

Itch: More than Skin Deep

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Key Words

Itch · Tickle · Mediators · Opioid peptides · Treatment of itch

Abstract

Recent research in neurophysiology of itch has indicated the existence of itch-dedicated nociceptor neurones. The perception of itch is regulated by tonically inhibitory descending neuronal pathways and nociceptor spinal neuronal circuits. There is at present no convincing evidence of an 'itch centre' in the brain. A classification of itch has been proposed, based on neurophysiological considerations, which stresses the importance of neurogenic and neuropathic itch, and assists in differential diagnosis and selection of treatment. However, more than one class of itch can occur concurrently in the same patient. The importance of cross-talk between dermal mast cells and nociceptor nerve terminals, involving cleavage of proteinase-activated receptor 2 by mast cell tryptase, is highlighted. The pruritus of cholestasis is mediated at least in part by opioid peptides synthesized by the liver, and elevated levels of these mediators are found in the plasma and skin of patients with itch due to cholestasis. The combined use of both μ -receptor antagonists and κ -receptor agonists (anti-pruritic) is worth exploring.

Introduction

That published reviews, original articles and even textbooks on the subject of itch are becoming more plentiful of late [1–4] encourages the hope that this Cinderella of neuro- and skin physiology is at last beginning to receive the attention that it deserves.

Most reviews of itch begin with a definition of itch on the lines of '... an unpleasant sensation leading to a desire to scratch'. However, this is an oversimplification. Unlike eczema sufferers, patients with urticaria do not scratch to obtain relief from their very intense itch, they rub, pinch or even slap the affected skin to the extent of bruising, but excoriations are rare in urticaria. This is important, because the sensation of itch is a complex and multi-dimensional experience involving a range of different qualities of sensation, such as pleasurable relief by local physical intervention which leads to itch/scratch cycles, and modulation by cognitive and psychological functions from higher centres. Comprehensive questionnaires [5] get round this problem to some extent, but depend on subjective, interpretive and educational variables. Visual analogue scales are widely used and dose-response relationships have been demonstrated for antipruritics such as H₁ antihistamines, but subjectivity is a major problem; does an increment on the scale denote an increased intensity, a change in quality or in extent, or any combination of

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these? Measurements of itch by quantification of scratch, limb movement meters or other indirect objective methods [6] are hard to interpret. Some patients with severe itch do not scratch, and conversely, patients may scratch persistently out of tension-relieving habit rather than the desire to suppress an itch. Animal models based upon scratching are also of doubtful value; it is not given that a scratching mouse must be an itching mouse.

Recent attempts to evaluate experimental itch centrally through its electrical representation in the cerebral cortex by positron emission tomography or by magnetic resonance imaging [7, 8] are of great interest, but the extent to which these techniques can yield satisfactory dose-response relationships is unclear. Thus inadequate methods of measurement of itch are a factor in the slow progress of research in this field.

Classification of Itch

In order to aid in diagnosis and treatment of the pruritic patient, itch has recently been classified into 4 categories on a pathophysiological basis [1, 2]. *Pruritoceptive itch* is itch generated in the skin, usually by a visible inflammatory or other pathological process. Sometimes, evidence of skin disease in pruritoceptive itch may be elusive, as in partially treated scabies and certain physical urticarias. *Neuropathic itch* is due to one or more lesions in the peripheral nerves or central nervous system. Examples include demyelinating lesions of multiple sclerosis, spinal cord tumours and post-herpes zoster dysaesthesia. This category will not be discussed further. *Neurogenic itch* is generated in the central nervous system in the absence of visible pathology, and is of two types. Neurogenic itch may be due to defective modulation of itch traffic within the central nervous system. In this model, imbalance of inhibitory and augmenting neuronal circuits results in the enhancement of the perception of itch. Neurogenic itch is probably an important component of the pruritus of atopic eczema (see below). Neurogenic itch may also be a result of the action of circulating factors which generate itch in the central nervous system. The itch of cholestasis due to the action of opioid peptides, synthesized in the liver, on central μ -opioid receptors represents a widely acknowledged example. *Psychogenic itch* is poorly understood, but parasitophobia is a dramatic and well-recognized example. These classes of itch are of course not mutually exclusive; the itch of atopic eczema may be due to both pruritoceptive and neurogenic elements.

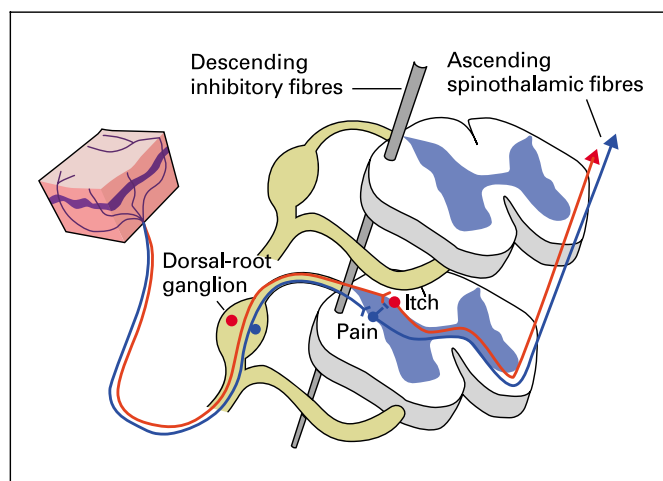


Fig. 1. Neurophysiology of itch. Unmyelinated C fibres subserving itch and those subserving pain originate in the skin. Information on itch and pain is conveyed centrally in two distinct systems that both use the same peripheral nerve bundle and spinothalamic tract. Reprinted with permission from Elsevier (The Lancet 2003, vol 361, pp 690–694).

Pathways for Itch

Although the responses to pain (withdrawal) and itch (scratch or rub) are very different, the neural pathways are almost identical (fig. 1). Microneurographic techniques in volunteers experiencing histamine-induced itch [9] have established the existence of afferent polymodal C neurones which are distinct from pain-transmitting fibres, and which appear to be itch dedicated. That these specialized neurones are not specific to itch evoked by histamine is recently suggested by similar microneurographic findings in a patient with chronic itch of prurigo nodularis [10]. In this patient, but not in healthy controls, microneurographic recordings revealed spontaneous neuronal activity in several afferent C fibres which innervated pruritic skin. The same method has also been used to study itch-conducting secondary transmission neurones in the lateral spinothalamic tract which project to the thalamus. In the cat, a subset of dedicated itch fibres has been identified which respond to histamine applied iontophoretically to the skin [11]. These neurones manifest slow conduction velocity and other properties resembling those of their peripheral counterparts.

Table 1. Candidate mediators of itch in atopic eczema

Candidate mediator	Receptor	Comment
Histamine	H ₁ , on polymodal C neurones	H ₁ antihistamines are generally disappointing in atopic eczema [12]
Acetyl choline	nicotinic and muscarinic, on autonomic neurones	causes itching on intradermal injection in atopic eczema [15]
Tryptase (from dermal mast cells)	PAR2	cleavage of PAR2 causes neuropeptide release [14]
Substance P	NK-1, -2, -3	releases histamine from dermal mast cells and has intrinsic pruritogenic properties [16]
Prostaglandin E	EP-1, -2, -3	lowers threshold for pruritus caused by other mediators including histamine [17]
Leukotrienes	activated phospholipase C	leukotriene B ₄ is pruritogenic in the mouse [18]
Cytokines (as yet unidentified) derived from CD4+ Th2/Th1 lymphocytes	N/A	evidence is indirect and based upon rapid relief of itch by cyclosporin [19]

Mediators of Itch

Itch associated with inflammatory skin disease is assumed to be, at least in part, a consequence of mediators formed or released in the lesional skin. The urticarial wheal is an obvious example, histamine derived from dermal mast cells being the principal, if not the only mediator of itching, a conclusion supported by the consistent response to H₁ antihistamines. In the itch of atopic eczema, the situation is more complex. H₁ antihistamines are poorly effective, and other mediators are likely to be involved [12, 13]. Given the pivotal role of the dermal mast cell in atopic eczema, proteinase-activated receptor 2 (PAR 2) is of special interest. PAR 2 is expressed in afferent nerve terminals and is cleaved by mast cell tryptase, leading to release of pruritic neuropeptides, including substance P [14].

Atopic eczema is a T lymphocyte-driven disease, mainly of the CD4 Th2 phenotype. That the itch of atopic eczema is probably mediated at least in part by cytokines including IL-2, is supported by the rapid response of the itch of atopic eczema to systemic cyclosporin. Other candidate mediators of the itch of atopic eczema are summarized in table 1.

Neurogenic (Central) Itch

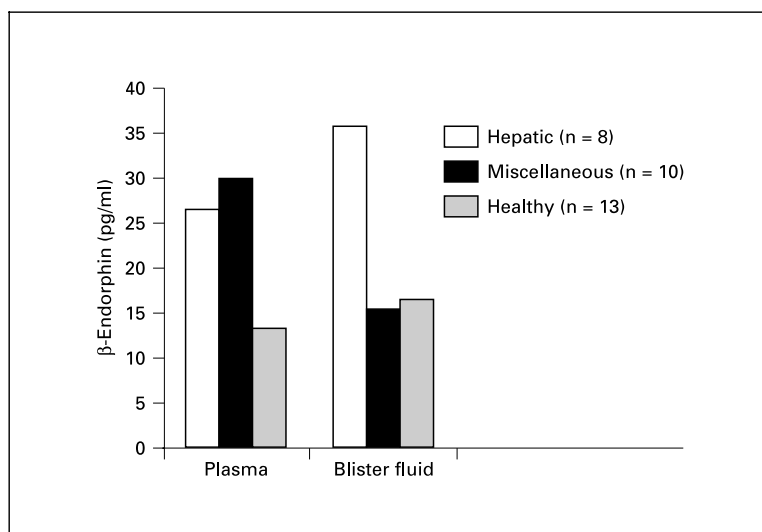
Not surprisingly, histamine pricked into lesional skin of atopic eczema sufferers provokes a paroxysm of intense

itching far greater than the reaction in healthy skin of normal volunteers. But surprisingly, the same dose of histamine injected into the non-lesional skin of eczema patients evoked significantly less itching than in the healthy subjects [20], along with smaller axon reflex flares, suggesting a diminished degree of afferent neuronal activation in clinically unaffected skin of atopic eczema sufferers. The combination of augmented itch response to histamine in lesional skin and reduced sensitivity in non-lesional skin is compatible with enhanced itch processing in the central nervous system – ‘central itch’ or neurogenic itch [21, 22]. Distortion of processing of itch traffic through the spinal cord, leading to central sensitization and amplified itching, explains the common clinical observation that eczema sufferers experience exacerbation due to trivial cutaneous stimuli such as sweating and abrupt temperature change (*alloknesis*). Two types of neurogenic itch are recognized: one due to disordered processing of itch traffic as exemplified by central itch in atopic eczema discussed above, and another due to systemic factors acting on receptors for pruritus in the central nervous system. The best-recognized example of the latter is the pruritus of cholestasis [23].

Opioid Peptides, Opioid Receptors and Neurogenic Itch

Pain suppresses itch, as we all know when we vigorously excoriate a mosquito bite. The same inference can be drawn from studies of the response of localized itch to capsaicin. Capsaicin cream applied topically causes burn-

Fig. 2. Immunoreactive β -endorphin in 8 patients with cholestasis (primary biliary cirrhosis: 2 patients; cirrhosis + hepatitis C, liver failure due to drug toxicity, liver cirrhosis of unknown cause, sclerosing cholangitis, chronic active hepatitis, Budd-Chiari syndrome with chronic liver failure: 1 patient each). Endorphin levels are elevated in cutaneous blister fluid from patients with cholestasis (mean $\pm$ SEM: 35.73 ± 20.73) compared with levels in healthy controls (mean $\pm$ SEM: 16.35 ± 9.29 , $p = 0.043$). Compared with levels in hepatic pruritus patients, the mean β -endorphin level was also reduced in 10 disease control patients with pruritus (idiopathic generalized pruritus: 6 patients; nodular pruritus: 2 patients; atopic dermatitis and cholinergic urticaria: 1 patient each) (mean $\pm$ SEM: 15.11 ± 18.11), but this difference did not reach statistical significance ($p = 0.058$) [28]; $p = 0.408$ for hepatic vs. healthy.



ing pain and hyperalgesia, followed by relief of itching [24].

Opioid analgesics frequently cause itching. Most patients receiving spinal opioid analgesia experience troublesome pruritus [25], and this can be relieved by opioid μ -receptor antagonists [26], thus demonstrating the presence of μ -opioid receptors in the central nervous system that can mediate itch. There is now accumulating evidence that the itch of cholestasis is mediated by opioid peptides produced by the liver [27], based upon identification of elevated levels of the opioid peptide β -endorphin in skin [28] (fig. 2), the pruritic response of monkeys to intrathecal injection of plasma from patients with cholestatic pruritus [29], and the response of patients with pruritus of cholestasis to naloxone infusion [6]. Of special interest is the observation that patients with hepatic pruritus treated with naloxone frequently experienced opioid withdrawal symptoms and signs when treated with naloxone [30]. However, a straightforward action of opioid peptides via the μ -receptor in cholestatic itch may turn out to be an oversimplification. κ -opioid receptor antagonists are pruritic in the mouse [31], whereas a κ -receptor agonist proved to be anti-pruritic in this species [32]. The possibility arises that the most effective treatment for opioid peptide-induced pruritus may turn out to be a combination of a μ -receptor antagonist such as naloxone and a κ -receptor agonist such as the investigational new drug TRK-820 [33]. A meta-analysis has demonstrated the effectiveness of a κ -receptor opioid agonist nalbuphine in the treatment of opioid-induced pruritus [34].

Neurogenic Itch: The Role of Central Processing

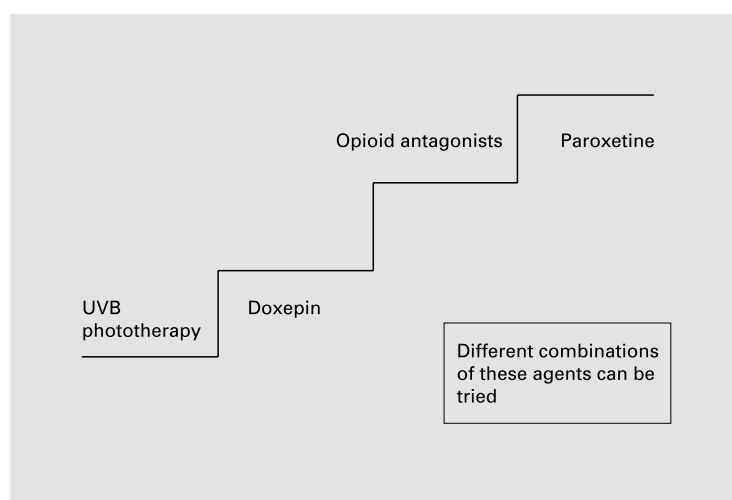
The well-recognized phenomenon of alloknesis in atopic eczema and other inflammatory skin disorders has already been discussed above.

How do scratching and rubbing alleviate itch? When a large area of skin is stimulated by scratching or rubbing, low-threshold touch and pressure-conducting myelinated A neurones are activated. These volleys cause a widespread surround inhibition due to down-regulation of itch processing by inhibitory neuronal circuits in the substantia gelatinosa. This hypothesis receives support from experimental evidence [35–38] and is the basis of trans-epidermal electrical stimulation as a treatment for itch [37]. The dorsal horn also receives descending modulatory signals via the mid-brain periaqueductal grey, enabling higher centres to influence the perception of itch. Thus, the severity of perceived itch depends on multiple factors besides the intensity of the provoking stimulus.

Relationship of Tickle to Itch

Tickle is a pleasurable or mildly unpleasant sensation following gentle tactile stimulation of the skin. Two forms are recognized: knismesis is the tickle sensation following light feathery stroking and can occur anywhere; gargalesis is the more pleasurable response to rougher rhythmic moving pressure – ‘the itch that moves’ – restricted to certain areas including the axillae, rib cage and soles of the feet, and which may result in uncontrollable laughter [39]. Tickle does not elicit scratching, but rather rapid with-

Fig. 3. Stepwise paradigm for treatment of severe and resistant pruritus. Broad-band UVB phototherapy (300 nm) is effective in pruritus due to a wide range of causes. Doxepin can be added as a single night-time dose of 10–50 mg (see text for details). Opioid μ -receptor antagonists, e.g., naltrexone 25–50 mg daily, are of proven value in cholestatic pruritus, but anecdotally may also be of value in pruritus of other aetiologies. Paroxetine, a selective serotonin re-uptake inhibitor, has mainly been used in pruritus of cancer patients in dosage 5–10 mg daily. It should not be used concurrently with doxepin.



drawal and avoidance. The receptors for tickle are rapidly adapting mechanoreceptors. Whether the neural pathways follow those of itch and pain, unmyelinated C neurones and transmission to higher centres via lateral spinothalamic tracts, or those for touch, thickly myelinated afferent neurones and ventral spinothalamic tracts, or both, is still unclear [40]. Unlike itch, self-induction of tickle is impossible owing to suppression by inhibitory influences from higher centres [41].

Treatment of Itch

The sensation of itch is temperature dependent [42], the threshold for itch being lowered in response to rise in temperature, thus explaining in part the common experience of patients that their itch is worse in bed. All patients suffering from itching, irrespective of cause, should be advised to wear light clothes, work and sleep in a cool environment and avoid alcoholic drinks. A tepid shower before retiring to bed is often helpful for patients rendered wakeful by nocturnal pruritus. Dry skin should be treated with emollients. One percent menthol in calamine lotion is also often helpful.

For guidance on more specific treatment, classification of the itch as described above is valuable. Pruritoceptive itch due to eczema or urticaria is best treated by topical corticosteroids or antihistamines, respectively. Neither neurogenic nor neuropathic itch is likely to respond to either of these agents, and the first step is to identify and treat the cause, if possible. We adopt a stepwise regime for 'difficult' pruritus (fig. 3).

Broad-band ultraviolet B (UVB) (90–320 nm) is an effective treatment for pruritus, due to a wide range of causes, and is well established in the itch of end-stage renal failure [43]. Other suggested indications include pruritus of human immunodeficiency virus infection [44], 'bath itch' of polycythaemia vera [45] and Hodgkin's lymphoma [46]. The role of narrow-band UVB (311 nm) in the management of intractable pruritus has yet to be evaluated but initial experience suggests it is effective.

Doxepin is a tricyclic compound with potent antidepressant and antihistaminic properties and a long half-life following ingestion. It blocks the re-uptake of adrenaline and serotonin, leading to increased levels of these neurotransmitters in the brain. It is effective in pruritus due to a variety of causes [47], most probably due to non-specific reduction in the perception of itch. It is best used as a single night-time dose of 10–50 mg. Owing to occasional intolerance, particularly in the elderly, it is prudent to begin with a low dose which can be gradually increased, if necessary. It should not be used concurrently with other antidepressants. Possible unwanted side effects include sedation, dry mouth, glaucoma and adverse interactions with other antidepressants, and drugs which interfere with cytochrome P450 enzyme pathways in the liver (e.g., macrolides, imidazoles). If withdrawal of doxepin treatment is contemplated, it should be tapered and not abruptly withdrawn.

Opioid antagonists such as naloxone (parenteral) or naltrexone (oral) are of established value in pruritus of cholestasis [6] (naltrexone dosage 25–50 mg once daily). Other suggested indications include pruritus of renal failure [48] and pruritus in a variety of other internal and

dermatological diseases [49]. Since opioid κ -receptor agonists are antipruritic, nalbuphine which combines μ -receptor antagonist and κ -receptor agonist properties may be superior to pure μ -receptor antagonists alone [50]. To avoid opioid withdrawal symptoms in patients receiving naloxone or other μ -receptor antagonists, dosage should be tapered and not abruptly withdrawn [30]. Opioid antagonists should not be given to patients receiving opioids for analgesia or to narcotic drug addicts. They should not be given to patients with severe liver function impairment.

Paroxetine, a selective serotonin uptake inhibitor, has established a track record in the treatment of pruritus associated with cancer [51]. It down-regulates serotonin type 1a receptors, leading to delayed anti-depressant action which takes 2 weeks to become evident, and also

down-regulates serotonin type 3 receptors, which causes a rapid onset of antipruritic action. Nausea can be overcome by concurrent administration of cisapride [52]. Paroxetine should not be given concurrently with other anti-depressants.

Other drugs worth considering when all else has failed include odansetron [53] and mirtazepine [54]. Odansetron has been claimed to be effective in pruritus of cholestasis and renal failure in open-labelled studies, but results of controlled trials have been unimpressive [53, 54]. Mirtazepine, an anti-depressant with 5-HT₂- and 5-HT₃-antagonist with H₁-antihistamine properties has been used successfully to relieve itch in malignant cholestasis, lymphoma and renal failure [55]. Neither of these agents has been subjected to the rigour of a controlled clinical trial.

References

- Twycross R, Greaves MW, Handwerker H, Jones EA, Libretto SE, Szepietowski JC, Zylicz Z: Itch: Scratching more than the surface. *QJM* 2003;96:7–26.
- Yosipovitch G, Greaves MW, Schmelz M: Itch. *Lancet* 2003;361:690–694.
- Stander S, Steinhoff M, Schmelz M, Weisshaar E, Metz D, Luger T: Neurophysiology of pruritus. *Arch Dermatol* 2003;139:1463–1470.
- Yosipovitch G, Greaves MW, Mc Glone F, Fleischer AB: Itch: Basic Mechanisms and Therapy. New York, Marcel Dekker, 2004.
- Darsow U, Scharein E, Simon D, Walter G, Bromm B, Ring J: New aspects of itch pathophysiology: Component analysis of atopic itch using the Eppendorf Itch Questionnaire. *Int Arch Allergy Immunol* 2001;124:326–331.
- Bergasa NV, Talbot DL, Alling DW, Schmitt JM, Walker EF, Baker BL, Korenman JC, Park Y, Hoofnagle JH, Jones EA: A controlled trial of naloxone infusions for the pruritus of chronic cholestasis. *Gastroenterology* 1992;102:544–549.
- Drzezga A, Darsow U, Treede RD: Central activation by histamine-induced itch: Analogies to pain processing. A correlational analysis of O-15 H₂O positron emission tomography studies. *Pain* 2001;92:295–305.
- Mc Glone F, Rukweid R, Hitchcock D, Howard M: Histamine-induced discriminative and affective responses revealed by functional MRI; in Yosipovitch G, Greaves MW, Mc Glone F, Fleischer AB (eds): *Itch: Basic Mechanisms and Therapy*. New York, Marcel Dekker, 2003, pp 53–62.
- Schmelz M: A neural pathway for itch. *Nat Neurosci* 2001;4:9–10.
- Schmelz M, Hilliges M, Schmidt RO, Orstavik K, Vahlquist C, Weidner C, Handwerker HO, Torebjork HE: Active itch fibres in chronic pruritus. *Neurology* 2003;26:564–566.
- Andrew D, Craig AD: Spinothalamic lamina 1 neurons selectively sensitive to histamine: A central neural pathway for itch. *Nat Neurosci* 2001;4:72–77.
- Krause L, Shuster S: Mechanism of action of anti-pruritic drugs. *Br Med J* 1983;287:1199–1200.
- Rukweid R, Lischetzki G, McGlone F, Heyer G, Schmelz M: Mast cell mediators other than histamine induce pruritus in atopic dermatitis patients: A dermal microdialysis study. *Br J Dermatol* 2000;142:1–8.
- Steinhoff M, Vergnolle M, Young SH, Tognetto M, et al: Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med* 2000;6:151–158.
- Heyer G, Vogelsang M, Hornstein OP: Acetylcholine is an inducer of itching in patients with atopic eczema. *J Dermatol* 1997;24:621–625.
- Jorizzo JL, Coutts A, Eady RAJ, Greaves MW: Vascular responses to injection of substance P and mechanism of action. *Eur J Pharmacol* 1983;87:67–76.
- Greaves MW, McDonald-Gibson W: Itch: Role of prostaglandins. *Br Med J* 1973;3:608–609.
- Andoh T, Kuraishi Y: Intradermal leukotriene B₄ but not prostaglandin E₂ induces itch-associated responses in mice. *Eur J Pharmacol* 1998;353:93–96.
- Wahlgren CF, Scheynius A, Hagermark O: Antipruritic effect of cyclosporin A in atopic dermatitis. *Acta Derm Venereol* 1990;70:323–329.
- Ikoma A, Rukweid R, Stander S, Steinhoff M, Miyachi Y, Schmelz M: Neuronal sensitization for histamine-induced itch in lesional skin of patients with atopic dermatitis. *Arch Dermatol* 2003;139:1455–1458.
- Twycross R, Greaves MW, Handwerker H, Jones EA, Libretto SE, Szepietowski JC, Zylicz Z: Itch: Scratching more than the surface. *QJM* 2003;96:7–26.
- Yosipovitch G, Greaves MW, Schmelz M: Itch. *Lancet* 2003;361:690–694.
- Jones EA, Bergasa NV: The pruritus of cholestasis. *Hepatology* 1999;29:1003–1006.
- Wallengren J, Klinker M: Successful treatment of notalgia paresthetica with topical capsaicin: Vehicle-controlled double-blind crossover study. *J Am Acad Dermatol* 1995;32:267–269.
- Ballantyne JC, Loach AB, Carr DB: Itching after spinal and epidural opiates. *Pain* 1988;33:149–160.
- Cohen SE, Ratner EF, Kreitzman TR, Archer JH, Mignano L: Nalbuphine is better than naloxone for treatment of side effects after epidural morphine. *Anesth Analg* 1992;75:747–752.
- Bergasa NV, Sabol SL, Yound WS, Kleiner DE, Jones EA: Cholestasis is associated with preproenkephalin mRNA expression in the adult rat liver. *Am J Physiol* 1995;268:346–354.
- Khalifa N: PhD thesis, London, 2003.
- Bergasa NV, Thomas DA, Vergalla J, Turner ML, Jones EA: Plasma from patients with pruritus of cholestasis induces opioid receptor-mediated scratching in monkeys. *Life Sci* 1993;53:1253–1257.
- Jones EA, Neuberger J, Bergasa NV: Opiate antagonist therapy for the pruritus of cholestasis: The avoidance of opioid withdrawal-like reactions. *QJM* 2002;95:1–6.
- Kamei J, Nagase H: Norbinaltorphimine, a selective κ -opioid receptor antagonist induces an itch-associated response in mice. *Eur J Pharmacol* 2001;418:141–145.
- Togashi Y, Umeuchi H, Okano K: Antipruritic activity of the kappa-opioid receptor agonist TRK-820. *Eur J Pharmacol* 2002;435:259–264.
- Kumagai H, Sasamura H, Hayashi M: Prospects for a novel opioid kappa receptor agonist TRK-820 in uraemic pruritus; in Yosipovitch G, Greaves MW, Mc Glone F, Fleischer AB (eds): *Itch: Basic Mechanisms and Therapy*. New York, Marcel Dekker, 2004, pp 279–286.

- 34 Kjellberg F, Tramer MR: Pharmacological control of opioid-induced pruritus: A quantitative systematic review of randomised trials. *Eur J Anaesthesiol* 2001;18:346–357.
- 35 Wall PD, Melzack R: Textbook of Pain, ed 3. Edinburgh, Churchill Livingstone, 1995.
- 36 Greaves MW, Wall PD: Pathophysiology of itching. *Lancet* 1996;348:938–940.
- 37 Wall PD, Sweet WH: Temporary abolition of pain in man. *Science* 1967;155:108–109.
- 38 Melzack R, Wall PD: Pain mechanisms: A new theory. *Science* 1965;150:971–979.
- 39 Mintz T: Tickle – the itch that moves. *Psychosom Med* 1967;29:606–611.
- 40 Harris CR: The mystery of ticklish laughter. *Am Sci* 1999;87:344–351.
- 41 Weiskrantz L, Elliott J, Darlington C: Preliminary observations on tickling oneself. *Nature* 1971;230:598–599.
- 42 Fruhstorfer H, Hermanns M, Latzke L: The effects of thermal stimulation on clinical and experimental itch. *Pain* 1986;24:259–269.
- 43 Gilchrist BA, Rowe JW, Brown RS: Ultraviolet phototherapy of uremic pruritus: Long-term results and possible mechanisms of action. *Ann Intern Med* 1979;91:17–21.
- 44 Lim HW, Vallurupalli S, Meola T, Soter NA: UVB phototherapy is an effective treatment for pruritus in patients infected with HIV. *J Am Acad Dermatol* 1997;37:414–417.
- 45 Baldo A, Sammarco E, Martinelli V, Monfrecola G: UVB phototherapy for pruritus in polycythemia vera. *J Dermatolog Treat* 1996;7:245–246.
- 46 Kaptanoglu AF, Oskay T: Ultraviolet B treatment for pruritus in Hodgkin's lymphoma. *J Eur Acad Dermatol Venereol* 2003;17:489–490.
- 47 Figueiredo A, Ribeiro CA, Goncalo M, Almeida L, Poiates-Baptista A, Teixeira F: Mechanism of action of doxepin in the treatment of chronic urticaria. *Fundam Clin Pharmacol* 1990;4:147–158.
- 48 Peer G, Kivity S, Agami O: Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996;349:1552–1554.
- 49 Metze D, Reimann S, Beissert S, Luger T: Efficacy and safety of naltrexone, an oral opiate antagonist in the treatment of pruritus in internal and dermatological diseases *J Am Acad Dermatol* 1999;41:533–559.
- 50 Cohen SE, Ratner EF, Kreitzman TR, Archer JH, Mignano LR: Nalbuphine is better than naloxone for treatment of side effects after epidural morphine. *Anesth Analg* 1992;75:747–752.
- 51 Zylicz Z, Smits C, Chem D, Krajnik M: Paroxetine for pruritus of advanced cancer. *J Pain Symptom Manage* 1998;16:121–24.
- 52 Bergeron R, Blier P: Cisapride for the treatment of nausea produced by selective serotonin reuptake Inhibitors. *Am J Psychiatry* 1994;151:1084–1086.
- 53 Schworer H, Hartman H, Ramadori G: Relief of cholestatic pruritus by a novel class of drugs: 5-hydroxytryptamine type 3 (5HT3) receptor antagonists: Effectiveness of ondansetron. *Pain* 1995;61:33–37.
- 54 Murphy M, Reaich D, Pai P, Finn P, Carmichael AJ: A randomised placebo-controlled double-blind trial of ondansetron in renal itch. *Br J Dermatol* 2001;145(suppl 59):20–21.
- 55 Kasper S: Clinical efficacy of mirtazepine: A review of meta-analyses of pooled data. *Int Clin Psychopharmacol* 1995;10(suppl 4):25–35.