and trkA immunoreactivity were detected in prurigo nodularis (Johansson et al., 2002) and also in pruritic lesions of psoriasis patients (Choi et al., 2005). These similarities between localized painful and pruritic lesions might suggest that similar mechanisms of neuronal sprouting and sensitization, exist both for pain and pruritus on a peripheral level. Anti-NGF strategies have already been used in animal pain models (Halvorson et al., 2005) and also in pain patients (Lane et al., 2005). Therapeutic anti-NGF approaches against pruritus have been performed in animal models of atopic dermatitis only (Takano et al., 2005). In this model (NC/Nga mice) increased epidermal NGF expression has been shown (Tanaka and Matsuda, 2005; Tominaga et al., 2007).

NGF is known to upregulate neuropeptides, especially substance P (SP) and calcitonin gene related peptide (CGRP) (Verge et al., 1995). For SP an important role in the induction of pain and hyperalgesia has been found in rodents (Laird et al., 2001), although there has not been much evidence for the clinical analgesic efficacy of NK1 antagonists (Hill, 2000). There is no confirmation for SP as an acute pruritogen in humans (Weidner et al., 2000), but it might contribute to itch by neuronal sensitisation and by its long-term interaction with mast cells (Yosipovitch et al., 2003). A sensitizing effect on nociceptors has also been found for CGRP in rodents (Mogil et al., 2005; Sun et al., 2004), but its role in pruritus is unclear (Ekblom et al., 1993). Interestingly, increased SP levels coexist with reduced CGRP levels in the NC/Nga mice, an atopic dermatitis mouse model (Katsuno et al., 2003). Given that heat pain sensitivity correlates with CGRP levels (Mogil et al., 2005), and pain sensitivity negatively correlates to sensitivity in itch models (Green et al., 2006), one might speculate about a preferred role of CGRP for nociception and SP for itch.

Currently, most research on the role of neurotrophins in itch is focussed on NGF, however, also brain derived neurotrophic factor (BDNF), neurotrophin 3 and 4 and glia cell derived neurotrophic factor are important modulators of intraepidermal nerve fibers and may be involved in chronic itch conditions (Grewe et al., 2000; Hon et al., 2007).

5. Central sensitization

Noxious neuronal input to the spinal cord is known to sensitize pain processing in the spinal cord termed "central sensitization" (Koltzenburg, 2000) that consists of hypersensitivity to touch ("allodynia") and to punctate mechanical stimuli ("punctate hyperalgesia"). Two types of mechanical hyperalgesia can be differentiated. Non-noxious touch stimuli in the uninjured surroundings of a trauma can be felt as painful 'touch

or brush-evoked hyperalgesia', or allodynia. Though this sensation is mediated by myelinated mechanoreceptor units, it requires ongoing activity of primary afferent C-nociceptors (Torebjörk et al., 1996). 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 termed 'punctate 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 hyperalgesia (LaMotte et al., 1991).

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' (Bickford, 1938; Simone et al., 1991). Like allodynia, it requires ongoing activity in primary afferents and is most probably elicited by low threshold mechanoreceptors (A-β fibers) (Heyer et al., 1995; Simone et al., 1991). Additionally, more intense prick-induced itch sensation in the surroundings, 'hyperknesis', has been reported following histamine iontophoresis in healthy volunteers (Atanassoff et al., 1999).

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 suffering from atopic dermatitis, who perceive normally painful electrical stimuli as itching when applied inside their lesional skin (Nilsson and Schouenborg, 1999). Furthermore, acetylcholine and bradykinin provoke itch instead of pain in patients with atopic dermatitis (Hosogi et al., 2006; Vogelsang et al., 1995) 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 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 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 (Baron et al., 2001; Birklein et al., 1997). This phenomenon is of special interest as it demonstrates spinal hypersensitivity to C-fiber 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 atopic dermatitis patients (Hosogi et al., 2006; Ikoma et al., 2004) suggesting that there is also spinal hypersensitivity to C-fiber input in chronic itch. Confirming this hypersensitivity in atopic dermatitis patients, repetitive scratching intensified their itch rather than inhibiting it (Ishiuji et al., 2008). Histamine prick tests in non-lesional skin of atopic dermatitis patients provoked less intense itching as compared to healthy controls. However, when applied inside their lesions, itch ratings were enhanced and lasted very protracted, whereas the axon reflex erythema was still smaller as compared to the controls (Heyer et al., 1995). Thus, in addition to peripheral sensitization there is evidence for a central sensitization of itch in chronic pruritus (Fig. 1).

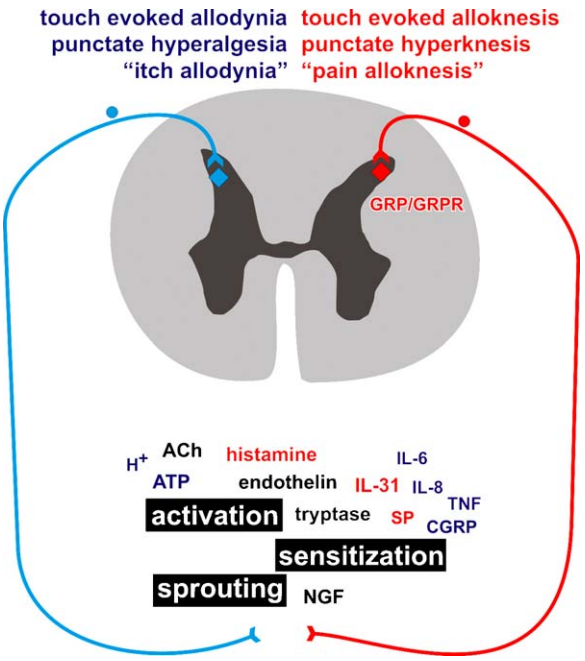

Fig. 1. Peripheral and central mechanisms of sensitization of pain and itch processing are shown. In the periphery, inflammatory mediators can activate and sensitize nociceptive and pruriceptive nerve endings. In addition to acute sensitization, trophic factors, such as nerve growth factor (NGF) induce long term sensitivity changes along with structural alterations (sprouting). In the spinal cord, itch and pain processing can be sensitized such that touch stimuli evoke itch (alloknesis) or pain (touch allodynia), that punctate mechanical stimuli evoke more intense pricking pain (punctate hyperalgesia) or itch (punctate hyperknesis). Moreover, normally painful stimuli can be misinterpreted as itch in chronic itch patients ("pain alloknesis") or normally itching stimuli can be misinterpreted as pain in chronic pain patients ("itch allodynia").

6. Neuropathic itch vs. neuropathic pain

The similar patterns of central sensitization found in itch and pain have led to antipruritic therapeutic approaches using drugs usually applied in the treatment of neuropathic pain. Thus far, there have been no controlled studies; however, anecdotal reports show success with carbamazepine, gabapentin and the recently developed pregabalin (Summey and Yosipovitch, 2005). Gabapentin and pregabalin inhibit the alpha(2)delta subunit of voltage-dependent Ca(2+) channels (Rogawski and Loscher, 2004). Gabapentin has also been proven to be effective for the treatment of neuropathic pruritus, particularly in the case of brachioradial pruritus and multiple sclerosis-related itch (Bueller et al., 1999; Winhoven et al., 2004). Gabapentin seems to alter the sensation of itch as well as the pruritus related to nerve damage in cutaneous and systemic diseases (Yesudian and Wilson, 2005).

The combination of neuropathic itch and neuropathic pain is present in some neuropathies, but only rarely has been investigated with a focus on the relation of the two: the intimate link between neuropathic pain and neuropathic itch has been shown in postherpetic itch (Oaklander et al., 2003), but data on the therapeutic implications are still rare. It will be of major interest to more closely study neuropathic diseases such as postherpetic neuralgia, meralgia paresthetica, and brachioradial pruritus with respect to the occurrence of central and peripheral sensitization in the pain and in the itch pathway, combining efforts of dermatologists, neurologists and anaesthesiologist.

7. Summary

Current data support two distinct neurophysiological concepts for itch, both of which can induce itch, but it is unclear which pathway is underlying clinical chronic itch conditions:

- A *specific neuronal pathway* for histamine induced pruritus composed of mechano-insensitive primary afferent fibers and mechano-insensitive dorsal horn spinothalamic projection neurons which might also be characterized by expressing gastrin releasing peptide receptors (GRPR).

- An unspecific pathway in which pruritus is based on the *central activation pattern* as induced by focal activation of nociceptors by intradermal stimulation such as cowhage spicules.

Traditionally, pain and itch have been perceived as antagonistic as pain suppresses itch and μ-opioids cause both itch and pain relief. Surprisingly, clinical itch conditions and chronic pain are characterized by sensitization of neurons in the periphery and in the spinal cord with strikingly similar patterns. These similarities support the combination of itch and pain research and moreover suggest that well-established therapeutic approaches against pain can also be validated in chronic itch conditions.

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