



International Association for the Study of Pain®

Technical Corner from *IASP Newsletter*
September/October 1996

This section, edited by Charles B. Berde, MD, PhD presents timely topics in pain research and treatment.

Neural Mechanisms of Itch Sensation

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Itch is an unpleasant sensation which evokes the desire to scratch.
—Samuel Hafenreffer, *Nosodochium, In Quo Cutis,...*, Ulm 1660

This definition given more than three centuries ago by a German physician is remarkably precise. Envisage yourself trying to spot that last mosquito late at night in a motel room, because you forgot to close the window before you switched on the light. And later you realize that there was another one when you wake up in the middle of the night scratching its bite.

Itch sensation is the second modality of nociception besides pain, and it is often not fully appreciated as an independent sensory modality despite the fact that itching may have an impressive impact on human behavior. We find early descriptions in books of Herodotus, a writer of travel guides in ancient Greece, and in treatises of Plato. There can be no doubt that itching is of eminent clinical importance; many systemic and skin diseases are accompanied by persistent itch or recurrent itch attacks. However, at the advent of modern sensory physiology in the middle of past century, itch was not recognized as a sense in its own right. Only in the mid-twentieth century was it rediscovered that itch was fundamentally different from pain—a fact clear to most people from everyday experience. Current knowledge suggests that itch has several features in common with pain but exhibits intriguing differences as well, which I shall try to outline briefly.

The Peripheral Nervous Apparatus Subserving Itch

Itching is the perfect example of an exteroceptive sensation. It can be elicited only by stimulation of the skin or skin-to-mucosa transitional surfaces on the outside of the body (cornea, lip, anus, vulva, etc.). Itch is induced by a variety of stimuli, including mechanical, chemical, thermal, and electrical stimulation of the skin. Cutaneous sensitivity to pruritic stimuli is discontinuous and has a spot-like distribution (itch points), whose density equals that of pain points (around 1/mm²; von Frey 1922; Bishop

1943; Shelley and Arthur 1957). A stratification of receptors limits itch to stimulation of the uppermost skin layers (epidermis and epidermal/dermal transition). Shelley and Arthur (1957) correlated the histologically verified injection depth of individual itch powder spicules (*Mucuna pruriens*) in skin with subjective reports of itch, and reported maximal sensitivity at the level of the basal cell layer. Removal of the upper skin layers, which are innervated by peptidergic free nerve endings only (Kruger et al. 1985), abolishes the ability to perceive itch (Török 1907; Shelley and Arthur 1957). Itch is never felt in muscle, joints, or inner organs, demonstrating the absence of an itch-signaling apparatus in deep tissue. The same substances that elicit itch upon intracutaneous injection (see below) elicit only pain when injected subcutaneously.

Congenitally pain-insensitive patients are also insensitive to itch (Kunkle and Chapman 1943). Itch sensitivity is lost in analgesic dermatomes following herpes zoster (Jancsó et al. 1983) or lepra (Török et al. 1907; Dash and Deshpande 1976). Itch is readily abolished in skin areas treated with the nociceptor excitotoxin capsaicin (Tóth-Kása et al. 1986; Handwerker et al. 1987). In contrast, it is unchanged in skin areas rendered touch-insensitive by pretreatment with saponins (Winkler 1910). Although experimentally induced itch can still be perceived under a complete A-fiber conduction block (Bickford 1938; Lewis 1942; Graham et al. 1951; Shelley and Arthur 1957; Keele and Armstrong 1964), it is significantly diminished (Magerl 1991). Electrical field stimulation of the skin elicits itching, the magnitude of which depends on stimulus frequency up to 40 Hz but is diminished at higher frequencies (Tuckett 1982). This notion is consistent with the operating range of nociceptors (Thalhammer et al. 1994). In aggregate, itch sensation is mediated by A-delta and C nociceptors located in the uppermost skin layers.

Human Microneurography

Few attempts have been made to record activity related to itch perception from human peripheral nerves innervating skin. Torebjörk (1974) has reported the excitation of human polymodal C fibers by the pruritic agent cowage accompanied by perceptions of itch. Histamine also excited a subgroup of polymodal C nociceptors to low-frequency discharge (Handwerker et al. 1991). However, with rare exception, these nociceptors were much more sensitive to mustard oil, a substance eliciting burning pain in humans. Very recently, a novel type of chemosensitive nociceptor, insensitive to strong mechanical and heat stimulation (a variety of the so-called "silent" nociceptor), has been identified in human peroneal nerve (Schmelz et al. 1996). These nerve fibers with extraordinary large receptive fields were exquisitely sensitive to histamine iontophoresis, but not to mustard oil. LaMotte, who first described this rare nociceptor species in monkey skin, hypothesized that these may be the peripheral nerve fibers mediating itch sensation (LaMotte et al. 1988). Similar to animal electrophysiology, not more than 5–10% of human nociceptors of any subgroup are excited by histamine.

An interesting observation arises from the technique of intra-neural microstimulation. Electrical stimulation of identified nerve fibers through the recording electrode may give rise to elementary perceptions relayed to the central nervous system by these particular nerve fibers. Occasionally, stimulation of C nociceptors gave rise to a robust sensation of

itch. In such cases the magnitude of itch was related to the stimulation frequency; itch never turned into pain, or vice versa (Torebjörk and Ochoa 1981; R. Schmidt and H.E. Torebjörk, personal communication, 1996). This suggests that there are nociceptive nerve fibers, though rare, that are predominantly sensitive to pruritic stimuli. These fibers may be characterized by their unique pattern of chemosensitivity. It is still open to discussion whether these nociceptors constitute the peripheral correlate of itch sensation in the form of a labeled line, or whether itch may be signaled by coactivation of sets of nociceptors displaying differential chemosensitivities, i.e., by a population code (McMahon and Koltzenburg 1992).

Substances Producing Itch and Psychophysics of Itch Sensation

Itching is reliably induced by a variety of chemical stimuli, the prime example of which is histamine acting on H1 receptors located on nociceptive neurons. Histamine can be exogenously applied by injection, pricking, or iontophoresis, or endogenously released from mast cells by other substances. Other biogenic amines (e.g., serotonin), kinins (bradykinin, kallidin, kallikrein; Hägermark 1974), some neuropeptides (e.g., substance P, VIP; Fjellner and Hägermark 1981), and enzymes (endopeptidases like trypsin, papain, etc.; Shelley and Arthur 1957; Keele and Armstrong 1964) also elicit itch. However, their effects appear largely mediated by histamine (and possibly other mediators) released from cutaneous mast cells. In these models, consequently, the magnitude of itch is significantly diminished by H1-receptor antagonists or, for histamine releasers, by prior depletion of mast cells (e.g., Hägermark et al. 1978, Heyer and Magerl 1995 for substance P effects). Many mast cells are strategically located close to free nerve endings. Some nerve endings even form quasi-synaptic bouton-like structures on mast cell membrane. This allows for high concentrations of mast cell-derived mediators at the nociceptive nerve endings and, conversely, for high concentration of mast cell-degranulating sensory neuropeptides (e.g., substance P) at the mast cell membrane.

Only few substances are known to induce a state of enhanced itch sensitivity (hyperknesis). Histamine-induced itch may be potentiated by prostaglandins (Hägermark et al. 1977). Prostaglandins are not, however, involved in histamine-induced itch, as evidenced by the fact that histamine-induced itch is not diminished by classical cyclooxygenase inhibitors like acetylsalicylic acid and indomethacin (Hägermark et al. 1973, 1977). Notably, although peripherally applied opioids have analgesic action in peripheral tissue, they aggravate histamine itch, an effect that is independent of the mast cell-degranulating properties of opioids or prostaglandin formation and can not be reversed by naloxone (Fjellner and Hägermark 1982).

Psychophysical studies using histamine as the stimulating agent agree that the stimulus-response function for itching is shallow. Exponents of power functions were 0.17–0.32 for histamine injection, histamine iontophoresis, or electrical field stimulation (Tuckett 1982; Simone et al. 1987; Magerl and Handwerker 1988), while the exponent was around 1 for, e.g., heat pain. According to the general principles of psychophysics, this may suggest that the itch channel is designed to code for an extended range of stimulus magnitudes.

Central Nervous Mechanisms of Itch and Itch-Related Behavior

Transduction and representation of pruritic stimuli in the central nervous system are only vaguely understood. The excitation of spinal dorsal horn neurons by cutaneous histamine injection has been investigated only recently. In contrast to the peripheral nervous system, where only a minority of nociceptors are sensitive to histamine, about 80% of class 2 wide-dynamic-range neurons are dose-dependently excited, irrespective of whether they are identified as neurons projecting into the spinothalamic tract (Li et al. 1995; Carstens 1996). No information is available about the role of spinal low-threshold mechanoreceptive (class 1) and high-threshold nociceptive-specific (class 3) neurons.

Itch-sensitive dorsal horn neurons are under control of descending inhibition. Histamine-induced discharge of dorsal horn neurons is strongly suppressed by stimulation of the midbrain periaqueductal gray (PAG), which governs descending inhibition (Carstens 1996). This may explain why removal of the descending inhibition key structures by ablation of the midbrain, but not of brain structures above midbrain level, resulted in disinhibition of the scratch reflex elicited by pruritic stimuli (Königstein 1948).

Itch induces a scratch reflex directed to the appropriate skin site in many animals and humans. The scratch behavior is specific for itching and differentiates itch from pain, which will rather lead to withdrawal or guarding behavior. Attempts to scratch the stimulated area have been observed in completely spinalized animals (Sherrington 1906). The scratch reflex may thus be present already at the spinal level. Scratch reflexes had a minimum latency of around 1.5 seconds, which is similar to the latency of itch perception elicited by punctate electrical stimuli in humans (Shelley and Arthur 1957), suggesting an unmyelinated afferent pathway. Pruritic stimuli also elicit autonomic vasoconstrictor reflexes in a somatotopically organized fashion, which may be spinal to a large extent (Magerl et al. 1996).

Itch is probably conducted in the same ascending spinal pathways as is pain. Cordotomy of the anterolateral tract blocks the perception of pain and itch (Foerster 1927; Bickford 1938). Nothing is known about long-term effects of cordotomy on experimentally induced or chronic itch.

The central representation of itch is an enigma. In a positron-emission tomography (PET) study, Hsieh et al. (1994) found extensive activation of cortical areas involved in motor planning. They found bilateral (but preferentially ipsilateral) activation of the supplementary motor area and the premotor cortex, and widespread activity in the prefrontal cortex but not the motor cortex. This is consistent with the intention to execute a complex motor task (the program "to move the contralateral arm to scratch the itch spot with the contralateral hand") without the actual execution (subjects were instructed not to scratch). Activation was also seen in the contralateral cingulate gyrus, which may represent any (or perhaps several) of the following: an integral part of the motor program, the sensory experience (the itch); the emotional aspect of that perception (the unpleasantness of itch); a motivational aspect (the urge to scratch); or autonomic activation linked to the itch stimulus. Interestingly, Hsieh et al. were not able to

demonstrate activation of primary or secondary somatosensory cortex, or of the thalamus. The thalamus is, however, likely involved in processing itch; there are case reports of central itch syndromes after stroke involving the thalamus (e.g., Shapiro and Braun 1987).

Central Nervous Modulation of Itch and Interaction with Other Sensory Channels

The magnitude of itch sensation can be reduced by thermal stimulation, either cold or warm (Lewis 1942; Fruhstorfer et al. 1986). Thermal stimulation may have an effect on peripheral receptors but is likely also to involve central mechanisms, since itch can be diminished by immersing the contralateral finger into cold water (Murray and Weaver 1975). Bromm et al. (1995) demonstrated that stimulation of cold receptors with menthol reduced the magnitude of histamine-induced itch to the same extent as did a matching true cold stimulus. The itch suppression by cold is, however, only transitory (Heyer et al. 1995), as is the marginal suppression by innocuous heat (Ward et al. 1996). Likewise, vibration or transcutaneous electrical nerve stimulation induce a moderate itch suppression never outlasting the conditioning stimulus (Ward et al. 1996). In any case, the efficacy of innocuous counterstimuli is moderate. Their relative ineffectiveness holds true for pruritic skin disease as well (Fjellner 1981).

Painful stimuli, can strongly counteract the ability to perceive itch and induce a long-lasting antipruritic state (Bickford 1938). Even short-lasting pain can suppress itch (Ward et al. 1996). Strong painful stimuli or prolonged slightly painful stimulation can fully block itch perception for many hours (Bickford 1938; Nilsson et al. 1996). Induction of the antipruritic state is most likely the behavioral rationale of the scratch reflex. In chronic pruritic disease scratching may, however, also be shaped by instrumental learning, since it represents a time-locked chain of signal (itch), behavior (scratching), and positive reinforcement (itch relief). Conditioned scratch behavior is likely resistant to extinction and may as an operant behavior gain a relative independence of itch perception.

Strong itching stimuli induce a cutaneous halo, itchy skin in which innocuous light touch can easily elicit itch (Bickford 1938). This phenomenon, now termed *alloknesis*, has been thoroughly studied in recent years. It is a state of spinal sensitization, similar to secondary hyperalgesia/allodynia (LaMotte et al. 1988; Simone et al. 1991). *Alloknesis* depends on the magnitude of the inducing itch stimulus and is controlled by nociceptive input from the peripheral itch focus. It is fully blocked by cooling the itch focus (Simone et al. 1991; Heyer et al. 1995).

Opioids have a conspicuous role in itch processing that is opposite to their role in pain. Generalized itching is a well-known though rare side effect (about 1%) of i.v. morphine. Itching is much more prevalent in opioid analgesia with epidural (8.5%) or intraspinal (45.8%) application (Ballantyne et al. 1988). In these cases a segmental pattern of itching is frequently seen. This may also lead to intense facial itching, when opioids spread in the intrathecal space to reach the medullary dorsal horn of the brain stem, a region particularly rich in opioid receptors. Injection of morphine into the medullary dorsal horn

elicits long-lasting and intense facially directed scratching in monkey and rat (Thomas et al. 1992; Thomas and Hammond 1995), which can be relieved either by systemic administration of the opioid antagonist nal-oxone, which antagonizes morphine at medullary dorsal horn receptors, or by systemic morphine, which probably activates endogenous antinociceptive systems. Opioids may thus have a dual role in the central nervous processing of itch. The medullary dorsal horn may be the medullary "scratch center" located close to the bottom of the fourth ventricle, which was described in early physiological experiments.

Some Considerations on Pruritic Disease

The data presented above were derived mainly from the analysis of experimentally induced itch sensation. Clinical pruritus, like clinical pain, is of course much more complex, and it is beyond the scope of this review to give a comprehensive representation of the pathophysiology of pruritus. I briefly outline the genesis of pruritus in select systemic and skin diseases to give a glimpse of the diversity of pruritogenic mechanisms in disease.

The role of histamine is less important in pruritic diseases than in experimental paradigms. The prototype of histamine-mediated itch would be urticaria, easily recognized by the wheal and flare response when, for example, induced by contact with allergens in sensitized subjects. Rarely, urticaria can also be induced by physical factors, as in heat or cold urticaria. In these patients, H1-receptor antagonists rapidly ameliorate the specific cutaneous symptoms, including the itch. Most pruritic diseases do not, however, exhibit any sign of urticaria, and treatment with histamine receptor antagonists is of limited or no value.

One of the clinically most important examples of pruritic skin disease is atopic dermatitis, an inherited disease that afflicts approximately 5% of the population in the industrialized world (Wahlgren 1991). It can be transferred to nonatopic recipients by transplantation of bone marrow from an atopic donor, and atopic recipients have reportedly been cured by bone marrow transplants from nonatopic donors. Its pathophysiology is immunological, with elevated activation of T-lymphocytes, hyperstimulatory Langerhans' cells with exaggerated presentation of antigens, a defect in cell-mediated immunity, and enhanced production of immunoglobulin E (IgE) by B-cells. Atopic dermatitis patients experience intermittent mast cell degranulation, and their level of prostaglandins and various cytokines is enhanced. Their abnormalities include an enhanced releasability of mast cell histamine, prostaglandins, and leukotrienes by immunological stimuli (for a review on pathogenesis see Cooper 1994). The density of presumably nociceptive peptidergic afferents staining for substance P and calcitonin gene-related peptide may be increased (Tobin et al. 1992). However, atopic dermatitis patients do not exhibit any hyperknesis to histamine. If anything, the response to histamine or substance P is selectively reduced, while the response to pain-eliciting mustard oil is unchanged (Heyer et al. 1989, 1991). Moreover, alloknesis could not be elicited, indicating the absence of central sensitization in chronic itch of atopic dermatitis (Heyer et al. 1995). In contrast, atopic dermatitis patients do exhibit an itch sensitivity to acetylcholine that is not present in normal

subjects (Vogelsang et al. 1995). There is no apparent correlation between pruritus and IgE level, nor is there any correlation between alteration in sensitivity to experimentally induced itch and IgE. Treatment of atopic dermatitis with H1 antihistamines is completely ineffective (Wahlgren 1991). In contrast, corticosteroids ameliorate the itch of dermatitis patients. These patients also respond to treatment with the immunosuppressant cyclosporin A, but the mechanism of action is poorly understood (Wahlgren 1991).

Itch is a frequent and disturbing side effect in patients undergoing long-term hemodialysis. Ståhle-Bäckdahl (1989) found that itching slowly increased and peaked at the second night without dialysis; it was lowest on the day following dialysis, suggesting the accumulation of pruritogens during dialysis-free intervals. Responses to histamine were enhanced, indicating an enhanced sensitivity to pruritogens. Immunohistochemistry revealed nerve fiber sprouting throughout all epidermal layers in many uremic patients, which was never seen in control subjects. Uremic pruritus may thus be characterized by the accumulation of pruritogens acting on an abnormal cutaneous innervation.

Itch is also a distressing sequel in various liver diseases. The pruritus of cholestasis can not be mimicked by injection of bile acids. However, the accumulation of endogenous opioids has been demonstrated in plasma of patients and in animal models. The microinjection of plasma from patients with cholestatic pruritus into the medullary dorsal horn of monkeys elicited facial scratching suggesting itch and was abolished by the opiate antagonist naloxone (Bergasa et al. 1993). In a controlled study, naloxone reduced but did not abolish pruritus and itch-related scratching in cholestatic patients (Bergasa et al. 1995). Endogenous opioids may thus modulate the pruritus of cholestasis, but other, unknown mediators may be involved.

These few examples may illustrate, admittedly in an arbitrary fashion, that the mechanisms of clinical itch syndromes are complex, diverse, and far from being understood. Considering that the neurophysiology of itch is poorly explained, this is even more applicable in pruritic disease. We have only just begun to understand their pathophysiology.

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