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How best to fight that nasty itch – from new insights into the neuroimmunological, neuroendocrine, and neurophysiological bases of pruritus to novel therapeutic approaches

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While the enormous clinical and psychosocial importance of pruritus in many areas of medicine and the detrimental effects of chronic 'itch' on the quality of life of an affected individual are widely appreciated, the complexity of this sensation is still often grossly underestimated. The current Controversies feature highlights this complexity by portraying pruritus as a truly interdisciplinary problem at the crossroads of neurophysiology, neuroimmunology, neuropharmacology, protease research, internal medicine, and dermatology, which is combated most successfully if one keeps the multilayered nature of 'itch' in mind and adopts a holistic treatment approach – beyond the customary, frequently frustrane monotherapy with histamine receptor antagonists. In view of the often unsatisfactory, unidimensional, and altogether rather crude standard instruments for pruritus management that we still tend to use in clinical practice today, an interdisciplinary team of pruritus experts here critically examines recent progress in pruritus research that future itch management must take into consideration. Focusing on new insights into the neuroimmunological, neuroendocrine, and neurophysiological bases of pruritus, and discussing available neuropharmacological tools, specific research avenues are highlighted, whose pursuit promises to lead to novel, and hopefully more effective, forms of pruritus management.

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Viewpoint 1

Setting:

Physiology seminar, Department of Physiology, University of Debrecen, Hungary

Teacher:

Good morning, Class! As you may all remember, during the previous seminars, we introduced the neurophysiological details of the mechanisms and interactions underlying one of the 'ugliest', yet most fascinating sensory phenomena – itch. Before reviewing your ideas that you collected as your 'home-work' (i.e. How would you best fight that nasty itch?), let me briefly summarize key features of our current understanding of itch.

Itch (pruritus) is an unpleasant cutaneous sensation which provokes the desire to scratch (1). Neurophysiologically, itch sensation is initiated by pruritogenic substances that stimulate a subset of specialized skin C-fibers. The latter are distinct from the polymodal C-type neurons which transmit nociceptive (i.e. painful) stimuli to the central nervous system (2). Many endogenous substances are regarded as 'mediators of itch' (3), e.g. amines

(such as histamine), proteases, opioids, lipid peroxidation metabolites (such as leukotrienes, prostaglandins), neuropeptides (e.g. substance P), cytokines, growth factors (e.g. nerve growth factor), and many others (reviewed in 3–5). These agents may either directly stimulate/sensitize the above itch-mediating sensory nerve endings to fire action potentials and to locally release various neuropeptides (such as substance P) (2,6); or the agents primarily act on skin mast cells, which are in close anatomical contact with cutaneous sensory afferents (7,8) and which release various substances (among which histamine functions as a key player) (9–11). These, in turn, initiate itch by stimulating the nerve fibers (3,4). Hence, the bi-directional sensory neuron – mast cell interaction is the central core of processes that give rise to the onset of pruritus.

From a medical point of view, itch – a key symptom associated with numerous skin disorders – may severely impair the quality of life and therefore mandates effective therapy. So, let's hear what your most clever suggestions for fighting pruritus are!

Juan (from Mexico, favorite leisure: cooking spicy food):

Well, Sir, my champion is capsaicin, the pungent ingredient of hot chili peppers (12). This natural product targets the vanilloid receptor-1 (or as recently termed, transient receptor potential vanilloid-1 receptor, VR1/TRPV1), a non-specific, calcium-permeable channel located on C-type sensory neurons (13,14). The activation of the receptor first excites these neurons (by initiating ionic fluxes and concomitant action potential firing and neuropeptide release) (14–16) and then, at higher doses and longer stimulation times, desensitizes the sensory afferents (16,17). This latter response provides the basis for the therapeutic application of capsaicin to mitigate pain and itch (16,18). That is, prolonged and/or repeated capsaicin application results in a depletion of neuropeptides such as substance P in the C-type sensory neurons, hence interrupting the unwelcome interplay between skin sensory neurons and mast cells (3,4,15–19). Indeed, topical capsaicin was shown to effectively prevent histamine-induced itch under experimental conditions (3,4,20). No wonder therefore that capsaicin is widely used in the therapy of pruritus in numerous skin diseases such as prurigo nodularis, notalgia paresthetica, pruritus ani, hemodialysis-related pruritus, uremic pruritus, etc. (3,4,18,19,21–25).

We should, furthermore, note, Sir, that recent findings provided a new 'hot' twist to the field. Namely, functional VR1/TRPV1 channels were described on numerous non-neuronal cell types (26–30) including, of greatest importance for our current debate, epidermal keratinocytes (31–35) and dermal mast cells (34,35)! In addition, it was also shown that the activation of the receptor, among others, results in the release of various cytokines and mediators from these cells that where shown to participate in itch sensation (26,28,29,33). So, what if topically applied capsaicin may not exclusively target sensory neurons, but also VR1/TRPV1-expressing mast cells and keratinocytes, and, hence, significantly alter the proposed neuronal – non-neuronal interaction network to terminate itch (34,35)? Indeed, the importance of keratinocyte-specific VR1/TRPV1 in pruritogenic dermatoses is suggested by the finding that the expression of the receptor is dramatically increased in epidermal keratinocytes of prurigo nodularis patients (35), a disease whose lead symptom (pruritus) and whose characteristic nodular skin lesions were very effectively normalized by topical capsaicin administration (19).

Another interesting dilemma: why capsaicin is often ineffective to alleviate the usually intolerable itch in atopic dermatitis (AD) patients (20,36)? Since both mast cell–sensory nerve contacts and neuropeptide contents are markedly increased in lesional and non-lesional skin of AD patients (37,38), one would expect a rather increased (but definitely not a decreased!) effectiveness of capsaicin to suppress itch. Thorough future investigations of possible alterations in the non-neuronal expression of VR1/TRPV1 in AD skin might help to clarify this conundrum.

Michel (from France, favorite leisure: thermal baths, spa activities):

In addition of the exogenous vanilloid capsaicin mentioned by Juan, let me supplement his statements: Naturally, there are also *endogenous* substances that activate/sensitize the VR1/TRPV1. The receptor was first described to be activated by low-threshold heat (43°C) and acidosis (13,14,16,17). Later, however, several other endogenous agents (collectively referred to as 'endovanilloids') (39) were shown to either directly activate the channel and/or, by initiating various intracellular signaling pathways, sensitize the VR1/TRPV1. These molecules are, for example, the eicosanoids (40,41), bradykinin (41,42), prostaglandins (40,43), and various neurotrophins (such as nerve growth factor, neurotrophin-3 and -4) (42,44), – exactly those pruritogenic agents, Sir, that you have listed in your introduction! In addition, it was also shown that the histamine-induced excitation of sensory neurons does involve the activation/sensitization of VR1/TRPV1 (45).

Taken together, these findings provide strong further support for the concept that VR1/TRPV1 is indeed a central integrator system in the itch pathway and therefore should be a key target of anti-itch therapy. However, this idea also suggests that, along with using the VR1/TRPV1 agonist capsaicin, in future clinical practice, we should also consider applying VR1/TRPV1 *antagonists* (such as capsazepine or iodo-resiniferatoxin) (46,47) to suppress itch.

Lars (from the Netherlands, favorite leisure: partying in Amsterdam):

And what about another, also very important endogenous signaling pathway, the cannabinoid system, which has a very intimate relationship with the VR1/TRPV1 signaling? Indeed, cannabinoid receptor-1 (CB1) agonists were shown to effectively suppress histamine-induced pruritus (48) suggesting the involvement of the CB1-related pathways in the initiation of itch. It is worth to note, however, that the CB1 and the VR1/TRPV1 show a marked colocalization pattern in the C-type sensory neurons (18). In addition, the endogenous cannabinoid substance anandamide, depending on its concentration and other local factors, may also stimulate VR1/TRPV1, acting as an 'endovanilloid' (39,49,50).

It is very likely therefore that CB1 ligands, at least in part, exert their antipruritic actions via stimulation of the VR1/TRPV1 pathway. Indeed, the effect of the CB1 agonist HU210 to attenuate histamine-induced itch was accompanied by a decreased neuropeptide release from the sensory endings (48), very similarly to the action of topically administered capsaicin (3,4,15–19). Finally, since cannabinoid receptors, very similarly to VR1/TRPV1, are also expressed by non-neuronal cell types of human skin (e.g. epidermal keratinocytes) (51,52), one would also propose their involvement in the neuronal–non-neuronal cellular network of pruritus pathogenesis.

Teacher:

Congratulations, guys, very nice ideas! Indeed, a possible therapeutic design 'to fight that nasty itch' would be the application of agents targeting the VR1/TRPV1 and/or CB1 systems. One noteworthy idea is the coadministration of VR1/TRPV1 agonists (such as capsaicin) and CB1 agonists. This approach, on the one hand, would result in additive efforts to alleviate itch. Since CB agonists (anandamide, HU210) were shown to prevent the excitation induced by capsaicin (53,54), the coapplication of the two agonists, on the other hand, would prevent the acute burning sensation initiated by capsaicin (which rises due to the activation of the nociceptive, but not pruritogenic, C-fibers).

Related to this latter phenomenon, let me conclude by adding a final thought to your wonderful summaries. The most notorious clinical limitation of capsaicin application is the capsaicin-induced burning sensation which is very often poorly tolerated by the patient (3,4,16,21). Therefore, another important goal would be to find and/or synthetically design VR1/TRPV1 agonists that cause only minor receptor excitation but still possess a significant desensitization power. A chief promising candidate to start the experiments with would be resiniferatoxin, another natural product of *Euphorbia resinifera* (a cactus-like plant) (16,17,55). Intriguingly, this VR1/TRPV1 agonist exerts a three-fold higher potency to induce desensitization (i.e. to treat pain and itch) than excitation (i.e. to induce pain) (16,17).

So, guys, this is it for today.

And, please, quit that enervating scratching, if you can . . . !

See you next week.

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Viewpoint 2

Itch (pruritus) is a symptom of many clinical disorders; it afflicts a large population of humans and is treated by a variety of pharmacological agents with variable success (1). Although little study has been devoted to the receptor/cellular mechanisms by which itch is provoked, recent pharmacological and neurophysiological studies have provided novel and exciting findings that should stimulate the skin-research community.

Itch is an unpleasant skin sensation leading to a desire to scratch. Researchers have expended a tremendous amount of effort to develop animal models of itch by measuring scratching behavior, but rodent models have largely proven unsatisfactory. Rodents do not display significant scratching responses when they are injected with substances known to induce itch in humans. For example, histamine has been widely used in humans to evoke itching sensation (2–4), but histamine does not evoke scratching in rodents (5,6). In addition, spinal administration of morphine evokes intense long-lasting itching sensation in humans (7,8), but spinal administration of morphine in rodents does not evoke profound long-lasting scratching (9,10).

On the other hand, a number of substances can evoke scratching in rodents (11), but some of these agents do not provoke scratching in primates (12). Species differences in the *in vivo* pharmacology of itch significantly contribute to different results and interpretations. The similarity and difference of receptor functions between rodents and primates should be carefully compared to develop hypotheses or make conclusions. Interestingly, serotonin (5-HT) provokes scratching in rodents (5,6), but 5-HT is weaker than histamine in provoking itch in humans (4,13,14). Furthermore, the fast onset and short duration of 5HT-induced itch in humans (4,14) is very different from the slow onset and long duration of scratching evoked by a large dose of 5-HT in rats (5,6). 5-HT in the periphery may induce more pain than itch in humans (14), and 5-HT receptors in the periphery also mediate hyperalgesia in rodents (15). Scratching in rodents may therefore not consistently reflect only itching. Some scratching responses in rodents can be attenuated by morphine, indicating that scratching sometimes represents a response to nociceptive stimulation in this species (16,17).

Non-human primates may be much better models for itching. Humans and monkeys have similar thresholds for detecting stimuli, and the neural systems responsible for these sensations in humans and monkeys are fundamentally similar (18). Monkeys have profound scratching responses when they receive either morphine or histamine, which are commonly known to induce itch in humans. Intrathecal administration of morphine induces both long-lasting (i.e. several hours) scratching and antinociception simultaneously in rhesus monkeys (19), and this observation parallels closely the behavioral effects of spinal morphine in humans (7,8). Intrathecal morphine probably produces the longest duration of substance-induced scratching observed in non-human primate models of itch (19,20). Intradermal administration of histamine into the hind limb of the monkey dose-dependently induces scratching (unpublished observations), and the duration (i.e. 15 min) of histamine-induced scratching in monkeys is similar to that reported in humans (2–4).

Taken together, drug-induced scratching in monkeys may represent a valuable model for the study of the function and behavioral effects of specific receptors that may mediate itch in humans. The monkey model has been providing answers to many of the questions raised about itch and may be able to answer many more. It has been suggested that itch can be inhibited by an enhanced input of painful stimuli and inhibition of pain may induce itch (21).

However, this theory cannot be applied to all opioid analgesics. Mu opioid receptor (MOR) agonists induce antinociception and scratching, but kappa opioid receptor (KOR) agonists or delta opioid receptor (DOR) agonists produce antinociception without provoking scratching in monkeys (20). It has been demonstrated that MOR in the central nervous system, but not KOR or DOR, is the primary mediator of itch associated with opioid analgesics in primates (20). Although itch-selective spinal neurons have been identified based on histamine-evoked responses in cats (22), it is not clear how these neurons respond to opioid analgesics.

Neurophysiologists have tried to identify the existence of pruriceptive neurons that respond specifically to pruritogenic as opposed to algogenic stimuli. Histamine-sensitive primary afferents in humans were recently found not to be specific for itch as these neurons also responded to painful chemical agents such as capsaicin (3,14). Similarly, nearly all spinothalamic tract neurons recorded in a monkey study exhibited vigorous and persistent responses to capsaicin and were neither specifically nor selectively responsive to histamine (23). Perhaps capsaicin cannot be used solely as a painful stimulus because capsaicin may also act as a pruritic stimulus (24). It is interesting to note that topical capsaicin can be used as both an analgesic and an antipruritic (24,25). Capsaicin acts as an agonist at the vanilloid receptor subtype 1 (VR1/TRPV1) (26), which is widely distributed in the human skin (27). Sensory dysfunction following capsaicin application results from nearly complete degeneration of epidermal nerve fibers (28). It will be valuable to investigate the role of VR1 in itch by using selective VR1 agonists and antagonists in monkeys.

What has the monkey model told us about the pharmacotherapy of chronic itch? Treating refractory itch has been a challenge in the clinics. The role of histamine may be minimal in chronic itch. Tachyphylaxis quickly develops to histamine-induced itch, and antihistamines are not effective in most dermatoses, systemic disease, and spinal opioid-induced itch (1). The KOR may be a prominent potential therapeutic target because several studies suggest that agonists at this receptor may be useful treating refractory itch. One potentially relevant finding was that scratching was a prominent withdrawal sign in monkeys treated chronically with and withdrawn from a selective KOR agonist (29). Many withdrawal symptoms from opioids appear to be opposite to the acute effects of agonist administration (30). Excessive scratching activity observed in KOR withdrawal indicated that acute administration of KOR agonists might have antipruritic function. Animal studies seem to support this notion, as systemic administration of KOR agonists inhibited scratching evoked by pruritogenic agents without interfering with locomotor activity in rodents (31,32). A recent study also demonstrated that non-sedative doses of a KOR agonist can attenuate intrathecal morphine-induced scratching without interfering with antinociception in monkeys (12). More important, these animal studies have led to a successful clinical trial of a novel KOR agonist, TRK-820, in hemodialysis patients suffering from uremic pruritus (33). The pharmacological profile of TRK-820 is different from that of prototypical KOR agonists such as U-50488H because TRK-820 also has MOR antagonist actions (34). Nevertheless, the findings of a good antipruritic effect with this compound encourage evaluation of other KOR agonists in non-human primates, and eventually in humans as well.

It is worth noting that opioid receptor antagonists produce parallel rightward shifts in dose–response curves of morphine-induced scratching (10,19). These observations indicate that antipruritic effects of naltrexone or nalmefene are derived at MOR by a competitive and reversible MOR antagonist action. In contrast, KOR agonists produce downward shifts in the dose–response curve of morphine-induced scratching, and the antipruritic actions of KOR agonists can be reversed by a selective KOR antagonist (12). These observations indicate that KOR agonists do not produce MOR antagonism, but inhibit MOR-mediated itch specifically through KOR activation. To date, the neurobiological mechanisms of the interaction between MOR and KOR in itch-selective neurons remain unclear. It is possible that activation of KOR in specific sensory neurons produces the antipruritic effect. Therefore, it is pivotal to verify whether KOR agonists have a broader application as antipruritics in primates. There are different pharmacological properties among a variety of KOR agonists (e.g. KOR subtypes, centrally vs. peripherally acting) (35,36). Future studies are required to establish different itch models in monkeys and to investigate the types of KOR agonists that have antipruritic effects against itch evoked by other pruritogenic agents in primates. These studies will provide a substantial contribution to the *in vivo* pharmacology of itch and offer functional evidence of KOR agonists as a new generation of antipruritics in humans.

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Viewpoint 3

Itch and pain use many body tools together: receptors of both sensations are ramified endings of the thinnest ($<1\,\mu m$) unmyelinated nerve fibers which conduct onto the spinal cord with velocities of less than 1 m/s. In the spinal cord, already at the level of entrance, they synapse with other afferent and efferent systems leading to scratch and flare reactions. Both pain and itch are projected toward the diencephalon through the so-called lateral system of somatosensation (1) and are turned over to the cortex in unspecific thalamic areas, such as the intralaminar and mediodorsal nuclei.

Cutaneous C-fiber inputs have not yet been shown to reach primary somato-sensory fields, true for pain and itch messages, but do clearly activate the cingulate cortex. Here is, presumably in intimate connections with the parietal lobe, the final associative processing in the cortex, which evaluates the 'nasty' emotional character of pain and itch (2). These brain structures are governed by the prefrontal lobe, which controls the threshold for tolerating and enduring the unpleasantness of pain and itch.

Because of these similarities, the question arose whether itch might be a submodality of pain. To challenge this idea, I suggest using analogue definitions: itch vs. pain on the subjective level, pruritoception vs. nociception for the afferent system, pruritofensive vs. nocifensive reactions for the efferent system.

Our knowledge in neuroanatomy, physiology, and psychology of pain has enormously accumulated in the past three decades, including the development of pharmacological and physical therapy, matching today that of all other sensory systems, such as vision, hearing, or mechanosensation. In contrast, however, itch still is a mystery. What actually causes itch, and for what reason? How can we measure itch? Are there similar aspects, such as the sensory-discriminative, emotional-affective, autonomous, and motoric components, as has been carefully described by questionnaires and evaluated by therapists in case of pain?

Let us again start with the periphery: Could it be that pain and itch use the same C-fibers as assumed by the majority of neurophysiologists? Already von Frey suggested that discharge frequency of action potentials in same fibers may differentiate between itch and pain: low-frequency firing causes itch, high-frequency discharges cause pain. This simplistic concept was ruled out by means of microstimulation in awake humans: thin needle electrodes were fed into the nearest neighborhood of cutaneous C fibers; stimulation with different frequencies always caused pain of various strength, but never itch (3). Moreover, recordings in single C-fibers proved that there are 'sleeping' itch afferents, which can only be waked up by histamine, the best experimental itch stimulus. Nevertheless, personally, I am not completely convinced of the idea of itch-specific afferents, because from my own human physiological experiments over many years with microelectroneurography, I am aware of the difficulty of an unambiguous coordination of single-fiber discharges and over-all sensation (4).

The mechanisms at entrance level in the spinal cord, too, provide little help to distinguish between pruritoception and nociception. In both cases, we see similar autonomous skin reactions to C-fiber input: smooth muscle relaxation of local blood vessels increases local blood flow, which causes reddening. Let us never forget: all itching dermatoses are inflammatory! The size of the flares, by the way, seems to correspond to the skin patches innervated by the sum of the branches (receptive field) of the single C-fiber: if one branch is affected, the elicited action potential depolarizes recurrently all other branches of the field, and depolarization opens channels for intracellular prostaglandins. This idea is supported by the fact that receptive fields in the periphery are much smaller than near, or at, the trunk; the same is true for flare reactions (5). Skeletal muscle reflexes are not initiated by spinal C-fiber input, neither in case of pain nor of itch. In contrast to nociceptive A-delta-fibers, C-fibers do not synapse with motor neurons at the level of spinal entrance. In fact, it is a hopeless endeavor to try escaping from torturing itch or pain by flight. All escape reactions to C-fiber input are supraspinally coordinated behavioral reactions.

In 1965, the gate control theory of pain was born, making its parents the best-known pain researchers in the world: Ron Melzack became president of the International Association for the Study of Pain (IASP, which sports by now more than 20 000 members). Pat Wall was elected livelong chief editor of the

famous journal *PAIN*, thus influencing profoundly the course of pain research. The gate control theory explained the well-known fact that rubbing of hurting sites of the body relieves pain by inhibitory interactions between myelinated and unmyelinated fibers. However, how important is this interaction really in case of itch?

We all know that the scratching that we engage in so as to relieve itch is a strong pruritofensive reaction, which may even lead to severe skin damage, along with bleeding and superinfection. An equivalent of such strong nociceptive reactions in the field of pain research is never or only very rarely described in the literature. Moreover, cold can clearly relieve itch, as has also been shown experimentally: A-delta-fibers activated by cold stimuli inhibit histamine-induced C-fiber activity (6). This is, in principle, also true for pain, but there cold helps only in special cases. No wonder that the German word 'jucken' means both, itch (intransitively) and scratching (transitively). One really wonders why no dermatologist has described this evident and crucial neurophysiological fact of itch before 1965, i.e. before the advent of the gate control theory of pain.

And there is yet another intriguing mechanism open for itch research: the descending noxious inhibitory control (DNIC), which starts in the midbrain and attenuates the pain message already at the level of entrance by descending fibers in the antero-lateral spinal tract (7). An analogue DPIC (with P standing for pruritus) has not yet been described for itch – as far I know, and one really wonders whether there is something like a DPIC that could be targeted and exploited therapeutically. The DNIC system ensures that permanent noxious input will be reduced by supraspinal mechanisms, which are controlled by the prefrontal lobe. The DNIC system is also the essential site of analgesic action for the gold standard in pain therapy, the narcoanalgesic morphine or its endogenous counterparts, endorphins and enkephalins. Morphine attenuates pain by activating the DNIC system. But it induces itch! Does this fact support the idea that itch is a prepain sensation? In the sense, that the torturing sensation-itch appears, when C-fiber-mediated pain is attenuated?

Yes, there are more findings, which prove transitions between itch and pain. Our institute developed the infrared laser heat pulse in order to selectively activate (A-delta- and) C-fibers in pain research (for review see, 8). To open new clinical fields for laser applications, we applied laser stimuli to patients with atopic dermatitis who suffered from unbearable itch, some of them scratching the skin bloody and running the risk to commit suicide. The idea was that subthreshold painful laser stimuli applied to any itching skin site might enlarge itch-inducing C-fiber activity just above the pain threshold, thus down-modulating the unbearable itch to a tolerable, tiny pain sensation and this idea seems to work! Several patients came back after a week or so asking for a further laser treatment. We have not published these observations so far, but I would be very pleased if somebody asks me to cooperate with him toward a further exploration of this concept.

Of course, as everybody knows, on the supraspinal, in particular cortical and subjective levels there are overwhelming differences between the feeling of itch and of pain. Most interestingly, the well-introduced pain questionnaires and diaries, which are used in every pain practice or pain clinic, do not work well in the case of itch! We developed the Eppendorf Itch Questionnaire (9) in analogy to Melzack's McGill Pain Questionnaire: the result of a 3-year monitoring with more than 100 patients was that by far most patients were not interested at all in describing carefully the kind, strength, or character of their itch, its time dependency, circadian rhythms, or its modulation by food or stress; they only wanted to get rid of their torture, describing itch in very simple words. Altogether we got the impression that itch is indeed a very protopathic sensation comparable to hunger or thirst and that itch patients are much simpler in reflecting their illness than pain patients who stress the doctor with the description of their aching torture in unending detail.

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Viewpoint 4

Histamine-sensitive, mechano-insensitive unmyelinated afferent nerve fibers have been identified that convey histamine-induced itch, and it has become clear that a specialized neuronal pathway for itch distinct from pain processing exists (1,2). However, antihistamines do not relieve chronic itch in many patients, suggesting that histamine is not the main mediator. Moreover, in atopic dermatitis, one of most abundant pruritic diseases, itch can often be induced mechanically (3), which contrasts the mechano-insensitivity of the histamine-sensitive C-fibers (1,2). Activation of mechano-insensitive fibers also has been shown to evoke a widespread axon reflex erythma (4), which is absent in itch induced by papain (5) and also in some clinical itch conditions.

Thus, although we have identified one itch pathway, it is insufficient to explain all the clinical itch phenomena neither to serve as the only basis for an antipruritic therapy.

Sensitization to itch

Increased intradermal nerve fiber density has been found in patients with chronic pruritus (6). In addition, increased epidermal levels of neurotrophin 4 (NT_4) have been found in patients with atopic dermatitis (7), and massively increased serum levels of NGF and Substance P have been found to correlate with the severity of the disease in such patients (8). Increased fiber density and higher local NGF concentrations were also found in patients with contact dermatitis (9). It is known that NGF and NT_4 can sensitize nociceptors.

These similarities between localized painful and pruritic lesions 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 itch. Activity in chemo-nociceptors leads not only to acute pain but, in addition, can sensitize second order neurons in the dorsal horn, thereby leading to increased sensitivity to pain (hyperalgesia).

In itch processing, touch or brush-evoked pruritus around an itching site has been termed 'itchy skin' (10,11). It requires ongoing activity in primary afferents and is most probably elicited by low threshold mechanoreceptors (A-β fibers) (11,12). Also, more intense prick-induced itch sensations in the surroundings, 'hyperknesis', have been reported following histamine iontophoresis in healthy volunteers (13).

The existence of central sensitization for itch can greatly improve our understanding of clinical itch. Under the conditions of central sensitization leading to punctuate hyperknesis, 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 (14). Furthermore, acetylcholine provokes itch instead of pain in patients with atopic dermatitis (15), 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 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 (16,17). This phenomenon is of special interest as it demonstrates spinal hypersensitivity to C-fiber input. Conversely, normally painful electrical, chemical, mechanical, and thermal stimulations are perceived as itching when applied in or close to lesional skin of atopic dermatitis patients (18).

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 long (19). Long-lasting activation of pruriceptors by histamine has been shown to experimentally induce central sensitization for itch in healthy volunteers (18). Ongoing activity of pruriceptors, which might underlie the development of central sensitization for itch, has already been confirmed microneurographically in a patient with chronic pruritus (20). Thus, there is emerging evidence, for a role of central sensitization for itch in chronic pruritus.

As there are many mediators and mechanisms, which are potentially algogenic in inflamed skin, many of them could provoke itch in a sensitized patient. Thus, a therapeutic approach, which targets only a single pruritic mediator, does not appear to be promising for patients with chronic pruritic skin 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.

In summary, we are beginning to expand our knowledge from experimental models to clinically relevant itch conditions. Although some progress has been made to date, we do not have a clear basis for mechanism-oriented treatment of itch. However, the close relation between central sensitization in chronic itch and chronic pain implicates that also similar therapeutic approaches such as gabapentin (21) or clonidine (22) might be beneficial for the treatment of neuropathic itch.

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Viewpoint 5

Enter the proteases!

During the last decade, scientists have learned that proteases are more than just agents of destruction in the extracellular space. Here, we argue that proteases deserve much more careful scrutiny in dealing with the problem of itch pathogenesis and improved itch management.

Proteases have become appreciated as signaling molecules. They signal by activating cell-surface receptors, thereby inducing a cascade of intracellular signals. Nature has developed several

strategies to signal to cells via proteases, by (a) conventional binding and activation (plasmin-activator receptor), (b) cleavage of a protein which subsequently activates a receptor, or (c) nibbling off a part of the extracellular domain of a receptor which activates the same (autoactivation) or the neighbored (transactivation) receptor (proteinase-activated receptor) (PAR) (1). The fact that approximately up to 1200 genes (4.5% of the human genome) encode proteases in the human gene and 475 proteases are described in the human body reflects the impact of proteases as signaling molecules in the body under physiological and pathophysiological conditions.

We differentiate between serine proteases, cysteine proteases, aspartic proteases, and metalloproteinases. They are generated by many skin cells, including epithelium, endothelium, leukocytes (T cells, mast cells, eosinophils, and neutrophils), bacteria, fungi, and viruses, some of them with a potential contribution to nerval stimulation (2,3).

Proteases involved in pruritus

A role of proteolytic enzymes for the induction of pruritus in humans was already suggested about 50 years ago (4–6). In 1955, Arthur and Shelley demonstrated that cutaneous injection of one spicule with friction or pressure led to a burning itch lasting up to 30 min even when the spiculae were immediately removed from the skin by washing or by applying an adhesive tape (1,2). Mucunain, a protein with endopeptidase and dipeptidase activity, was identified as the active pruritic agent. The protein was extractable only from the spicules using aqueous solutions and could be inactivated by autoclaving, changing the pH, or using a similar denaturing process that did not change the spicule structure. Further investigations confirmed the biochemical nature of this pruritic agent, identified as a thermolabile protein with a molecular weight of 40 000 (7). Depletion of mast cell histamine prior to the injection of trypsin or chymase markedly abrogated the itch response suggesting a role of trypsin and chymase as histamine liberators (4,6).

Thereafter, a variety of proteases were identified to be pruritogenic in humans *in vivo* including trypsin (8–10). Moreover, Hagermark and co-workers (11) postulated from their findings that serin proteases such as trypsin and mast cell chymase provoke itching and visible changes (edema, flare) when injected intracutaneously. Interestingly, injection of the cystein protease papain also provoked itch. Moreover, pretreatment with compound 40/80 did not influence papain-elicited itch indicating that papain-induced itch is independent from the release of histamine (12).

Thus, a direct role of proteases on primary afferent nerves could not be excluded although the proteolytic effects were merely interpreted as 'toxic agents' on 'free' sensory nerve endings. Later, from human studies with patients suffering from atopic dermatitis (AD), we learned that protease inhibitors such as epsilon-amino-caprinoic acid have beneficial effects for the treatment of pruritus in AD patients, although more efficient when combined with antihistamines than alone (13). In support of this idea, a specific mast cell chymase inhibitior, Y-40613 was tested in a mouse pruritus model. Y-40613 dose-dependently suppressed the scratching response, strengthening the hypothesis that chymase directly contributes to the development of pruritus (14). (Table 1).

Proteinase-activated receptors

On a receptor level, most evidence for a receptor-mediated effect of serine proteases on pruritus comes from studying PARs. PARs are G protein-coupled receptors with seven transmembrane domains. These receptors are activated by a unique mechanism where proteinases hydrolyze, at a specific cleavage site, the extracellular amino terminus of the receptor. This cleavage exposes a new amino terminus that acts as a tethered ligand, which binds intramolecularly to initiate cellular signals (15,16). Short synthetic peptides based on the tethered ligand sequences of the different PARs (PAR-activating peptides: PAR-APs) mimic the effects of proteinases, activating selectively the different members of the PAR family. Four PARs have been cloned thus far: PAR_1, PAR_3, and PAR_4 are targeted by thrombin and cathepsin G (PAR_4) while PAR_2 is activated by trypsin, mast cell tryptase, and other endogenous or exogenous serine proteases of different origin (3). To a lesser extent, other proteinases like factor Xa, cathepsin G, plasmin, and granzyme A are also capable of activating PARs. The development of receptor-selective PAR-APs has allowed accurately discerning the physiological consequences of PAR activation *in vivo*, describing a role for PARs in platelet activation, vascular functions, inflammatory or even nociceptive responses. PAR_4 was the most recent member of the PAR family that has been described. With exception of a clear role in thrombin-induced human platelet activation, very little is known about the physiological and pathophysiological importance of PAR_4.

PARs are highly expressed in the nervous system. Both PAR_1 and PAR_2 have been described in neurons and the brain (17–21). Only recently, expression of PAR_1 and PAR_2 on neurons of the peripheral nervous system has been revealed. Both PAR_1 and PAR_2 were localized in guinea-pig enteric neurons (22). Activation of isolated myenteric neurons by thrombin, trypsin, tryptase, PAR_1-AP and PAR_2-AP resulted in calcium signal in more than 50% of isolated neurons. More than 60% of guinea-pig enteric neurons expressed PAR_1 and PAR_2. A large portion of these neurons also expresses neuropeptides such as substance P or vasoactive intestinal peptide and neurotransmitters such as nitric oxide and respond to adenosine triphosphate (22). Moreover, agonists of PAR_1, PAR_2, and PAR_4 evoke depolarizing responses in Dogiel multipolar morphologic type II neurons with AH-type electrophysiologic behavior and Dogiel uniaxonal morphologic type I neurons with S-type electrophysiology (2). Importantly, functional PAR_1 and PAR_2 are present on primary spinal afferents, where their activation causes rapid intracellular calcium mobilization (21,23,24). In serial sections of human renal peripheral nerves, differential PAR expression was observed in healthy donors. Interestingly, PAR_4 appears to be the most abundant PAR present in this particular peripheral nerve (2). PAR expression patterns in human and murine skin have not

Table 1. Proteases identified in the stimulation of itch and inflammatory skin responses

Protease	Specification	Species	Reference
Mucunain	Itch	Human	5, 6
Trypsin	Itch, erythema, wheal, flare	Human	9, 11
Mast cell chymase	Itch	Human	11
Kallikrein	Itch	Mice	Ny A Acta Derm Venereol. 2004; Hägermark Ö. Acta Derm Venereol. 1974
Papain	Itch	Human	11
Tryptase/Trypsin (Synthetic PAR2 agonist, SLIGKV)	Itch, pain, erythema	Human	27

been fully explored yet, under normal and pathophysiological conditions.

PARs and itch

Recently, PAR_2 has been localized on rat sensory neurons (25). Moreover, functional data strongly support the idea that the peripheral nervous system is directly regulated by PAR_2 during neurogenic inflammation, pain, and pruritus (21,26,27). In rat skin, PAR_2 is localized on approximately 63% of primary afferent sensory neurons, 30–40% of them colocalizing with SP or calcitonin-gene related peptide (CGRP). Later, PAR_1 was described to contribute to neurogenic inflammation in murine skin (24). In rat skin, neuropeptides such as calcitonin gene-related peptide and substance P from primary spinal afferent neurons are known as important mediators of neurogenic inflammation and pain and probably contribute to pruritus. We speculated that serine proteinases including PAR_2 agonists may activate PAR_2 on sensory neurons to trigger itch in AD patients based on the following facts: there exists a close proximity of tryptase-containing mast cells to spinal afferent fibers and agonists of PAR_2 cause effects similar to those of tryptase in many tissues, comprising many of the characteristics of itching.

Itching is one of the most frequent symptoms in dermatologic diseases and accompanies inflammatory and immune responses of many diseases such as AD, hypersensitivity reactions, or urticaria, for example. Indeed, neuronal PAR_2 appears to be involved in the induction of pruritus in human skin (28). Importantly, the endogenous PAR_2 agonist tryptase was increased up to fourfold in AD patients, and PAR_2 expression was markedly enhanced on primary afferent nerve fibers in lesional skin biopsies of AD patients. In contrast, no significant differences in histamine concentrations were observed between AD patients and healthy controls.

On this background, one may speculate that tryptase may be more important for the transmission of itch responses in AD than histamine. Intracutaneous injection of specific PAR_2 agonists provoked enhanced and prolonged itch when applied intralesionally. These effects were not diminished when cetirizine, a histamine type-1 blocker, was used indicating the specificity of these effects. Additionally, this observation may also explain why antisedative histamines are poorly effective in AD patients (29). Thus, PAR_2 activation on cutaneous sensory nerves may be a novel pathway for the transmission of itch and inflammatory responses during AD and probably other skin diseases. PAR_2 antagonists may be promising therapeutic targets for the treatment of pruritus (28).

We postulate that different qualities of itch exist among various diseases based on the inducing 'itchy' molecule (histamine, tryptase, cytokine, protons, etc.) and the corresponding receptor on primary afferent neurons. In other words, in order to treat pruritus, future investigations have to focus on the characterization of the crucial molecules/receptors in each itchy disease.

Future aspects

After the unexpected discovery of proteases as mediators of G protein-coupled receptors and their role during inflammation, immunity, tumor growth, and now itch, our view about proteases is more astonishing than ever. Besides neuropeptides, cytokines, amines, and kinins, serine proteases enter the stage as mediators of neuronal regulation. Using specific synthetic agonist peptides, PAR_2 has been identified as a novel receptor for itch responses on primary afferent sensory nerves of patients with AD.

This observation expands our knowledge of potential classes of itch mediators and supports the idea of a complex and multidimensional itch system. In particular, this implies that distinct itch mediators may be of differing relative importance during defined pruritic skin diseases (prurigo, AD, urticaria, renal pruritus, etc.). Thus, future research will have to focus on the different molecules that regulate the itch responses in a particular disease and will have to work out the underlying mechanisms that are crucial for the transmission of itch on the molecular level. With regard to PARs, further studies are necessary to fully explain the underlying direct or indirect effects of PAR_2-induced itch. For example, neuropeptides released from neurons upon PAR_2 stimulation may activate the release of nociceptive mast cell mediators such as kinins or prostanoids (30).

We conclude that, in certain pruritic skin diseases and under defined circumstances, endogenous serine proteinases (including tryptase) as well as exogenous proteases may activate PAR_2 on cutaneous sensory nerves, thereby mediating itch. Beyond this scenario, proteases may also induce itch responses by other mechanisms or as yet unknown 'protease-receptors' by activating specific intracellular signal transduction pathways (e.g. chymase). This will be a fascinating field within the 'itch research community' in the future.

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Commentary 1

Itch, defined by Hafenreffer (1) as 'an unpleasant sensation that provokes the desire to scratch', is considered the hallmark of skin diseases such as atopic dermatitis, contact dermatitis, and urticaria. It greatly affects the quality of life of patients suffering from any of the abovementioned diseases, and although to some extent the cycle itch–scratch becomes enjoyable for those that itchness can be controlled; an intense, persistent, and nasty itch can cause considerable morbidity to the affected ones and to the people around them.

Itch treatment is still a subject to be investigated more thoroughly. If we consider that both the etiology and pathophysiology of itch differ according to the type of the disease to which it is related (2) and that there is a variety of chemical mediators and receptors involved in the pruritic responses (3–5), then it is not very difficult to figure out why the alternatives to treat itch-associated diseases increase as the research in this field deepens.

If we refer to the data obtained in our laboratory, it is possible to say that H1 antagonists such as chlorpheniramine and diphenhydramine showed significant inhibition of itch induced by compound 48/80 in BALB/c mice (6), but failed to inhibit itch induced by the H3 antagonists iodophenpropit and clobenpropit (histamine and substance P releasers) in mast cell-deficient mice and their normal littermates (7). Loratadine, fexofenadine, and chlorpheniramine were also tested in antigen-antibody-induced scratching behavior in ICR mice. All the drugs decreased the elicited pruritus, but only loratadine showed significant inhibitory effects.

Going through a list of different receptors potentially involved in itch, there is evidence that – even though chemical mediators such as leukotrienes and thromboxanes have been suggested to be involved in pruritus-associated responses – zafirlukast as well as ramatroban failed to inhibit scratching behavior induced by iodophenpropit and clobenpropit in mast cell-deficient mice. On the contrary, good results were obtained with the mast cell stabilizer tranilast, which significantly inhibited compound 48/80-induced itch in ICR mice (6).

Immunomodulatory therapy has also been established for the treatment of allergic diseases. Regarding skin disorders, the immunosupressants tacrolimus and pimecrolimus have been reported to be effective as antipruritic agents (8,9).

The reports related to the treatment of itch by natural products are increasing in a considerable fashion. Propolis, a substance made by honeybees to protect their hives, inhibited compound 48/80-induced but not histamine-induced scratching behavior in ICR mice (10). Similar results were observed with the flower extract of German chamomile in ddY mice (11).

There are, indeed, many different ways to treat itch; but which one is the best? Antihistamines, immunomodulatory agents, and even traditional medicine show different perspectives depending on the situation in which they are analyzed. There lies the answer: the best way to treat that nasty itch varies upon the influence of many factors and this is the reason why the interaction of patient-drug-physician as well as the creation of unique combined therapies for each individual are of great importance.

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Commentary 2

If ion-channel proteins discretely encode temperature sensations (1,2), one would intuitively expect drug activation of cool and cold receptors (e.g. TRP (transient receptor potential)-M8, TRP-A1) to functionally suppress irritation, pain, and itch. Cold temperatures and menthol have some antipruritic activity, but for nasty itch, you want a drug that is more powerful.

Icilin (Fig. 1) is qualitatively different from menthol in its pharmacology; hence, direct comparison of potency between the two is spurious (3–6). However, on common bioassay endpoints such as 'wet-dog shake behavior' (7) and calcium entry into cells expressing the cool receptor TRP-M8, icilin is 400–800 times more active than menthol. Icilin administered into the oral cavity produces sensations of cold in humans, but such sensations were not obtained when a 5% wt/vol solution in dimethylsulfoxide was applied to the forearm skin (7). Surprisingly, 2% icilin in Aquaphor® ointment was found to suppress pruritus when applied on the legs of a woman with xerosis, on the hands of a man with atopic dermatitis, on the anus of a man with hemorrhoids, and on the lips of a man with onset of cold sores. The icilin ointment had no odor or irritancy and its duration of action was 3–5 h. Such results motivated studies on the activity of icilin in an animal model of itching.

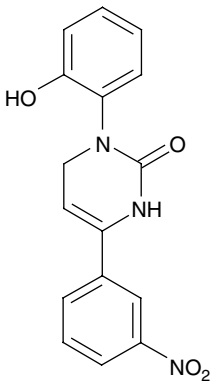

Figure 1. Icilin. Synonyms: AG-3-5, 3,6-Dihydro-1-(2-hydroxyphenyl)-4-(3-nitrophenyl)-2(1*H*)-pyrimidinone, 1-[2-hydroxy]-4-[3-nitrophenyl]-1,2,3,6-tetrahydropyrimidine-2-one.

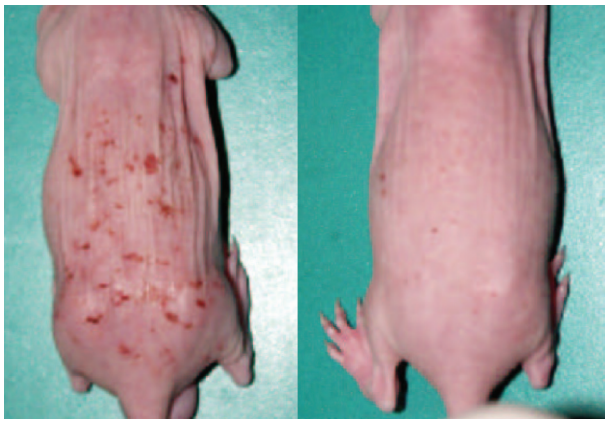

Figure 2. Hairless hypomagnesemic rats on day 5 of treatment. Left panel: vehicle-treated animal with severe bite and scratch marks, taken as signs of generalized pruritus; right panel: animal treated topically once daily with 2% icilin lotion.

Weaned hairless rats maintained on a diet low in magnesium develop a transient erythematous maculopapulous rash with signs of generalized pruritus (8,9). The rats scratch and bite themselves leading to skin lesions (Fig. 2, left panel). Icilin, as a 2% powder suspended in Walgreens Advanced Care Lotion, applied once daily for 5 days significantly reduced bite and scratch marks in each animal (Fig. 2, right panel). Reduction in diseased animals was already observed after the first application and was overall 52% relative to vehicle-treated control animals (mean of 24 animals examined for 5 days in three independent studies). Worth mentioning, erythema was not inhibited and signs of pruritus returned upon cessation of treatment. The animals exhibited transiently 'wet dog behavior' after application of icilin at the tested concentration.

Preliminary studies showed that the single oral median lethal dose of icilin in male and female mice and rats was 5–7 g/kg body weight, putting icilin into the category of a chemical with slight toxic potential for short-term effects (10). Purified icilin was not mutagenic in the Ames test system in strains TA 97, 98, 100, 102, 1535, 1537, 1538, with or without liver enzyme activation. Icilin is virtually water-insoluble; hence, administration of icilin onto the rectal mucosa of animals did not raise plasma levels above 1 µg/ml.

Now the stage is set for the entrance of new players – clinical dermatologists – who must tell us if topical icilin or a related pyrimidine-2-one analog really manages to suppress that nasty itch.

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Commentary 3

The sensation of intense 'itch' (pruritus) can reach a level of suffering that approaches that of pain or suffocation. Nonetheless, there are numerous patients with pruritus whom we are unable to treat effectively. If histamine is the main mediator of itch, antihistamines are effective. But this case is not as frequent as often assumed. Indeed, the nasty sensation of itch and its control are associated with many other pruritogenic substances, such as neuropeptides (mainly opioids), acetylcholine, serotonin, interferons, interleukin-2, eicosanoids, and/or enzymes (e.g. tryptase).

Recent findings have shown the importance of these other substances and have explored the course of itch. A better understanding of the pathophysiology of itch will also allow the discovery of new treatments. Hence, we know the activated areas in the brain when itch occurs and the existence of specific histaminergic neurones in spinal cord and in the skin. The main unresolved question is: Where in the skin is pruritus 'born'? Is it in the epidermis, the dermis, or in the basal membrane? Also, though significant progress has been made in research on pruritus during the past decade, a major hindrance is the lack of *in vitro* model for studies on this topic. In therapeutic itch research, another major brake on progress is the confusing effect of placebo on pruritus, which could be (1) about 66%!

Currently and in the future, creams containing local anesthetics (2), glycocolle, oligosaccharides (3), calamine (4), capsaicin, doxepin (5), strontium nitrate (6), or nedocromil sodium (7) may all be helpful in the treatment of itch. But it is not possible to apply them on large surfaces. After steroids, new treatments such as tacrolimus and pimecrolimus appear as effective treatments of pruritus (8). Itch is often widespread, justifying the use of systemic treatments. Antihistamines anti-H1 are the reference treatment. But they are ineffective in numerous diseases. Nowadays, there is no real alternative. But I think that new therapeutic ways are hopeful. In my opinion, the most interesting is opiate antagonist. Naltrexone, which is available per os, could be a promising treatment (9,10). Gabapentin and its family represent another interesting field of research. H3 agonists might be also useful (11), but antiserotonines (anti-SSTR3) are disappointing. Cyclosporine is effective not only in atopic dermatitis and pruritus, but also in non-inflammatory circumstances, like the 'rebel' senile pruritus (12). Thalidomide might be helpful, but its prescription is excruciatingly regulated.

The psyche is not only involved in psychogenic pruritus but in all pruritus. Indeed, anxiety or depression is known to modulate the burden of itching, and the thresholds of perception and tolerability are variable according to each patient. Psychological interventions, like cognitive-behavioral methods, hypnosis, or biofeedback could be probably helpful in some patients (13). Psychotropic drugs, like hydroxyzine, doxepin, fluoxetine, paroxetine, or sertraline exert both antipruritic and psychic effects.

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Commentary 4

Itch is related to pain. Just like in pain research, it is important to distinguish different kinds of pruritus. The causes and consequent therapeutic strategy for acute itching will not be the same as in chronic itching. An acute itching in urticaria seems to be histamine dependent. However, a chronic itching in atopic dermatitis or prurigo will involve several different inflammatory molecules and neuropeptides, such as opioids. We will look into some of the controversies on opioids.

Opioid receptor antagonists have successfully been used to treat several different pruritic conditions such as atopic dermatitis (1), cutaneous lymphoma, dry skin dermatitis, amyloidosis, psoriasis, prurigo nodularis (2), and hepatogenic pruritus (3). Some authors suggest that the opiate receptor system is more important in induction of chronic itch in atopic dermatitis than the histamine system (4).

However, there are two major controversies involving opioids and itching.

1. Can opioids induce itching independently from histamine? Some groups suggested that the opioid-induced itching in the periphery is only due to opioid-induced histamine release from mast cells in the dermis. However, in a placebo-controlled, double-blind study on histamine-induced focal itch and alloknesis with healthy subjects using the opioid receptor antagonist naltrexone and the H_1-blocking agent cetirizine, naltrexone was found to reduce significantly both itching and alloknesis. Cetirizine reduced focal itch but failed to influence the alloknesis phenomenon involved in chronic itch in atopic dermatitis (5). In a dry skin mouse model for chronic itching, there was no apparent difference of spontaneous scratching between mast cell-deficient mice and normal littermates. Subcutaneously administered opioid antagonists significantly suppressed spontaneous scratching in the dry skin model mice. These results could explain why non-sedative, second and third generation H_1-antagonists have very limited effects on chronic itch and support the hypothesis that there is indeed an important histamine-independent opioid-induced pruritus.
2. Do opioids induce itching only in the central nervous system (CNS) or are the nerve endings in skin involved as well? Although several authors describe an important role of opioids in the induction of itch, most of them believe that this effect is limited to the CNS. However, methylnaltrexone significantly decreases opioid-induced pruritus without affecting analgesia (6). Methylnaltrexone is a novel quaternary deriative of naltrexone that does not cross the blood–brain barrier and acts as a selective peripheral opioid receptor antagonist. Our own studies strongly suggest that epidermal opioid receptors are involved in chronic itching in atopic dermatitis and prurigo. We discovered a functional active opioid receptor system in human skin, including peripheral nerve endings and keratinocytes (7,8). Additionally, we observed an internalization of the μ-opiate receptors on keratinocytes in atopic dermatitis. The free opioid receptor ligands bind to the receptors on the thin and stretched peripheral nerve endings in hypertrophic epidermis in chronic dermatitis. This could lead to a strong itch signal to the CNS, where it will be further processed (8). We performed clinical studies using topically applied opioid receptor antagonists to treat chronic pruritus. The results show an increase of μ-opiate receptor expression in keratinocytes and a change of the nerve quality in the epidermis after local treatment. These changes correlated with the clinical response to the topically applied drug (unpublished data).

Just recently we postulated the 'Layer Hypothesis' as our working hypothesis. This hypothesis is a result of the above-described observations in chronic pruritus in patients and mice. The 'Layer Hypothesis' suggests that 'itch' is elicited in the epidermal unmyelinated nerve C-fibers and 'pain' in unmyelinated nerve fibers in the dermis (9). This theory combines elements from the neurophysiological 'Pattern' and 'Intensity' hypothesis and is supported by the observation that the removal of epidermis eliminates itch but not pain (10). Maybe these epidermal nerve fibers are the low electrical threshold and histamine-insensitive C-fibers described recently by Ikoma et al. (11). The stronger stimulation which causes pain will activate mostly the dermal nerve endings. The 'Layer Hypothesis' can open a new discussion in itch research and will raise again some controversies in this field.

The physiological mechanisms of itching remain to be elucidated and tested in a reliable, comprehensive experimental model, which should cover different itch elicitor and different kinds of itching. Likewise, future treatments of itching should not be only restricted to the use of antihistaminics. To understand the involvement of different cytokines and neuropeptides in the different forms of itching will not only solve the 'itching' puzzle but also help to find new strategies to treat this very common, but sometimes devastating symptom. Our patients will be grateful.

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Commentary 5

In the context of the current debate, atopic dermatitis (AD) provides a few lessons on the role of mental stress as pruritus-aggravating factor, which may be of general importance when discussing more effective itch management.

Itching is a cardinal symptom in AD, affecting more than 10% of the youth worldwide (1). The patients are suffering from intolerable itching night and day, which is triggered by physiological and psychic stimuli. Generally, levels of itching as measured by visual analog scale (VAS) are low while working at the office and studying at the school during the daytime. However, once they are at home in the evening, itching is gradually intensified toward the end of the day (2), when the patients are abruptly set free from daily stresses. Itching in AD involves both peripheral and central components (3,4). The patients are not always benefited by antagonizing histamines, one of the most authentic chemical mediators responsible for itch.

The patients with AD have a higher anxiety level than non-sufferers (5). Recent studies have revealed that stress elaborates anxiety on one hand and affects immune functions on the other (6,7). We have shown that AD with stronger perception of trait anxiety (TA; the anxiety felt in general) than state anxiety (SA; the anxiety felt at present) as expressed by high TA/SA ratios (mean, 1.13 ± 0.2 vs. 0.93 ± 0.2 in normal non-atopics, $P < 0.006$) enhances serum IgE synthesis and has Th2-shifting in the circulation (8). Stressors stimulate the hypothalamus–pituitary–adrenal axis and sympathetic nervous system, releasing adrenal glucocorticosteroids and norepinephrin, respectively (9), favoring a tilt toward Th2 response. Thus, everyday stressors may repeatedly stimulate a Th2 immune response and distort the regulatory immune mechanism, resulting in protracted atopic allergy.

Tandospirone is a serotonin 1A receptor agonist exerting anti-anxiety and antidepression effects. We carried out an open trial to examine the effect of tandospirone, 30 mg per day for 4 weeks, on relief of skin symptoms in adult AD patients, while administrating 10 mg of cetiridine chloride, per day, and topical corticosteroids with the medium to strong class. This regimen was not changed during the trial. In the AD patients with TA/SA of >1.0, the TA/SA ratio significantly decreased when treated with tandospirone compared without it (Fig. 1). Such effect was not observed in the patients perceiving anxiety levels comparable to those of normal

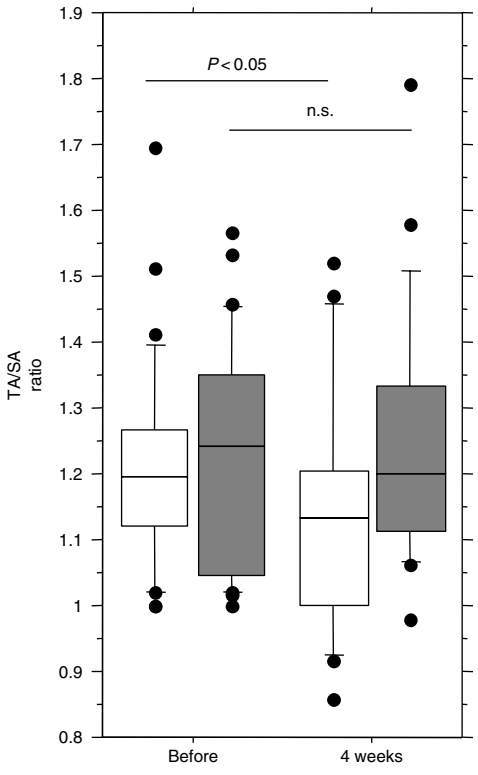

Figure 1. Change of TA/SA ratios with (white, $n = 18$) and without (gray, $n = 17$) tandospirone treatment. TA and SA were assessed by the Spielberger's method (10). A box, the 90% range of the total; a black dot, the rest sample data; a vertical bar, SD; and a horizontal bar in the box, a mean value. Data are analyzed by Wilcoxon's signed rank test.

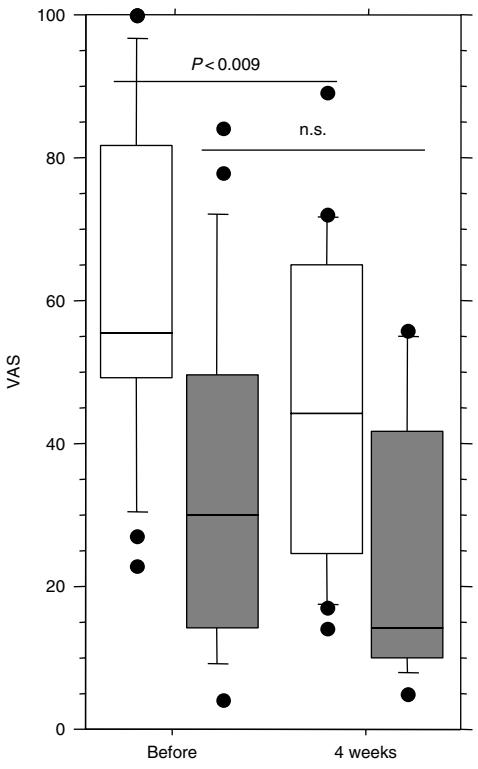

Figure 2. Change of itching levels (VAS) with (white, $n = 17$) and without (gray, $n = 15$) tandospirone treatment. A box, the 90% range of the total; black dot, the rest sample data; a vertical bar, SD; and a horizontal bar in the box, a mean value. Data are analyzed by Wilcoxon's signed rank test.

subjects. Moreover, in the patients with intense anxiety (TA/SA > 1.0 and TA > 45), the VAS decreased more significantly in the treated group than the non-treated group, although there was difference in the background VAS level between the two (Fig. 2).

Our findings suggest that successful control of mental stresses attenuates itching and suggest to employ drugs with antianxiety effect as part of the management strategy in stress-associated itching, in AD patients and possibly beyond.

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Commentary 6

Itch is among the cardinal symptoms of several dermatological diseases such as lichen simplex, lichen planus, and atopic dermatitis (1–3). Pruritus is often the most crippling feature of the disease, causing the patient severe discomfort. However, the therapeutic arsenal to reduce the symptom of itch is rather limited and the effect of the various treatments to date highly variable (2–4). Here, we discuss the possibility that itch may be combated effectively by activation of endogenous memory-like inhibitory mechanisms.

Itch is often defined as a sensation that induces the urge to scratch. Scratching, in turn, provides instant relief from itch, presumably through activation of mechano-nociceptors in the skin (3–5). It is known that painful stimuli inhibit the sensation of itch (4). Unfortunately, scratching will in the long run exacerbate the underlying skin condition by inducing additional lesions in the skin. The itch may in fact sustain the underlying disease by inducing a vicious itch–scratch circle (3). A treatment method that mimics the beneficial effects of scratching without hurting the skin would therefore be valuable.

On this basis, a therapy has been developed in our laboratory that permits controlled electrical stimulation preferentially of thin nerve fibers, including nociceptors, in the dermo-epidermal junction (6,7). This technique, termed Cutaneous Field Stimulation (CFS), has in experimental and clinical studies proved to induce very robust (usually complete) and long-lasting (4–8 h) inhibition of acute histamine-evoked itch in healthy subjects (4,6,8) and chronic itch in patients with atopic dermatitis (7).

Maximal effects are reached already after a treatment time of 8–10 min (6). Notably, the effective stimulation parameters (1–10 Hz) are similar to those known to cause long-term depression (5,6) – a memory-like mechanism – in the spinal cord. Because CFS utilize endogenous mechanisms, the aversive side effects are minimal. Ongoing studies on patients suffering from neurodermitis also indicate that the skin condition may improve by CFS treatment, presumably as a consequence of the reduced scratching (9).

In view of the strong and long-lasting effects, as well as the lack of aversive side effects, CFS should be considered as the first-line symptomatic therapy for combating pruritic conditions that are sustained by scratching.

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Commentary 7

Pruritus is a complication of liver diseases, in particular those characterized by cholestasis. The reason some and not all patients with cholestasis report pruritus is unknown, but it tends to suggest that there is a subject-dependent mechanism (i.e. ability to perceive pruritus).

The etiology of the pruritus of cholestasis is unknown. The idea that the pruritus of cholestasis arises from the stimulation of 'itch fibers' at the level of the skin by 'toxic compounds' that accumulate in tissues as a result of cholestasis is seductive and plausible; at present, however, there are no scientific data to demonstrate that this occurs.

There is evidence to suggest that in cholestasis, there is increased opioidergic neurotransmission, summarized as follows: (i) patients with cholestasis can experience an unpleasant constellation of symptoms and signs suggestive of an opiate withdrawal-like reaction when administered opiate antagonists (1); (ii) a stereospecific

naloxone reversible state of antinociception (analgesic) can be displayed by rats with cholestasis secondary to bile duct resection (2); and (iii) there is down-regulation of mu opioid receptors in rats with cholestasis secondary to bile duct resection (3).

Analogous to the pruritus that results from the pharmacological increase in opioidergic tone by central morphine (4,5), it is hypothesized that increased opioidergic tone in cholestasis may mediate the pruritus, at least in part, by a central mechanism (6). The reason for altered central neurotransmission in cholestasis is unknown; however, increased plasma levels of Met and Leu-enkephalin, two of the endogenous opioid peptides, have been reported in patients with liver disease, including those with Primary biliary cirrhosis (PBC) (1,7).

The source of peripheral endogenous opioids in cholestasis is unknown; however, the liver may contribute to the increased availability of opioids in liver disease as suggested by the expression of Met-enkephalin immunoreactivity in the cholestatic liver (8). It is not known whether opioids derived from the liver in cholestasis mediate what has been interpreted as centrally increased opioidergic neurotransmission; however, there is evidence to suggest that opiate transport systems are found in the blood–brain barrier (9,10); furthermore, transport proteins found in the basolateral domain of the hepatocyte are also found in the choroid plexus and in the blood–brain barrier and can transport opiates *in vitro* and may potentially transport periphery-derived opioids into the central nervous system (11–13).

Pruritus is a subjective sensation, and it cannot be directly quantitated. However, a system that records the behavior that results from pruritus, scratching, has been developed, providing the possibility to obtain objective data (14). The use of opiate antagonists (e.g. naloxone and naltrexone) is supported by data from controlled clinical trials that used behavioral methodology (15–18). Experimental data in a primate model of morphine-induced scratching (19,20) suggested that activation of kappa receptors prevented opioid receptor-mediated pruritus. Butorphanol is an agonist at the kappa opioid receptor and an antagonist at the mu opioid receptor with minimal or absent abuse potential. Unpublished experience with the use of butorphanol in patients with cholestasis and pruritus supports this idea, as the pruritus has been substantially relieved in a patient with intractable pruritus from chronic hepatitis C. Accordingly, the use of butorphanol spray in selective patients may be a therapeutic alternative.

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Commentary 8

One is tempted to claim that the question posed by the current debate feature – *How best to fight that nasty itch?* – is 'the wrong question at the right time'.

We have to admit that, as of today, there is very limited knowledge as to what exactly causes itch. While this is especially true for the so-called neuropathic and psychogenic forms of pruritus, in pruritoceptive itch, we at least know that sensory nerves (SNs) of the skin are required for the induction. This, however, does not help much in view of the large and ever-growing family of SN-activating factors, as we simply do not know, which of these signals are relevant in settings associated with pruritoceptive itchiness.

More effective treatment options, which are undoubtedly called for, require us to first identify the mechanisms and signals involved in the induction of pruritus. Thus, if we do not want to put the cart in front of the horse and jump to conclusions, the right question to ask is: How to induce that nasty itch? In other words, we can only attempt to identify relevant SN-activating mechanisms, once we will have managed to develop experimental models of pruritus that allow us to study its underlying mechanisms of induction. In our view, none of the responses to the frequently used itch-inducing substances (1) such as benzoic acid, fumarates, dimethylsulfoxide, or capsaicin truly mimic any of the frequent skin conditions associated with itching.

Once these models have been established, the most promising approach for the identification of relevant skin-activating signals, at least in our view, involves 'educated fishing', i.e. we must first limit the huge number of contenders to a few highly likely candidates, e.g. by asking: What skin conditions are frequently associated with pruritus? Those factors that are known to be up-regulated in such skin conditions and which also exhibit SN-activating effects are most likely to be our therapeutic targets, which can then be tested (trial and error) in the models developed. For example, most chronic inflammatory skin conditions are invariably associated with pruritus, e.g. atopic dermatitis, chronic urticaria, and prurigo nodularis. Virtually, all of these skin conditions involve the effects of activated skin mast cells (MCs) and their pro-inflammatory mediators including histamine, tryptase, prostaglandins, leukotrienes, and various cytokines, many of which have been described as potent activators of skin SNs.

Could it be then, that MCs and SNs are 'partners in crime', i.e. in the induction of pruritus, and could some MC mediators be targets of novel and more effective therapeutic measurements? Several independent lines of evidence indicate that this could indeed be the case: (i) activation of MCs and MC mediators are very likely to contribute to the induction of itch (2), (ii) MC stabilizers, e.g. cromoglycate, ketotifen, and nedocromil, have been shown to reduce itching (3–5), and (iii) potent inhibitors and/or antagonists

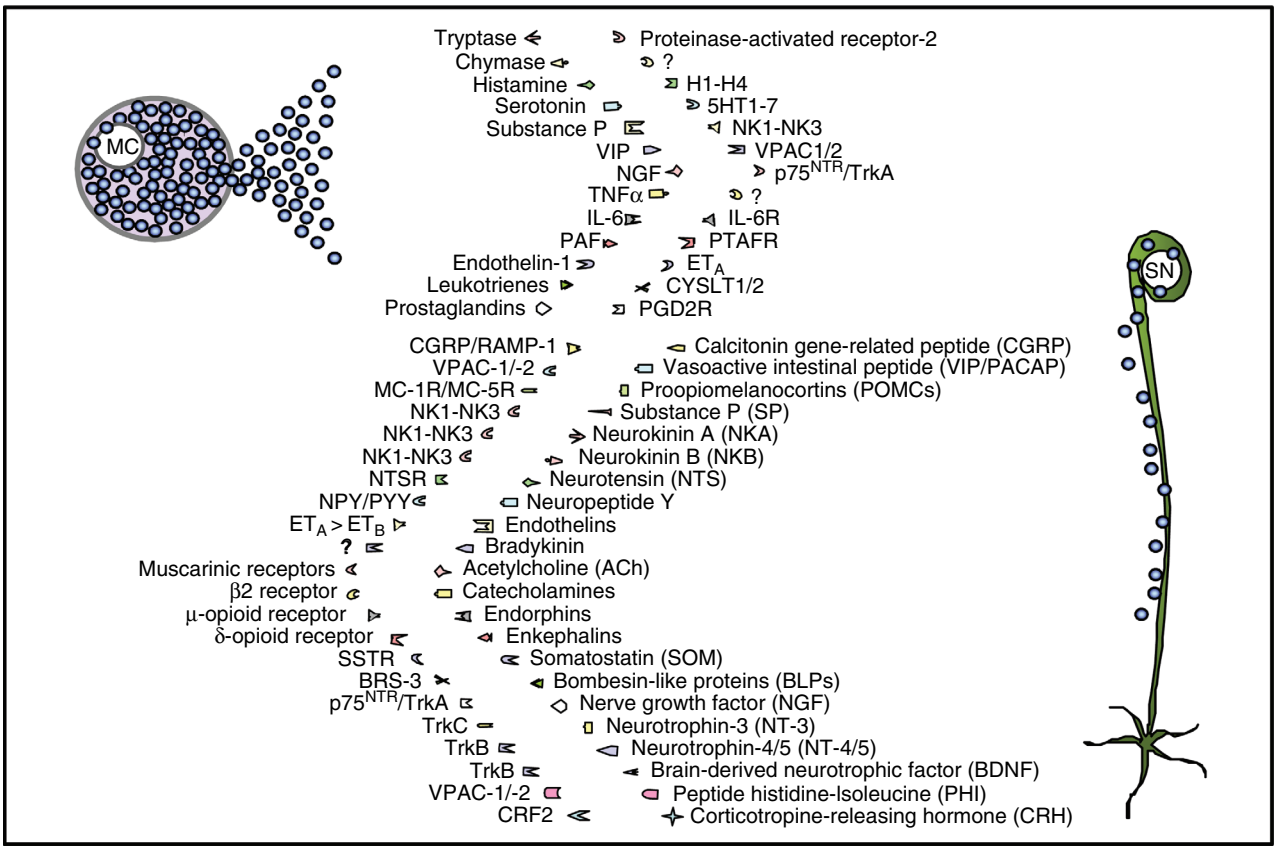

Figure 1. Potential candidates for the interaction between mast cells (MCs) and sensory nerves (SNs). Novel and more effective therapeutic measurements for the treatment of itchiness require first to identify the mechanisms and signals involved in the induction of pruritus. Several lines of evidence indicate that activated skin MCs and SNs do interact in the induction and maintenance of itch. Once there have been appropriate models established to limit this huge number of potential candidates, these models could be used to prove the contribution of selected mediators in settings of pruritus.

of selected pruritogenic MC products, e.g. histamine, serotonin, tumor necrosis factor-α, or leukotrienes, are able to relieve pruritus (6–10). Moreover, MCs and skin SNs can interact in the spreading and enhancement of itch signals (Fig. 1).

Thus, while the circumstancial evidence for the contribution of MCs and MC mediators in the induction of pruritogenic itching appears convincing, we simply do not and will not know for certain, unless or until we have developed and used appropriate models to prove the contribution of selected MC mediators in settings of skin itchiness.

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