

Pathogenesis and Treatment of Pruritus

Malcolm W. Greaves

© Springer Science+Business Media, LLC 2010

Abstract Classification of itch into four categories—pruritoceptive, neurogenic, neuropathic, and psychogenic—has proven to be of utility to clinicians and investigators. Itch is recognized to be transmitted by dedicated afferent neurons, and a matrix of cerebral cortical loci involved in perception and the desire to scratch has been recognized. This highlights the multidimensional nature of the itch sensation. Some of the many mediators of itch, especially relevant in pruritogenic itch, are the result of cross-talk between dermal mast cells and adjacent cutaneous afferents. Keratinocytes of the epidermis express many neuropeptides, and their receptors are far from passive bystanders in the neurophysiology of itch. Mediators can also act centrally (eg, opioid peptides that act on μ receptors in the central nervous system). The pathophysiology of pruritus in neurogenic itch caused by common systemic diseases is gradually being elucidated, especially in the itch of cholestasis, although the molecular basis of itching in chronic renal failure remains elusive. Better understanding of the mediators of itch and their receptors has led to the imminent development of novel anti-itch compounds, including interleukin-31 inhibitors, histamine H4-receptor antagonists, and neurokinin-1 receptor antagonists.

Keywords Pruritus · Neurophysiology · Neuropeptides · Antipruritics

Introduction

Itch is the dominant symptom of skin disease and a frequent and important manifestation of underlying systemic disease. Conventionally defined as an unpleasant cutaneous sensation that provokes a desire to scratch, itch has attracted surprisingly little attention until recently despite the advent of the molecular era of biomedical research in the 20th century. Reasons for such slow progress have included lack of convincing animal models, deficiencies in methodology for measurement of itch, and tardiness in discarding classical but outdated 19th century concepts of the nature of the skin sensorium. Itch is a complex multidimensional sensation with discriminative cognitive, evaluative, and motivational components. Although murine models can be made to scratch, injection of histamine locally in skin and morphine systemically fails to consistently evoke itch, and when these models do scratch, an assumption must be made that the eliciting stimulus is an itch as perceived by humans. However, recently, despite these problems, some progress has been made in understanding the pathophysiology of itch, with exciting potential for the development of new anti-itch treatments. Most importantly, it is becoming generally recognized that the symptom of itch can be a result of intracutaneous (“pruritoceptive”) or central (within the central nervous system) “neurogenic” pathomechanisms, or both [1–3].

Classification of Itch

For consideration of pathomechanisms and for establishing an investigational and therapeutic plan for the patient, classification of itch has considerable utility. Although not without deficiencies, the classification proposed by Yosipovitch et al.

M. W. Greaves (✉)
Cutaneous Allergy Clinic,
St. John's Institute of Dermatology, St. Thomas' Hospital,
London SE1 7EH, United Kingdom
e-mail: malcolmgreaves@clinidermsolutions.co.uk

[1] and Twycross et al. [4] has yet to be improved upon and thus is used in the subsequent account. This classification includes four categories [2]:

- **Pruritoceptive:** generated in the skin, usually by an inflammatory or other visible pathological process (eg, scabies, urticaria)
- **Neurogenic:** generated in the central nervous system in response to circulating pruritogens, as in cholestasis, or in response to intraspinal morphine. Pruritus due to central excitation or abnormal processing of afferent sensory information from the periphery is also included within this category
- **Neuropathic:** due to anatomic lesions of the central or peripheral nervous system (eg, nerve entrapment, as in *notalgia paraesthetica*) and tumors of the central or peripheral nervous system
- **Psychogenic:** includes delusional parasitosis, picker's nodules, and stress-related chronic anogenital pruritus.

In many patients, more than one of these categories can coexist concurrently.

Neurophysiology of Itch

Itch Receptors

In the early 20th century, it was believed that itch was the result of stimulation of specialized itch receptors in the skin [5]. There is an abundance of unmyelinated free sensory nerve endings in the skin, as demonstrated by light and electron microscopy, and although it has not been positively proven, it seems increasingly likely that the epidermis as a whole, along with associated fine epidermal afferent terminals collectively represent the "itch receptor." The free, unspecialized nerve endings stain positively for neuropeptides, and the keratinocytes themselves express neuropeptides, their receptors, and other neuromediators, including nerve growth factor (NGF), vanilloid receptors, proteinase-activated receptor type 2 (PAR2), and voltage-gated adenosine triphosphate channels—all features of neuronally functioning cells [6–8]. Although histamine, acting via H1-receptors and the recently described H4-receptors [9], is an important mediator of itch in urticaria, its role as a pruritogen in other dermatoses, including atopic eczema, has been overstated previously.

Cold usually ameliorates itch, and warmth makes it worse. The transient receptor potential (TRP) superfamily of calcium-permeable sensory transduction channels is expressed on cutaneous nociceptive afferents and keratinocytes. Activation of these receptors leads to firing of action potentials in itch afferent neurons and release of mediators from keratinocytes. Some of these channels act as temper-

ature sensors for cooling, and menthol, a traditional antipruritic topical coolant, activates certain subtypes of TRP receptors [10].

Neural Pathways: Itch Versus Pain

Itch and pain have a great deal in common. Both sensations have apparently identical receptors, namely free unmyelinated C neuron endings within the epidermis and dermoepidermal junction. Both sensations involve secondary transmission neurons that ascend via the contralateral spinothalamic tract to the thalamus. There, the two sensations are projected by undetermined pathways to the cingulate and other cortical areas for final associative processing involving the parietal lobes, thus allowing perception of the unpleasant and distressing qualities of pain and itch. These areas recently have been further defined by functional positron emission tomography scan [11]. The prefrontal lobe determines the individual's itch and pain "thresholds." These similarities naturally led to the widespread notion that itch was merely a low-intensity form of pain involving the same afferent C neurons, but there are several experiential inconsistencies. For example, pain elicits limb withdrawal, whereas itch elicits scratching, and morphine ameliorates pain but aggravates itch.

Recently, using microneurographic technology, it has proven possible to measure action potentials in individual C neurons, and it has emerged that histamine-induced itch can be transmitted by a subset of C neurons and central transmission neurons [12, 13]. It subsequently became clear that subtypes of C neurons are capable of transmitting itch of different qualities. Mechanoinsensitive C fibers express histamine H1-receptors and transmit itch. However mechanosensitive C intraepidermal neurons have been identified that mediate pain and itch. Receptors involved include TRP vanilloid-1, which mediates pain and itch, and PAR2, which mediates itch. In any case, histamine-sensitive C neurons cannot account for all the different qualities of itch and other types of primary afferents are involved.

Modulation of Itch and Effect of Rubbing and Scratching

Like cold, painful stimuli mitigate the intensity of itch, and positron emission tomography scan functional studies implicate the periaqueductal gray in the central modulation of itch traffic [14]. Itching is also temporarily ameliorated by scratching and rubbing. These physical stimuli activate fast-conducting, thickly myelinated, low-threshold A- δ neurons. The activated neurons are inhibitory on C neuron activity and itch traffic via a gated mechanism similar to that originally described by Wall and McMahon [15] for pain. Whether, for itch, there exist descending inhibitory

control pathways originating in the periaqueductal region similar to those regulating pain is presently unclear.

It is widely recognized that chronic skin inflammation lowers the threshold for itch stimuli, leading to peripheral itch sensitization. Chronic itch can also lead to secondary central sensitization. Clinically, this heightened sensitivity for itching is recognized as *alloknesis* and *atmoknesis*. *Alloknesis* occurs when trivial normally nonpruritic stimuli (wetting the skin by sweat; contact with clothes) cause bouts of intense itching in the surrounding skin. *Atmoknesis* describes essentially the same pruritic response taking place as a reaction to small changes in skin temperature that is often experienced by atopic eczema sufferers when they get dressed in the early morning. These phenomena are analogous to the better known *allodynia*, in which injured skin reacts to mechanical stimuli by eliciting pain. These responses share a common pathomechanism in which excitation of secondary transmission neurons occurs in the region of the dorsal root ganglia as a result of continuing activation of itch-transmitting C fibers.

Mediators of Pruritus

The principal candidate mediators of pruritceptive itch in humans are listed in Table 1. Histamine is the ligand for H1-receptors located on a subset of C neuron afferents. Three other histamine receptors are recognized, but in only one of these—the H4-receptor—is there significant evidence of involvement in itching [9•, 16]. Mice with gain-of-function mutations in the H4-receptor show intense scratching behavior and eczematization, and similar changes are seen in transgenic mice overexpressing H4.

The dermal mast cell is a prolific source of mediators of itch, and cross-talk between dermal mast cells and C neuron afferent nerve endings has been recognized recently [17]. Mast cell-derived proteases, including tryptase, act as

signalling molecules on afferent neuron terminals via PAR. Inflammation ensues, mediated in part by the action of neuron-derived tachykinins, including calcitonin gene-related peptide on calcitonin gene-related peptide-1 receptors and substance P on neurokinin-1 receptors.

Opioid peptides have long been implicated as mediators of itch. Intraspinal administration of morphine to induce analgesia causes pruritus via central μ -opioid receptors [18]. Increased tissue levels of opioid peptides, including met-enkephalin, have been demonstrated in the skin of patients with cholestatic pruritus [2], and opioid peptide μ receptor antagonists such as naloxone have been demonstrated to be effective in the pruritus of cholestasis [19]. Opioid agonists causing pruritus appear to act on central rather than peripheral opioid μ receptors. As κ -opioid receptors antagonize itch, generalized itching has been ascribed to an imbalance between μ - and κ -opioid tone in the central nervous system.

Interactions between the immune system and the nervous system are increasingly recognized as important in the pathophysiology of inflammation, including itch. Tachykinins such as substance P can activate transcription factors for proinflammatory cytokines. Interleukin-2, a product of activated T lymphocytes, causes pruritus when injected intradermally [20]. Recently, interleukin-31 has received attention as a candidate mediator of pruritus, especially in atopic eczema [21•]. Overexpression of interleukin-31 in lymphocytes of mice causes a pruritic dermatosis resembling atopic dermatitis, and interleukin-31 is overexpressed in the skin of those with atopic dermatitis and other dermatoses [22, 23]. Interleukin-31 receptor protein OSMR- β is found in the dermis and spinal cord, and recent evidence has implicated interleukin-31 in the pathogenesis of the pruritic dermatosis known as familial primary localized cutaneous amyloidosis [24].

In the skin, keratinocytes are a major source of NGF, and NGF and its receptor, TrkA, are overexpressed in the

Table 1 Mediators of itch

Mediator	Receptor(s)	Comment
Histamine	H1, H4	Mice showing gain-of-function mutations in H4-receptor manifest pruritus, scratching; reviewed by De Esch et al. [48]
Acetylcholine	Nicotinic and muscarinic receptors	Important mediators in atopic eczema [49]
Tryptase	PAR2 receptor	PAR2 is expressed on primary afferents, releasing tachykinins, which activate dermal mast cells via neurokinin-1 receptors
Prostaglandin E	Prostanoid receptors	Sensitize receptors to itch evoked by other mediators
Opioid peptides	μ - and κ -opioid receptors	Cause itch via central μ receptors, but κ receptors are antipruritic
Nerve growth factor	TrkA receptors	Increased in atopic eczema [25]
Leukotriene B ₄	Leukotriene receptors	Leukotriene B ₄ induces itch [50]
Cytokines: interleukin-31	Interleukin-31 receptor	Interleukin-31 and its receptor are upregulated in atopic eczema [22]

PAR2 proteinase-activated receptor type 2

keratinocytes in psoriasis, atopic eczema, and prurigo [25–27]. NGF appears to control skin innervation, and increased expression of NGF not only increases sensory innervation but also upregulates expression of other neuroreceptors and neuropeptides and lowers itch threshold in the skin. NGF plasma levels are also useful biomarkers of disease activity in atopic dermatitis [28].

Some “Difficult” Itches

Neurogenic Itch, Including Itch Associated with Systemic Disease

The cause(s) of the itch of chronic renal failure, which may be localized or, in 25% to 50% of patients, generalized, remain elusive, and its treatment is equally challenging. It does not occur in patients with acute renal failure and is rare in children with chronic renal failure. Patients receiving continuous ambulatory peritoneal dialysis are less likely to suffer pruritus than those on hemodialysis, and improvements in dialysis technology have led to a fall in incidence from about 70% 20 years ago to about 15%. Multiple pathomechanisms have been proposed, including increased dermal mast cells, increased plasma histamine (although H1 antihistamine treatment is generally ineffective), secondary hyperparathyroidism (although pruritus correlates poorly with parathormone levels), and increased opioid peptide levels (although hemodialysis, which ameliorates the pruritus, does not affect plasma opioid levels, and the effects of μ -opioid antagonists such as naltrexone have been controversial) [29, 30]. Dry skin is almost invariable in patients with end-stage chronic renal failure, and correction by emollients is helpful. Pruritus frequently results in secondary eczematization, but the severity of pruritus correlates poorly with xerosis, which is not the primary cause of the itching. Treatments that probably do or do not work in pruritus of chronic renal failure are listed in Table 2. A meta-analysis of results of randomized controlled trials concluded that broadband UVB phototherapy

is the treatment of choice for moderate to severe pruritus of chronic renal failure [31].

The pruritus of cholestasis is frequently widespread, but unlike other forms of systemic pruritus, it has a predilection for the palms and soles. Unlike pruritus of chronic renal failure, patients with cholestatic pruritus tend to rub rather than scratch, so secondary eczematization and infection are less common. Causes include primary biliary cirrhosis, primary sclerosing cholangitis, gallstones, carcinoma of the head of the pancreas, viral hepatitis, and rarely cirrhosis. The itch is the result of a combination of elevated plasma bile acids and opioid peptides acting on μ -opioid receptors in the central nervous system [32]. Antihistamines are generally ineffective. Oral cholestyramine (4 g administered before and after breakfast) is a treatment hallowed by tradition but poorly tolerated and not supported by randomized controlled trials. Oral ursodeoxycholic acid, a hydrophilic bile salt, was found to be effective in only 2 of 11 clinical trials in a recent meta-analysis [33]. Rifampicin induces cytochrome P450 in the liver and thereby reduces liver pruritogens. It was effective in reducing cholestatic pruritus in two randomized controlled studies [34, 35]. Opioid peptide μ receptor antagonists such as oral nalmefene or naltrexone were effective in two randomized controlled studies [36, 37]. They may occasionally cause symptoms resembling opioid withdrawal in these patients.

Pruritus is associated with several endocrine diseases. Pruritus in diabetes is common but rarely if ever generalized unless it is caused by chronic renal failure. Anogenital pruritus is a common symptom of diabetes and is usually a result of candidosis [38]. Pruritus is an occasional manifestation of diabetic neuropathy. Generalized pruritus may be a presenting symptom of hyperthyroidism and is associated with a warm, moist skin, but its cause is unclear.

Itching is a presenting symptom in several hematologic disorders. Polycythemia vera may present with pruritus, typically itch provoked by contact with water (“bath itch”). Any patient in whom itching without a visible rash is provoked by contact with water at any temperature (aquagenic pruritus) should be screened for polycythemia vera [39]. This symptom can also be triggered by other bone marrow disorders, including myelodysplasia and leukemia. Itching occurs in about 40% of patients with polycythemia vera and is associated with raised plasma histamine levels [39]. It responds poorly to antihistamines, and the treatment of choice is psoralen UVA photochemotherapy or narrow-band UVB phototherapy [40].

In the context of a progressively aging population, pruritus associated with aging skin (pruritus of senescence) is a mounting problem. In the older adult patient with chronic, widespread itching, the first consideration should always be to exclude skin disease (pruritogenic itch, including infestations, xerosis, chronic eczematous derma-

Table 2 Effective and ineffective treatments for pruritus of renal failure

Probably effective	Ineffective
Emollients	H1 antihistamine
UVB phototherapy [51]	Topical tacrolimus [52]
Hemodialysis	Opioid antagonist [30]
Renal transplant	Odansetron [53]
Gabapentin [54]	
κ -opioid antagonist (TRK 820) [55]	

titis, urticaria, cutaneous T-cell lymphoma) and systemic disease (neurogenic itch, including chronic liver or kidney disease, endocrine, or hematologic disorders). However, in many patients, no cause can be found, and the “diagnosis” of senescent pruritus is made. The cause is unknown, but age-related structural or functional changes in afferent neurons and a loss of “tone” in pain neurons leading to central disinhibition of itch traffic have been postulated [41]. Impairment of barrier function is probably also important.

Systemic Drug Treatment of Itch

Most patients with widespread pruritus, regardless of cause, will at some point receive an H1 antihistamine to ameliorate the itch. Four subclasses of histamine receptors are recognised. H2-receptors are involved in gastric acid secretion but also have proinflammatory and immunomodulatory actions; they are not directly involved in itch. Presynaptic H3-receptors mediate release of neurotransmitters from central and peripheral neurons but have not yet been implicated in the generation of itching. Experimental evidence for the possible role of the recently characterized H4-receptors has been covered previously [9•, 16]. H1-receptors mediate allergic inflammation, including the associated itching, and also influence cytokine, adhesion molecule, and chemotactic mediator synthesis via nuclear factor- κ B and may regulate mediator release via calcium ion channels [42]. Thus, H1 antihistamine treatment may involve wider anti-inflammatory actions over and above downregulation of histamine activity. H1 antihistamines are classified as “first generation”—with significant sedative and anticholinergic side effects—and “second generation”—low-sedation compounds with little or no sedative or anticholinergic activity, mainly due to low lipophilicity and the consequent inability to traverse the blood–brain barrier. In practice, low-sedation, second-generation antihistamines are the treatment of choice for the pruritogenic itch of chronic urticaria, although sedative first-generation compounds may be useful at night to combat sleep deprivation. H1 antihistamines are of controversial value in managing the itch of atopic eczema. Low-sedation, second-generation compounds are poorly effective in the itch of atopic eczema. As the itch of atopic eczema is neurogenic as well as pruritocptive, sedative first-generation H1 antihistamines are often effective. Their anti-inflammatory actions may also be significant [43].

Oral doxepin, a tricyclic compound and a highly potent H1 antihistamine, is useful in chronic pruritus [44] but should be used with caution, especially in older adults and in patients with liver or cardiac disease, and should not be withdrawn abruptly or prescribed concurrently with other antidepressants. Chronic renal disease is not a contraindication,

and doxepin can be useful in the itch accompanying chronic renal failure. The itch of cholestasis is the main dermatologic indication for opioid antagonists, but naltrexone and naloxone have been advocated as antipruritics in a range of pruritic dermatoses [45]. Opioids are contraindicated in patients with severe liver disease, in patients addicted to opioids, and in those receiving opioid analgesia. Butorphanol, a combined μ -opioid receptor antagonist and κ -opioid agonist administered as a nasal spray, shows some promise in intractable pruritus [46].

Neurokinin-1 receptors, the ligands for which include substance P and other tachykinins, are receiving increasing attention as targets for therapeutic intervention in itch. Increased expression of this class of receptor has been demonstrated in several pruritic skin diseases [27]. Aprepitant is an oral neurokinin-1 receptor antagonist that has recently been reported as highly effective in relieving pruritus in the severe pruritocptive itch (visual analogue score, 7–9 out of a maximum score of 10) of cutaneous T-cell lymphoma (Sézary syndrome) [47•]. The effectiveness of this new drug in treating pruritus in other conditions remains to be determined.

Conclusions

The advent of newer neurophysiologic technology has enabled important progress to be made in the elucidation of neural pathways for itch and its amelioration by scratching or rubbing. More importantly, inhibitory and excitatory influences via pathways from higher centers as well as from the periphery represent a system of checks and balances that go some way toward explaining daily fluctuations in intensity of pruritus and offer opportunities for therapeutic intervention. Despite these advances, understanding of the pathomechanisms of itch in common dermatoses and systemic disorders has been disappointing. This is partly due to lack of convincing animal models. Although no selective antipruritic drugs of general clinical utility currently exist, development of exciting novel compounds seems to be around the corner.

Disclosure No potential conflict of interest relevant to this article was reported.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Yosipovitch G, Greaves MW, Schmelz M: Itch. *Lancet* 2003, 361:690–694.

2. Greaves MW, Khalifa N: Itch—more than skin deep. *Int Arch Allergy Immunol* 2004, 135:166–172.
3. Paus R, Schmelz M, Biro T, Steinhoff M: Frontiers in pruritus research: scratching the brain for more effective therapy. *J Clin Invest* 2006, 116:1174–1186.
4. Twycross R, Greaves MW, Handwerker H, et al.: Itch: scratching more than the surface. *Q J Med* 2003, 96:7–26.
5. Frey M: Zur Physiologie der Juckempfindung [in German]. *Arch Neurol Physiol Neerl* 1922, 7:142–145.
6. Inoue K, Koizumi S, Fuzuwara S, et al.: Functional vanilloid receptors in cultured human epidermal keratinocytes. *Biochem Biophys Res Commun* 2002, 291:124–129.
7. Bigliardi-Qi M, Lipp B, Sumanovski LT, et al.: Changes of epidermal mu-opiate receptor expression and nerve endings in atopic dermatitis. *Dermatology* 2005, 210:91–99.
8. Pincelli C: Neurotrophins in healthy and diseased skin [abstract]. *J Invest Dermatol* 2009, 129:S102.
9. • Dunford PJ, Williams KN, Desai PJ, et al.: Histamine H4 receptor antagonists are superior to traditional antihistamines in the attenuation of experimental pruritus. *J Allergy Clin Immunol* 2007, 119:176–183. *Discovery of the H4 receptor and its potential role in itching offers the prospect of novel therapeutic approaches to treatment of itch.*
10. McKemy DD, Neuhasser WM, Julius D: Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature* 2002, 416:52–58.
11. Darsow U, Drzezga A, Frisch M, et al.: Processing of histamine-induced itch in the human cerebral cortex: a correlation analysis with dermal reactions. *J Invest Dermatol* 2000, 115:1029–1033.
12. Schmelz M: A neural pathway for itch. *Nat Neurosci* 2001, 4:9–10.
13. Andrew D, Craig AD: Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. *Nat Neurosci* 2001, 4:72–77.
14. Mochizuki H: Imaging of central itch modulation in the human brain using positron emission tomography. *Pain* 2003, 105:339–346.
15. Wall PD, McMahon SB: Microneuronography and its relation to perceived sensation. A critical review. *Pain* 1985, 21:209–229.
16. Bell JK, McQueen DS, Rees JL: Involvement of histamine H4 and H1 receptors in scratching induced by histamine receptor agonists in Balb C mice. *Br J Pharmacol* 2004, 142:374–380.
17. Vergnolle N, Ferazzini M, D'Andrea MR, et al.: Proteinase-activated receptors: novel signals for peripheral nerves. *Trends Neurosci* 2003, 26:496–500.
18. Ballantyne JC, Loach AB, Carr DB: Itching after epidural and spinal opiates. *Pain* 1988, 33:19–60.
19. Bergasa NV, Talbot TL, Alling DW, et al.: A controlled trial of naloxone infusions for the pruritus of chronic cholestasis. *Gastroenterology* 1992, 102:544–559.
20. Wahlgren CF, Tengvall Linder M, Hagermark O, Scheynius A: Itch and inflammation induced by intradermally injected interleukin-2 in atopic dermatitis patients and healthy subjects. *Arch Dermatol Res* 1995, 287:572–580.
21. • Zhang Q, Puthu P, Zhou Q, et al.: Structure and biological functions of IL-31 and IL-31 receptors. *Cytokine Growth Factor Rev* 2008, 19:347–356. *The recent discovery of interleukin-31 and its receptor, which is overexpressed in the itchy skin of atopic dermatitis, promises a new therapeutic approach to antipruritic therapy in this disorders.*
22. Sonkoly E, Muller A, Lauerma AI, et al.: IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006, 117:411–417.
23. Dillon SR, Sprecher C, Hammond A, et al.: Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol* 2004, 5:752–760.
24. Tanaka A, Arita K, Lai-Chong JE, et al.: New insight into mechanisms of pruritus from molecular studies on familial primary localised cutaneous amyloidosis. *Br J Dermatol* 2009, 161:1217–1224.
25. Johansson O, Liang Y, Emtestam L: Increased nerve growth factor and tyrosine kinase- like immunoreactivities in prurigo nodularis skin: an exploration of the cause of neurohyperplasia. *Arch Derm Res* 2002, 293:614–619.
26. Tanaka A, Matsuda H: Expression of nerve growth factor in itchy skins of atopic NC/NgaTnd mice. *J Vet Med Sci* 2005, 67:915–919.
27. Chang S-E, Han S-S, Jung H-J, Choi J-H: Neuropeptides and their receptors in psoriatic skin in relation to pruritus. *Br J Dermatol* 2007, 156:1272–1277.
28. Toyoda M, Nakamura M, Makino T, et al.: Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis. *Br J Dermatol* 2002, 147:71–79.
29. Peer G, Kivity S, Agami O, et al.: Randomised cross-over trial of naltrexone in uremic pruritus. *Lancet* 1996, 348:1552–1554.
30. Pauli-Magnus C, Mikus G, Alscher DM, et al.: Naltrexone does not relieve uremic pruritus. Results of a randomised double blind, placebo controlled cross over study. *J Am Soc Nephrol* 2000, 11:514–519.
31. Tan KL, Haberman HF, Coldman AJ: Identifying effective treatments for uremic pruritus. *J Am Acad Dermatol* 1991, 24:811–818.
32. Bergasa, NV, Thomas DA, Vergalla J, et al.: Plasma from patients with pruritus of cholestasis induces opioid receptor-mediated scratching in monkeys. *Life Sci* 1993, 53:1253–1257.
33. Goulis, J, Leandro G, Burroughs AK: Randomised controlled trials of ursodeoxycholic acid therapy for primary biliary cirrhosis: a meta analysis. *Lancet* 1999, 355:657–658.
34. Ghent CN, Carruthers SG: Treatment of pruritus in primary biliary cirrhosis with rifampicin: results of a double blind crossover randomised trial. *Gastroenterology* 1988, 94:488–493.
35. Bachs L, Pares A, Elena M, et al.: Comparison of rifampicin with phenobarbitone for the treatment of pruritus in biliary cirrhosis. *Lancet* 1989, 638:574–576.
36. Bergasa N, Alling DW, Talbot TL, et al.: Oral nalmefene therapy reduces scratching activity due to the pruritus of cholestasis: a controlled study. *J Am Acad Dermatol* 1999, 41:431–444.
37. Bergasa N, Alling DW, Talbot TL, et al.: Naloxone ameliorates the pruritus of cholestasis: results of a double blind, randomized, placebo-controlled trial. *Ann Intern Med* 1995, 123:161–167.
38. Neilly JB, Martin A, Simpson N, MacCuish AC: Pruritus in diabetes mellitus: investigation of prevalence and correlation with diabetes control. *Diabetes Care* 1986, 9:273–275.
39. Steinman HK, Black AK, Lotti TM, et al.: Polycythaemia vera and water-induced pruritus. Blood histamine levels and cutaneous fibrinolytic activity before and after water challenge. *Br J Dermatol* 1987, 116:329–333.
40. du Peloux Menagé H, Greaves MW: Aquagenic pruritus. *Semin Dermatol* 1995, 14:313–316.
41. Ward JR, Bernhard JD: Willan's itch and other causes of pruritus in the elderly. *Int J Dermatol* 2005, 44:267–273.
42. Simons FER: Advances in H1 antihistamines. *N Engl J Med* 2004, 351:2203–2217.
43. Klein PA, Clark RAE: An evidence-based review of the efficacy of antihistamines in relieving the pruritus of atopic dermatitis. *Arch Dermatol* 1999, 135:484–488.
44. Figueiredo A, Ribeiro A, Goncalo M, et al.: Mechanism of action of doxepin in the treatment of chronic urticaria. *Fundam Clin Pharmacol* 1990, 4:147–158.
45. Metze D, Reimann S, Beissert S, Luger T: Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of

- pruritus in internal and dermatological diseases. *J Am Acad Dermatol* 1999, 41:553–559.
46. Dawn AG, Yosipovitch G: Butorphenol for treatment of intractable pruritus. *J Am Acad Dermatol* 2006, 54:527–531.
47. • Duval A, Dubetret L: Aprepitant as an antipruritic agent? *N Engl J Med* 2009, 361:1415–1416. *This neurokinin receptor antagonist has been shown to ameliorate one of the most intractable generalized itches—the pruritus of Sézary syndrome.*
48. De Esch IJP, Thurmond RL, Jongelan A, Leurs R: The histamine H4 receptor as a new therapeutic target for inflammation. *Trends Pharmacol Sci* 2005, 26:462–469.
49. Vogelsang M, Heyer G, Hornstein OP: Acetyl choline induces different sensations in atopic and non-atopic subjects. *Acta Derm Venereol* 1995, 75:434–436.
50. Andoh T, Saito A, Kuraishi Y: Leukotriene B4 mediates sphingosylphosphorylcholine-induced itch-associated responses in mouse skin. *J Invest Dermatol* 2009, 129:2854–2860.
51. Rivard J, Lim HW: Ultraviolet phototherapy for pruritus. *Dermatol Ther* 2005, 18:344–354.
52. Duque MI, Yosipovitch G, Fleischer AB, et al.: Lack of efficacy of tacrolimus ointment 0.1% for the treatment of hemodialysis-related pruritus: a randomized, double-blind, vehicle-controlled study. *J Am Acad Dermatol* 2005, 52:519–521.
53. Ashmore SD, Jones CH, Newstead CD, et al.: Odansetron therapy for uremic pruritus in hemodialysis patients. *Am J Kidney Dis* 2000, 35:827–831.
54. Gunal AI, Ozalp G, Yoldas TK, et al.: Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. *Nephrol Dial Transplant* 2004, 19:3137–3139.
55. Wikstrom B, Gellert R, Ladefoged SD, et al.: Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol* 2005, 16:3742–3747.