

# The pathophysiology of pruritus – A review for clinicians

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Pruritus is a troubling and occasionally disabling symptom. For clinicians, over time, ignorance of mechanism has often led to therapeutic frustration. The last decade has seen significant progress in the understanding of the complex pathophysiology of pruritus. Most of that literature has emerged in neurobiology, immunology, and experimental dermatology; little has appeared in palliative care literature. This review synthesizes the current understanding of the mechanism of pruritus and argues that a well-informed knowledge of pathophysiology is necessary to both illuminate this area of clinical practice and enhance strategies of management.

**Keywords:** Pruritus, Pathophysiology, Cytokines, Pruritogens, Histamine, Dorsal horn, Itch receptors

## Introduction

The symptom of pruritus is the source of enormous suffering. Whether it manifests in an acute or chronic state, it is a troubling and occasionally disabling symptom. As clinicians, we have a duty to treat our patients with competency and compassion. That competency should include an informed response to the symptom of pruritus. The last decade has seen an extraordinary progress in the understanding of the basic pathophysiology of pruritus. Few of those developments have been incorporated or taught in the multiple disciplines where itch is a source of considerable suffering to patients. Without that knowledge, itch remains a ‘Cinderella symptom’ where management is simply directed to the underlying disease, treatment remains empirical, myths about pathogenesis persist, clinicians become nihilistic, or patients suffer in silence. Much work needs to be done to integrate this maturation of understanding of the general pathogenesis of pruritus with specific clinical syndromes, such as uremic and cholestatic pruritus. The success of that integration has clear implications for management. Logically, any review of the management of pruritus should also conscientiously attempt to apply these significant developments in pathogenesis to the discussion. The objective of this article is to review the current understanding of the pathogenesis of pruritus. Throughout, basic neuroscience will be tied to the known immunochemical milieu of specific pruritic conditions.

Itch is defined as ‘an unpleasant cutaneous sensation which provokes the desire to scratch’.<sup>1</sup> The

importance of the sensory modality of pruritus – and certainly its evolutionary advantage – lies in the rapid signalling to the brain of the presence of irritating agents and allergens disturbing the integrity of the skin which directly culminates in the initiation of a scratch response. Pruritus may be acute or chronic (6 weeks or more in duration). In 2007, the International Forum for the Study of Itch (IFSI) published a clinical classification of pruritus.<sup>2</sup> This classification consisted of six categories: dermatologic (arising from diseases of the skin), systemic (arising from systemic diseases such as uremic and cholestatic pruritus), neurological (pruritus secondary to nerve damage or irritation such as post-herpetic neuralgia), psychogenic, mixed, and ‘others’ of undetermined origins.

## *The classic somatosensory pathway*

Pruritus is one of the many sensory modalities. Before exploring the current and expanding knowledge of the physiology of pruritus, it is appropriate to summarize the classic sensory pathway. Peripheral sensation is transmitted via free sensory nerve endings in the skin. An action potential is set off along the peripheral nerves to, respectively, the dorsal root ganglia and onto the spinal cord, and the trigeminal ganglion neurons to the trigeminal subnucleus caudalis of the brainstem. Each, in turn, transmits via the spinothalamic and trigeminothalamic tract neurons to the somatosensory cortex in the brain. In addition to a positive signalling ascending from the periphery to the brain, there is a natural inhibitory pathway, well described in pain, that commences in the peri-aqueductal grey matter (PAG) of the mid-brain and descends to the dorsal horn.

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## The pruritus pathway

### *The normal skin*

The site of the initial signalling of pruritus is the complex environment of the human skin, that is, an outer layer (the epidermis), an epidermal–dermal junction, the dermis, and the subcutis. The epidermis contains keratinocytes, Langerhan's cells, melanocytes, and Merkel cells. The dermis is composed of a fibrous matrix and contains dermal mast cells, fibroblasts, macrophages, and dendritic cells. Immune and inflammatory cells such as T-lymphocytes, eosinophils, and basophils may also be present. In addition to this discrete cellular distribution, there is a complex neural network within the dermis and nerve fibres enter the epidermis as afferent free nerve endings.

### *Itch fibres*

For some time, conventional wisdom held several beliefs:

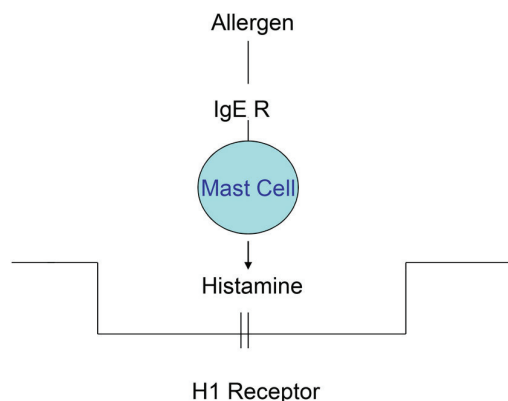
1. That the sensation of itch is transmitted via pain fibres<sup>3</sup> and that there are no discrete itch fibres.
2. That the symptom of itch is a form of low-intensity pain.<sup>3</sup>
3. That itch, of whatever aetiology, is a result of peripheral histamine release by dermal mast cells triggering histamine receptors on afferent nerve fibres.

Research has revealed that these beliefs are false. We now know the following:

1. Itch and pain are separate sensory modalities. While there are communications between the two, they are distinct sensations.<sup>4</sup>
2. A small cohort (approximately 5%) of C fibres is dedicated to the transmission of the sensation of itch.<sup>5</sup>
3. Of those itch-sensitive C fibres, 10% are histamine dependent and 90% are histamine independent.<sup>6</sup> These are mutually exclusive populations of neurons.<sup>6</sup>
4. In addition to unmyelinated C fibres, itch is also transmitted via myelinated A-delta afferents.<sup>7</sup>

These facts have important therapeutic implications. Over time an orthodoxy emerged, and in many quarters continues to prevail, that the best first-line management for pruritus, of whatever origin, are anti-histamines. This orthodoxy is significantly challenged by the above facts and, indeed, overborne in conditions where pruritus is non-histaminergic in origin.

What is the mechanism of the initiation of the itch signal?. While the complete answer to that question is incomplete, we now understand that the initiation of the itch signal involves a complex interaction between skin cells and afferent nerve fibres. The two cohorts of itch fibres – histamine dependent and independent – will be examined.



**Figure 1** The classic model of histamine release secondary to allergens.

### *Histamine-dependent itch fibres*

The classic model of histamine release is an allergen stimulating IgE receptors on the surface of dermal mast cells triggering cell degranulation and release of histamine. Histamine stimulates H1 receptors on afferent nerve endings<sup>8</sup> (see Fig. 1). Histamine may also be released from mast cells by non-IgE stimuli including cytokines, opioids, physical factors, certain antibiotics, and viral and bacterial antigens. Histamine release from dermal mast cells leads to urticaria which is characterized by wheal, flare, and itch.<sup>9</sup> In addition to Histamine 1 receptors, another channel – the transient receptor potential vullinoid-1 (TRPV1 channel) – is needed for histamine transmission.<sup>10</sup> Histamine evokes inward currents only when H1 receptors and TRPV1 are co-expressed.<sup>11</sup> The H1-receptor controls second messenger pathways which activate TRPV1 channels.<sup>12</sup>

Besides the H1 receptor, other histamine receptors that have been identified are H2, H3, and H4 receptors. What, if any, are their role in pruritus?

1. H2 receptors have little if any involvement in pruritus.<sup>8</sup>
2. H3 receptors: H3 receptor activation decreases pruritogen-evoked scratching in mice,<sup>13</sup> while H3 receptor antagonists aggravate itch symptoms, possibly due to an unregulated substance P (SP) release.<sup>14</sup> Histamine regulates SP release via H3 receptors located on afferent nerve endings.<sup>15</sup>
3. H4 receptors have a higher affinity for histamine compared with the H1 receptor.<sup>16</sup> H4 receptor antagonists have shown promising results in experimental models of asthma and pruritus.<sup>17</sup> H4 receptors are expressed on skin cells including Th2 lymphocytes. The role of the latter in pruritus shall be described later in this review.

### *Histamine-independent itch fibres*

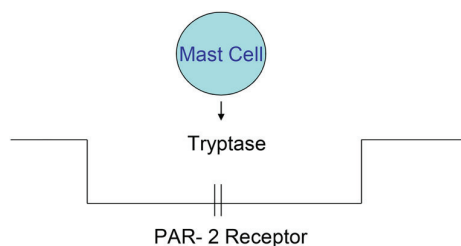
The mechanism of activating histamine-independent itch is complex and involves an altered immunological milieu of the epidermal and dermal layer of

the skin. Central to this complexity is a communication or cross-talking between multiple skin cells and the afferent nerve endings. Research in the last decade has described and verified a series of non-histamine pruritogens and itch receptors. Despite a plethora of receptors, described below, currently there are only two itch pathways from the skin to the brain that have been described.<sup>18</sup> The first is histaminergic. The other is via protease-activated receptor-2 (PAR-2). The mechanism of pruritus involving the activation by pruritogens of other itch receptors is not known. A convenient place to commence this survey is the mast cell–nerve functional unit – the interface of dermal mast cells and afferent nerve endings.

### Mast cells pruritogens and associated itch receptors

Besides histamine, dermal mast cells produce multiple other pruritogens. Those pruritogens activate a series of non-histaminergic itch receptors. Those pruritogens and their respective receptors include:

1. *Tryptase*: Tryptase is a serine protease that activates the PAR-2 receptor (see Fig. 2). In atopic dermatitis, a notoriously pruritic condition, there is an enhanced expression of both tryptase and PAR-2 receptors in the lesional skin.<sup>19</sup> In haemodialysis patients with uremic pruritus, there is an increased serum level of mast cell tryptase.<sup>20</sup>
2. *Thromboxane A2*: Thromboxane A2 is a pruritogen that triggers the TP receptor.<sup>21</sup> In Polycythaemia Rubra Vera, a highly pruritic condition, there is a marked increase in Thromboxane A2.
3. *Tumour Necrosis Factor-alpha (TNF-alpha)*: TNF-alpha activates the TNF receptor. TNF-alpha sensitizes nociceptive nerve endings and decreases the threshold of their activation.
4. *Leukotriene B4 (LB4)*: LB4 is a potent proinflammatory lipid mediator derived from arachidonic acid. It is highly pruritogenic.<sup>22</sup> LB4 activates the TRPV-1 channel and BLT-2 receptors.<sup>23,24</sup> The TRPV-1 channel is vital to itch, histaminergic and non-histaminergic, and will be described in more detail later. LB4 is increased in patients with uremic pruritus and in the lesional skin of patients with atopic dermatitis<sup>25</sup> and psoriasis.<sup>26</sup>



**Figure 2** Mast cell tryptase activates protease-activated receptors-2 (PAR-2 receptors).

5. *Substance P (SP)*: SP is an important neurotransmitter of sensory modalities, including pain and pruritus. SP is produced by dermal mast cells. There are several important autocrine mechanism involving mast cells and SP that shall be described in detail latter.
6. *Interleukin-31 (IL-31)*: IL-31 is pruritogenic.<sup>27</sup> It activates IL-31 receptors. In addition to dermal mast cells, IL-31 is also produced by keratinocytes and Th-2 lymphocytes.<sup>28</sup> In atopic dermatitis, IL-31 is increased and there is a clear correlation with the severity of pruritus.<sup>29</sup> The lesional skin of prurigo nodularis has high levels of IL-31.<sup>30</sup>
7. *Endothelin-1 (ET-1)* is a potent pruritogen.<sup>31</sup> It is produced by mast cells, keratinocytes, and endothelial cells. It stimulates ET-A receptors.<sup>32</sup>
8. *Nerve growth factor (NGF)*: NGF is a neurotrophin that affects nerve growth and survival. Among the sources of NGF are dermal mast cells. NGF has multiple roles in the transmission of sensory modalities, including itch. Those roles of NGF include:
  - (a) Initiating the sprouting of epidermal nerve fibres so increasing sensory nerve innervation.<sup>33</sup>
  - (b) Sensitizing some receptors including TRPV-1. This sensitization lowers the activation threshold for itch signalling.
  - (c) Inducing mast cell degranulation.
  - (d) Upregulating the expression of other neuropeptides such as SP, a critical peptide in the transmission of the pruritus signal.
  - (e) NGF is transported along axons towards the dorsal root ganglion to induce, in turn, an upregulation of proteins involved in nerve growth and sensitivity. NGF is elevated in several pruritic conditions such as atopic dermatitis and prurigo nodularis.<sup>34</sup> NGF plays a crucial role in the peripheral sensitization associated with chronic pruritus. This shall be described in more detail later in this review. A summary of the histaminergic and non-histaminergic pruritogens produced by dermal mast cells appears in Fig. 3.

### Itch receptors on afferent nerve endings

Research has revealed multiple itch receptors – histaminergic and non-histaminergic – on afferent nerve endings. These receptors include:

- (a) Histamine receptors.
- (b) *PAR-2 receptors*: This receptor is activated by multiple proteases including mast cell tryptase. Activation of PAR-2 receptors has many effects. First, the activation of PAR-2 receptors sensitizes TRPV-1 channels. In addition, their activation stimulates the release of SP and calcitonin gene-related peptide (CGRP) from sensory nerve endings.<sup>35</sup> SP, in turn, stimulates mast cell degranulation, providing a positive feedback mechanism. CGRP inhibits SP degradation and enhances the release of SP amplifying its effects. Counteracting

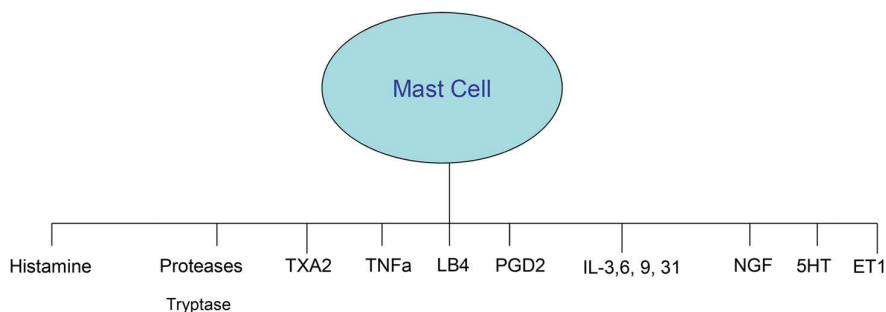


Figure 3 Cytokines and other products released by dermal cells that may participate in the pathogenesis of pruritus.

this process, tryptases inactivate CGRP (see Fig. 10).

- (c) *TNF receptors*: This receptor is activated by TNF-alpha. Once activated these receptors sensitize afferent nerve endings.<sup>5</sup>
- (d) *TRPV-1 channels*: These channels belong to an important superfamily of TRP channels that act as non-selective calcium-permeable transduction channels. The TRPV-1 channels are important for the transmission of the itch signal. Their role in histaminergic itch transmission was described previously. TRPV-1 channels are triggered by noxious heat (>42°C), an acidic pH (pH < 5.9), LB4, and capsaicin<sup>33</sup> (see Fig. 4). TRPV-1 channels are sensitized by PAR-2 agonists (see Fig. 5). This, in turn, leads to a lowered threshold for TRPV-1 stimulation. There is a phenomenon of short-term and chronic stimulation of TRPV-1 channels.<sup>36</sup> With short-term activation, cation channels open, calcium ions enter, depolarization occurs and there is an acute sensation of pain and pruritus. Over time, with chronic stimulation of these channels, calcium influx desensitizes the channel as a protection against the toxic presence of calcium, SP is deleted and there is now an analgesic, anti-pruritic effect. This effect is the basis for the therapeutic application of capsaicin to treat itch in many conditions, including uremic pruritus, brachioradial pruritus, and prurigo nodularis.<sup>36,37</sup>

TRPV-1 channels may form part of the mechanism of itch transmission in cholestatic pruritus. In recent years, an important breakthrough occurred

in the understanding of the precise mechanism of this often disabling condition. In cholestatic pruritus, there is a significant increase in autotaxin and lysophosphatidic acid (LPA).<sup>38</sup> Autotaxin is an enzyme that converts lysophosphatidylcholine to LPA. Serum levels of autotaxin are markedly higher in cholestatic patients with itch than those without itch and these levels are correlated with the intensity of the itch.<sup>39</sup> Three facts are intriguing – LPA evokes scratching behaviour in mice,<sup>40</sup> LPA activates its own receptors, and LPA is capable of directly activating TRPV-1 channels.<sup>41</sup>

- (e) *TP receptors*.
- (f) *IL-31 receptors*: IL-31 signals through a receptor composed of IL-31RA co-expressed with the oncostatin M receptor<sup>28</sup> as a heterodimeric receptor.
- (g) *G protein-coupled receptors (GPCR)*: This is a large family of receptors. In addition to histamine receptors and PAR-2 receptors other members of this family that are relevant to pruritus include:
  - A. *MrgprA3 receptors*: These receptors are activated by chloroquine, an anti-malarial medication.<sup>42</sup> This explains the notoriously pruritogenic qualities of this medication and the fact that this pruritus is unresponsive to antihistamines.
  - B. *MrgpC11 receptor*: This receptor is activated by BAM8-22.<sup>43</sup>
  - C. *TGR5 receptor*: Also known as the G-protein coupled bile acid receptor-1. This receptor is expressed on small-size sensory neurons. Bile acids selectively act at this receptor.

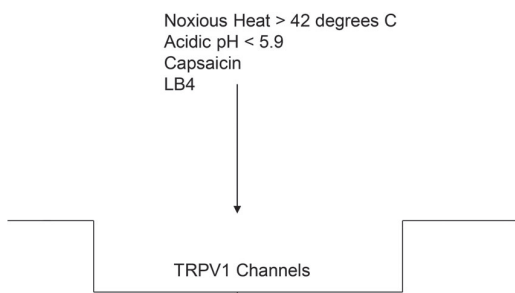


Figure 4 TRPV-1 channels are activated by several conditions, substances, and cytokines. Note – LB4 is leukotriene B4.

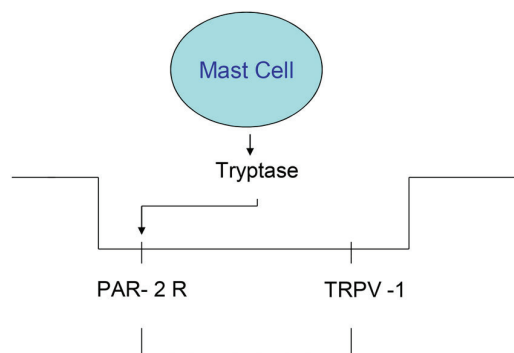


Figure 5 TRPV-1 receptors are sensitized by PAR-2 agonists.

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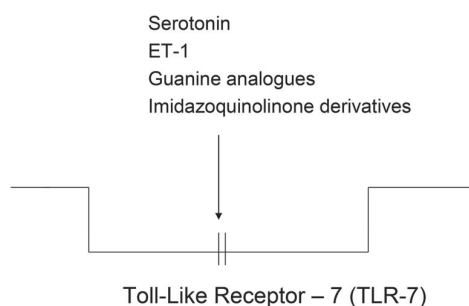


Figure 6 Toll-like receptor-7 (TLR-7).

- (h) *Toll-like receptor-7 (TLR-7)*:<sup>44</sup> TLRs detect foreign pathogens and endogenous ligands leading to rapid defensive responses such as scratching. The TLR-7 is activated by certain anti-viral agents as guanine analogues and imidazoquinolone derivatives, serotonin, and ET-1 causing pruritus.<sup>44,45</sup> This receptor is co-located with the TRPV-1 channel and GPCR (MrgprA3) receptor<sup>44</sup> (see Fig. 6). In addition, TLR-3 receptors are highly co-localized with TRPV-1 and may also serve as itch receptors.<sup>46</sup>
- (i) *TRPM8 receptors*: These are cold receptors. Activation of these receptors suppresses itch.<sup>36</sup> It is proposed that the mechanism of action of cold compresses and menthol in suppressing itch is through the activation of these receptors.<sup>47</sup>
- (j) *5-HT receptors subtype-2*: The intradermal injection of 5-HT (serotonin) evokes scratching in rodents via this receptor.<sup>48</sup>
- (k) *TRPA-1 channels*: These channels play a significant role in acute histamine independent pruritus. Both MrgprA3 and MrgpC11 receptors require the activation of co-located TRPA-1 channels to initiate the itch signal.<sup>43</sup> TRPA-1 channels are also required for the dramatic skin changes triggered by chronic itch and scratching, including epidermal hyperplasia and changes in gene expression in the skin.<sup>43</sup> In atopic dermatitis, keratinocytes release the cytokine thymic stromal lymphoietin which acts directly on TRPA1 sensory neurons to trigger pruritus.<sup>49</sup>
- (l) *Endocannabinoid receptor 1 (CB-1)*: This receptor is co-located with TRPV-1 channels on sensory neurons.<sup>50</sup> CB-1 agonists suppress histamine-induced pruritus.<sup>51</sup>

### Mast cell receptors and autocrine mechanisms of feedback

In addition to dermal mast cells producing and releasing substances that stimulate afferent nerve endings, they also have itch-specific receptors themselves that are involved in a complex autocrine mechanism that affects a positive or negative feedback mechanism on mast cell activity. These receptors may be activated by substances produced by the dermal mast cells themselves or other cells within the skin. Dermal mast cell receptors relevant to pruritus include:

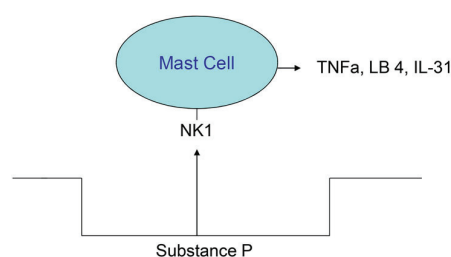


Figure 7 Afferent nerve endings release SP which activates NK-1 receptors on the surface of dermal mast cells triggering the release of TNF-alpha, LB4, and IL-31.

### SP-related system

At the afferent nerve membrane, SP is involved in a common pathway of itch signalling along the afferent nerve. In addition, SP is released in a retrograde fashion back into the peri-neural area adjacent to dermal mast cells. There are two main effects. First, relevant to histaminergic pruritus, SP activates dermal mast cells to produce further histamine. Second, SP stimulates NK-1, a receptor on the surface of dermal mast cells. This stimulates mast cells to release TNF-alpha, LB4, and IL-31, all of which are pruritogens (see Fig. 7). TNF-alpha, in turn, sensitizes nociceptive nerve endings producing a self-amplifying loop between the neurons and the dermal mast cells. NK-1 receptors are over expressed in the skin of patients with atopic dermatitis.

### Tryptase-related system

Tryptase released by dermal mast cells stimulates PAR-2 receptors and, in turn, stimulates PAR-2 receptors on the surface of dermal mast cells. As stated above, this activation leads to the release of SP and CGRP from the afferent nerve endings. CGRP enhances the release of SP and protects it from degradation. Tryptase inactivates CGRP (see Figs. 8–10).

### ET-1-related system

On the surface of dermal mast cells, there are two endothelin receptors – ETA and ETB receptors.<sup>52</sup> Stimulating ETA receptors has a pro-pruritogenic effect. Activating ETB receptors has an anti-

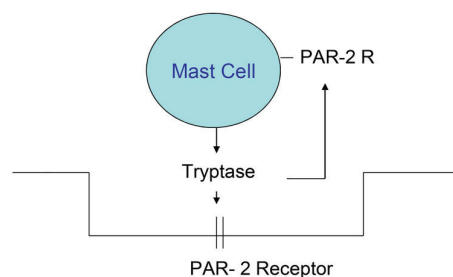
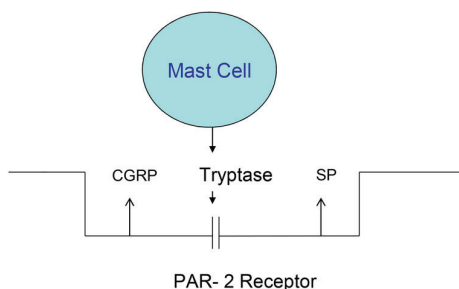
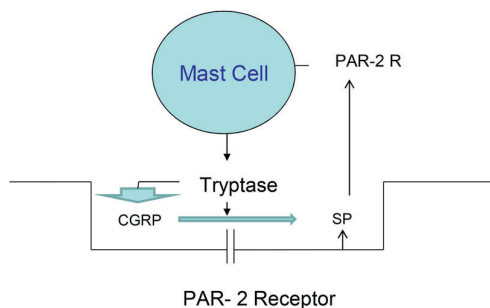


Figure 8 Tryptase activates PAR-2 receptors on both the afferent nerve endings and on the surface of dermal mast cells.



**Figure 9** The activation of PAR-2 receptors on sensory afferents leads to the release of Substance P (SP) and calcitonin gene-related peptide (CGRP).



**Figure 10** SP, released by the sensory afferents, activates PAR-2 receptors on dermal mast cells to release further tryptase. CGRP enhances the release of SP from sensory afferents and protects it from degradation. Tryptase inactivates CGRP.

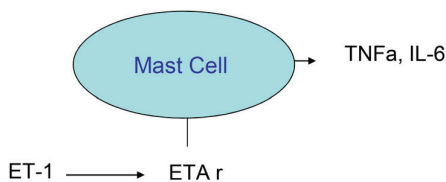
pruritogenic effect. ET-1 stimulates ETA receptors which, in turn, stimulate dermal mast cells to release TNF-alpha and IL-6 (see Fig. 11).

**BLT-2-receptor-related system**

BLT-2 receptors lie on the surface of dermal mast cells. LB4 stimulates this receptor.<sup>53</sup> In addition, 12 (S)-HPETE, synthesized from arachidonic acid, stimulates BLT-2 receptors on mast cells to release serotonin which, in turn, induces scratching in mice. The involvement of 12 (S) HPETE in humans is unknown.

**Endocannabinoid receptors**

Dermal mast cells have two endocannabinoid receptors – CB-1 and CB-2. In addition to dermal mast cells, these receptors also lie on keratinocytes and



**Figure 11** Endothelin-1 activates ETA receptors on the surface of dermal mast cells, triggering them to release TNF-alpha and IL-6.

fibroblasts. Their activation leads to an inhibition of pruritus.<sup>54</sup>

**Kappa-opioid receptors (KOR)**

Activation of these receptors has an anti-pruritic effect.<sup>55</sup>

**TRPV channels**

Activation of TRPV2 channels causes mast cells to degranulate. TRPV-3 may act as a regulator of TRPV-1-mediated itch.<sup>56</sup> TRPV-4 channels are activated by eicosanoids such as prostaglandins.

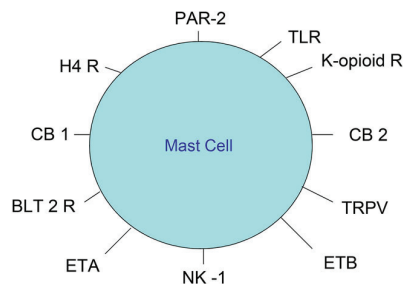
A summary of these dermal mast cell receptors relevant to pruritus appears in Fig. 12.

*The role of lymphocytes*

The immune system of the skin is complex. The two main lymphocytes are Th-1 and Th-2 lymphocytes. At any one time, there is a balance in the presence and activity of these lymphocytes. Each class of lymphocyte produces specific cytokines that exert actions, directly or indirectly, on the immuno-chemical milieu of the skin and facilitates cross-talking with other skin cells. It appears that both class of lymphocytes play a role in the pathophysiology of pruritus:

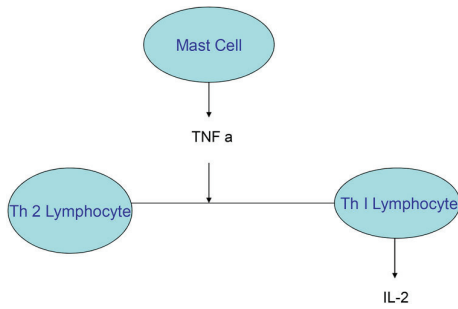
1. *Th1 lymphocytes* produce IL-2, IL-6, and IFN-gamma. IL-2 is pruritogenic. IFN-gamma substantially upregulates IL-31 receptors.<sup>28</sup>
2. *Th2 lymphocytes* produce IL-3, IL-4, IL-10, and IL-31. IL-3, -4, and -10 regulate mast cell activity and IL-31 is pruritogenic.

In pruritic states, there may be a preponderance of the presence and activity of one of these lymphocytes. In uremic pruritus, for instance, there is a preponderance of Th-1 lymphocytes and IL-2 levels are significantly raised.<sup>57</sup> That preponderance is driven by, among other factors, TNF-alpha produced by dermal mast cells. This is a good example of cross-talking between cells: TNF-alpha produced by dermal mast cells shifts the preponderance of



**Figure 12** A summary of receptors relevant to pruritus on the surface of dermal mast cells. H4R, Histamine 4 receptor; TLR, toll-like receptor; CB, endocannabinoid receptors; ET, endothelin receptors; NK-1, neurokinin-1 receptor; K-opioid, kappa-opioid receptor; TRPV, transient receptor potential vanilloid receptors.

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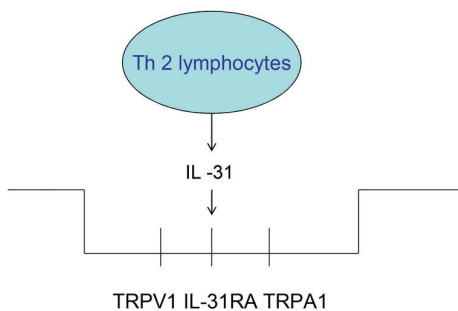
**Figure 13** TNF-alpha shifts the expression of Th lymphocytes to a preponderance of Th1 lymphocytes. The latter produce IL-2 which is pruritogenic.

lymphocytes towards Th-1 lymphocytes which, in turn, produces IL-2 which is pruritogenic (see Fig. 13).

The pruritogenic qualities of IL-2 are also relevant in medical oncology. High-dose IL-2 is given to patients with certain malignancies including metastatic renal cell carcinoma and malignant melanoma. This treatment often causes intense itch.<sup>58</sup> This itch is not relieved by anti-histamines. Calcineurin inhibitors, which block the production of IL-2, can relieve this itch.

While Th-1 lymphocytes predominate in uremic pruritus, Th-2 lymphocytes predominate in other pruritic conditions such as atopic dermatitis and cutaneous T-cell lymphoma. In atopic dermatitis, IL-31 is markedly released by Th-2 lymphocytes.<sup>59</sup> In cutaneous T-cell lymphoma, the production of IL-31 and the presence of IL-31RA 'can be seen as the long-discussed neuroimmune link between ... Th-2 cells and sensory nerves for the generation of T-cell mediated itch'.<sup>30</sup> Cevikbas *et al.*<sup>60</sup> showed that IL-31 RA is a functional receptor on a small sub-population of itch neurons that co-express IL-31RA, TRPV-1, and TRPA-1. This is a crucial link between Th-2 lymphocytes and sensory neurons for the generation of T-cell-mediated pruritus<sup>60</sup> (see Fig. 14).

Histamine 4 receptors lie on the surface of Th-2 lymphocytes.<sup>61</sup> In atopic dermatitis, these receptors are activated by foreign antigens. Cutaneous



**Figure 14** Th-2 lymphocytes release IL-31. IL-31 activates the IL-31 receptor. That receptor is co-expressed on a sub-population of neurons with TRPV-1 and TRPA-1 receptors.

Staphylococcus Aureus superantigens bind to the H4 receptors triggering the Th-2 lymphocytes to release IL-31. This may explain the surge in pruritus in patients with atopic dermatitis when there is a bacterial infection.<sup>54</sup>

### Eosinophils

Eosinophils are granulocytes that develop and mature in the bone marrow before migrating into the blood. They migrate to inflammatory sites in tissues in response to certain chemokines and LB4. They produce multiple substances that are relevant to pruritus, including eosinophilic cationic protein (ECP), eosinophilic-derived neurotoxin, major basis protein, brain-derived neurotropic factor (BDNF), NGF, SP, and vasoactive intestinal peptide (see Fig. 15). The levels of ECP correlate with the severity of pruritus,<sup>54</sup> levels of BDNF correlates with disease activity in atopic dermatitis<sup>62</sup>, and NGF released by eosinophils leads to the growth of afferent nerve endings.

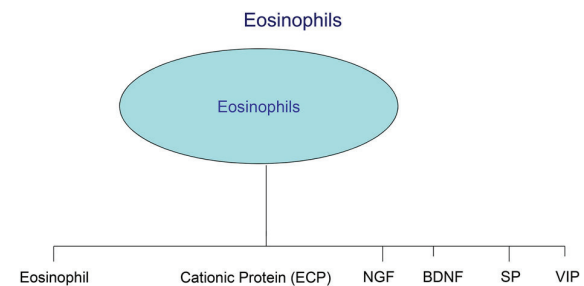
### Basophils

Basophils are granulocytes. They contain large cytoplasmic granules. They have surface receptors that bind IgE. When activated, basophils degranulate to release histamine,<sup>63</sup> proteoglycans, and proteolytic enzymes. That degranulation is enhanced in response to various secretagogues including LB4.<sup>64</sup> In polycythaemia rubra vera with aquagenic pruritus, serum levels of CD + 63 basophils are increased.<sup>65</sup>

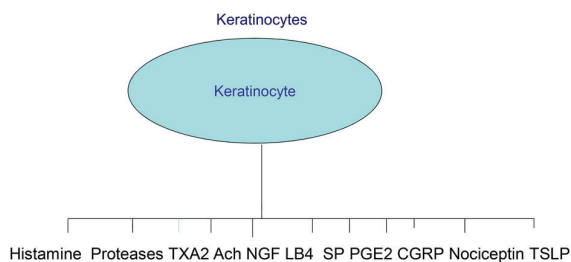
### Keratinocytes

Keratinocytes are highly sophisticated cells. They have several critical roles in the pathogenesis of pruritus. They produce multiple cytokines and peptides that directly or indirectly stimulate itch receptors on afferent nerve endings (see Fig. 16).

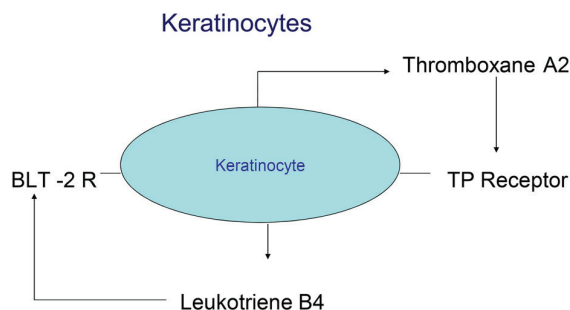
These products are involved in complex cross-talking between relevant skin cells, including dermal mast cells and T-lymphocytes, and sensory nerve afferents. Keratinocytes have multiple receptors on their surface relevant to pruritus. Keratinocytes have ATP voltage gated ion channels and receptor ligands



**Figure 15** Products of eosinophils that are relevant to pruritus. NGF = nerve growth factor; BDNF, brain-derived neurotrophic factor; SP = substance P; VIP, vasoactive intestinal peptide.



**Figure 16** Products of keratinocytes that are relevant to pruritus. NGF, nerve growth factor; LB4, leukotriene B4; SP, substance P; PGE2, prostaglandin E2; CGRP, calcitonin gene-related peptide; TXA2, thromboxane A2; Ach, acetylcholine; TSLP, thymic stromal lymphopoietin.



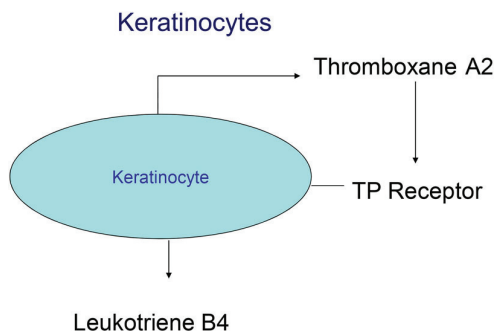
**Figure 18** An autocrine process whereby keratinocytes release Thromboxane A2, activating the TP receptors which, in turn, stimulates the release of LB4 which activates BLT-2 receptors on the surface of keratinocytes.

similar to the C fibres themselves. Keratinocyte receptors may be stimulated by substances released by other skin cells including dermal mast cells and, in an auto-crine fashion, by the keratinocytes themselves. The surface receptors on keratinocytes include:

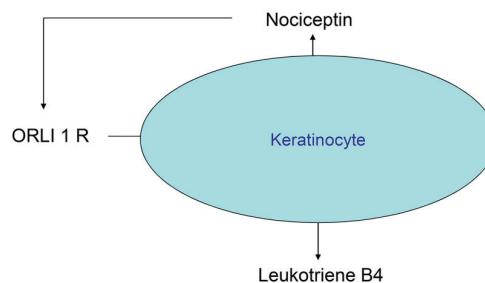
1. *Histamine-1 receptors*: Activation of these receptors by histamine causes keratinocytes to release NGF.
2. *Tropomyosin-related kinase A receptors (TrkA receptors)* (see Fig. 20): This is a high-affinity receptor for NGF.<sup>66</sup> Both NGF and TrkA receptors are over expressed in the keratinocytes of patients with atopic dermatitis, pruritic psoriasis, and prurigo nodularis.
3. *TP receptors*: Keratinocytes release Thromboxane A2. This stimulates TP receptors on the surface of keratinocytes.<sup>21</sup> This, in turn, causes keratinocytes to release LB4 (see Fig. 17).
4. *BLT-2 receptors*: LB4 activates BLT-2 receptors. An autocrine process occurs whereby this and the process outlined above combine: keratinocytes release Thromboxane A2 which activates the TP receptor on their surface causing keratinocytes to release LB4 which, in turn, activates the BLT-2 receptor (see Fig. 18).
5. *Opioid receptor-like 1 receptor (ORLI-1 receptor)*: Keratinocytes release nociceptin which stimulates ORLI-1 receptors on the surface of keratinocytes.

This, in turn, causes the keratinocyte to release LB4 (see Fig. 19).

6. *SP receptor*: There is a positive feedback whereby SP stimulates the SP receptor on the surface of keratinocytes to further release SP.
7. *PAR-2 receptors*: These receptors are stimulated by Tryptase. Activation of PAR-2 receptors on keratinocytes induces LB4 production<sup>67</sup> and keratinocyte maturation.<sup>68</sup>
8. *TRPV-1 receptors*: These receptors are dramatically over expressed in patients with prurigo nodularis.
9. *IL-31 receptors*: In atopic dermatitis, there is an upregulation of IL-31 receptors on keratinocytes. This fact completes a triad of observations in atopic dermatitis: an increase in serum IL-31, an increased concentration of IL-31 in the skin and, as described, an up-regulation of IL-31 receptors on keratinocytes.
10. *IL-2 receptor*: This receptor is expressed weakly.
11. *Endocannabinoid receptors*: There are two endocannabinoid receptors on the surface of keratinocytes: CB1 and CB2 receptors.<sup>69</sup> Activation of these receptors inhibits pruritus.
12. *NK-1 receptors*: They are stimulated by SP.
13. *Mu-opioid receptors (MOR)*.<sup>70</sup>
14. *KOR*.<sup>71</sup>
15. *TRPV3 receptors*.<sup>36</sup>
16. *TNF receptors*: TNF-alpha enhances the production of NGF by keratinocytes by activating this receptor.<sup>72</sup>



**Figure 17** Keratinocytes produce thromboxane A2 which activates TP receptors on their surface. This, in turn, causes keratinocytes to release leukotriene B4 (LB4). LB4 is very pruritogenic.



**Figure 19** Keratinocytes produce nociceptin which activates the ORLI-1 receptor which, in turn, triggers keratinocytes to release leukotriene B4.



A summary diagram of keratinocyte receptors relevant to pruritus appears in Fig. 20.

### Cross-talking between skin cells and the itch-specific afferent nerve endings

In the process of the formation of an immunochemical milieu initiating an itch signal, there is a sophisticated cross-talking between skin cells and the itch-specific afferent nerve endings. Given the multiple substances released by skin cells and the range of receptors present, this interchange may be very complex. This is a relatively new area of enquiry and further research will be needed to 'map' out these cross-communications in any given pruritic condition. In addition, and foundationally, the question that remains unanswered in many pruritic conditions is what are the initial triggers, the first steps, in this cascade of immunological and chemical response that culminates in the stimulation of itch receptors on the afferent nerve fibres.

### Central transmission of the itch signal

#### Afferent fibres to the dorsal horn of the spinal cord

Once itch receptors are stimulated in itch-specific terminal afferent fibres the itch signal is transmitted centrally, first to the dorsal root ganglia and then onto the dorsal horn of the spinal cord. As stated, currently, there are two itch pathways from the skin to the brain that have been described.<sup>18</sup> The first is histaminergic. The other is via PAR-2 receptors. The mechanism of pruritus involving the activation by pruritogens of other itch receptors is not known and calls for further research.

Histaminergic and non-histaminergic primary afferents converge on and activate distinct secondary neurons. This suggests mutually exclusive projections in the spinothalamic tract.<sup>6</sup> At the dorsal horn synapse, two processes occur in relation to the itch signal – modulation and transmission. In terms of modulation, some, although not a complete, understanding has emerged of a natural inhibitory

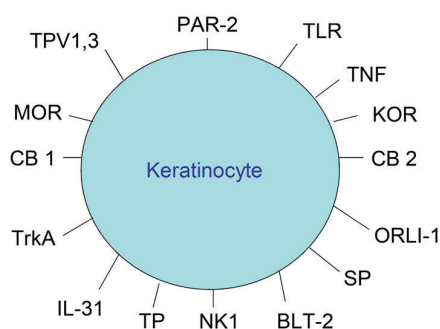


Figure 20 Keratinocyte receptors relevant to pruritus. See text for the complete name of each receptor.

pathway for itch descending from PAG. This will be discussed later in this article. In addition, there are interneurons (Bhlhb5 neurons) that transmit an inhibitory signal from the pain pathway.<sup>73</sup>

At the pre-synaptic membrane, in the dorsal horn, multiple pre-synaptic neurotransmitters may be involved in the signalling across the synaptic junction to the post-synaptic membrane. Certainly, our knowledge from the pathophysiology of pain indicates the involvement, among others, of SP and glutamate. With itch, two other neurotransmitters are likely to be involved – CGRP and gastrin releasing peptide (GRP). At the post-synaptic membrane, which itch receptors transmit the itch signal at the dorsal horn?. To date, several have been identified:

1. *Gastrin releasing peptide receptor (GRPR)*:<sup>74</sup> It is predominantly, if not solely, a receptor for histaminergic-independent transmission of itch.<sup>75</sup> With the discovery of this receptor, it was surmised that GRP, released from the pre-synaptic membrane, would be the principal neurotransmitter stimulating the GRP receptor. Further research has found that this is not true. In 2011, Koga *et al.*<sup>76</sup> showed that glutamate acts as 'the principal neurotransmitter' for the GRPR in the mammalian spinal cord (see Fig. 21).
2. *Neuromedin B receptor (NMBR)*: Neuromedin and bombesin (two peptides that are related to GRP) cause itch and their effect appears to be mediated by the NMBR.<sup>77</sup> Su and Ko<sup>77</sup> demonstrated that NMBR and the central GRPR act independently to elicit scratching behaviour.
3. *NK-1 receptor*: This is activated by SP (see Fig. 22). As stated above, NK-1 receptors also occur peripherally on dermal mast cells and keratinocytes. Aprepitant, a selective NK-1 receptor antagonist, attenuated itch severity in patients with intractable chronic pruritus of various aetiologies,<sup>78</sup> solid tumours<sup>79</sup>, and cutaneous T-cell lymphomas.<sup>80,81</sup>
4. *Opioid receptors*: For some years one of the proposed theories for the pathogenesis of pruritus was the 'opioid hypothesis'. In essence, this states that pruritus was caused solely, or at least in part, due to an

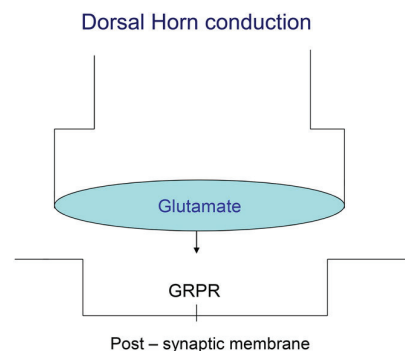
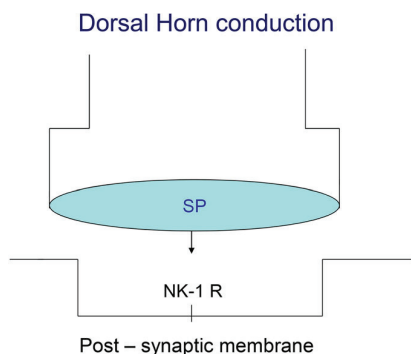
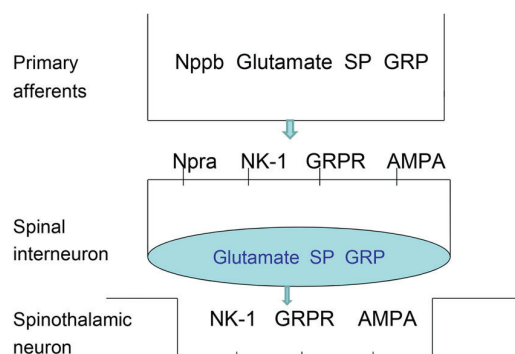


Figure 21 At the dorsal horn, glutamate activates the gastrin-releasing peptide receptor (GRPR) on the post-synaptic membrane.



**Figure 22** At the dorsal horn, substance P activates the NK-1 receptor on the post-synaptic membrane.



**Figure 23** Primary afferents release neurotransmitters to receptors on the surface of spinal interneurons. These then, in turn, release neurotransmitters to the surface of spinothalamic neurons which transmits the signal of itch.

increased opioidergic tone. We know the following facts:

- (a) The systemic administration of opioids can result in pruritus. It is a rare side effect.
  - (b) Spinal/epidural administration of morphine frequently causes segmental pruritus.<sup>82</sup> This is a dose-dependent phenomenon.
  - (c) At the post-synaptic membrane in the dorsal horn, there are two main opioid receptors – MOR and KOR.
  - (d) Activation of the MOR at the dorsal horn causes a transmission of itch.
  - (e) The GRPR is extensively co-located with the morphine receptor-1D isoform in the spinal cord. Antagonism of GRPR abolishes morphine-induced itch.<sup>83</sup> The GRPR receptor is, therefore, almost certainly implicated in opioid-induced itch.<sup>84</sup>
  - (f) Activation of the KORs suppresses itch transmission, peripherally and centrally.<sup>85</sup> The kappa-opioid agonist, nalfurafine, for instance, is effective in relieving intractable uremic pruritus.<sup>86</sup>
  - (g) It is speculated that endogenous opioid peptides accumulate in the plasma of patients with cholestatic pruritus contributing to the pruritus of cholestasis by activating opioid receptors.<sup>87</sup>
5. *Natriuretic peptide receptor A (Npra)*: Natriuretic polypeptide B (Nppb) is involved in the spinal transmission of itch. Npra is the receptor for Nppb. Mishra and Hoon reported that Nppb is released from a subset of afferent itch fibers, exciting interneurons that express Npra receptors.<sup>88</sup> Once activated, these interneurons ultimately excite downstream GRPR-expressing neurons. This is one example of the complex neurocircuitry of itch at the dorsal horn that is being steadily explored (see Fig. 23).
  6. *AMPA receptors*: Glutamate activates the AMPA receptor, a likely candidate for itch transmission.<sup>76</sup>

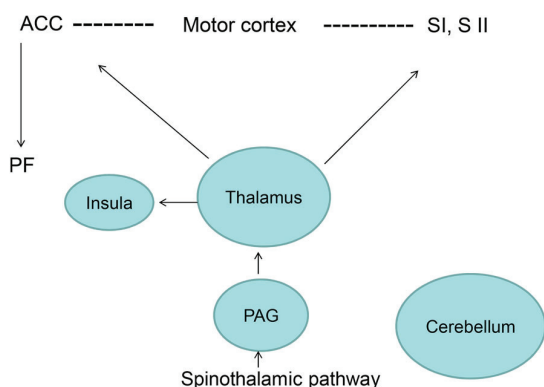
### Spinal cord to brain

The current understanding of the central processing of pruritus and the subsequent scratch response is derived from human studies using the positron emission

tomography and fractional MRI during stimulation with pruritogens. The signalling of itch follows the conventional somatosensory pathway: primary afferent neuron transmission to spinothalamic neurons that decussate in the spinal cord and ascend in the lateral spinothalamic tracts to the thalamus. From the thalamus, there is a co-activation of multiple areas of the brain. There is no single central itch centre. The areas of the brain that are co-activated are:

1. The somatosensory cortex areas I and II. These areas reflect the detection, localization, and discrimination of itch.
2. The somatosensory cortex area II, the insular cortex and the claustrum have discrete areas that respond to both presence of itch and the intensity of itch.<sup>88</sup>
3. Anterior cingulate cortex and the insular cortex. These areas integrate the sensory and emotional experience of pruritus. That includes the suffering associated with pruritus and the memory of past experiences with pruritus.<sup>47</sup>
4. Pre-motor area and the supplementary motor area.<sup>88</sup> Here, the scratching response is planned. In the pre-motor area, there is ipsilateral activation: an itch felt on the right arm leads to the left hand scratching that area. In addition, signals travel to the cerebellum to coordinate this motor response.<sup>89</sup>
5. The motivation and craving to scratch is centred in the prefrontal cortex and striatum.<sup>88</sup>
6. There is a strong correlation between the relief of itch with scratching and the activity of the brain's reward circuits, especially in discrete formations of the mid-brain including the substantia nigra, ventral tegmental area, and the raphe nucleus.<sup>90</sup> This evidence, drawn from functional neuroimaging, may answer the question of why scratching is pleasurable.

An interesting phenomenon is 'contagious itching' – seeing other people scratch can induce a sensation of itch and an urge to scratch oneself.<sup>91</sup> This may be due to the presence of mirror neurons that fire when a primate observes an action performed by another. In humans, brain activity consistent with mirror



**Figure 24 Central processing of pruritus.** Itch fibres ascend in the spinothalamic pathway to the thalamus. Multiple areas of the brain are coactivated including the primary and secondary somatosensory cortices (SI, SII), anterior cingulate cortex (ACC), insula cortex, and the prefrontal cortex (PF).

neurons have been found in the premotor cortex, the supplementary motor area, the primary somatosensory cortex, and the inferior parietal cortex.<sup>92</sup>

For a summary of these central pathways see Fig. 24.

### An intrinsic anti-pruritic system

The inhibitory pathway for pain has been well described. Does the body have a mechanism for inhibiting itch? An intrinsic system for pruritus is being gradually described. It has several components:

1. *An intrinsic inhibitory pathway:* There are two main pathways. The first is an *ascending* signal from the PAG to the thalamus.<sup>93</sup> The second is a *descending* signal from the PAG to the dorsal horn.<sup>93</sup>
2. At the dorsal horn, there are interneurons that give an inhibitory signal reducing the final itch signalling.
3. In addition, there are interneurons that transmit an inhibitory signal from the pain pathway. These spinal interneurons are Bhlhb5 fibres. This may explain, at least partly, why pain inhibits an acute itch.<sup>73</sup>
4. KORs which are located both peripherally and centrally: peripherally on dermal mast cells, keratinocytes, and fibroblasts and centrally at the dorsal horn.
5. Peripheral receptors including:
  - (a) CB1 and CB2 endocannabinoid receptors.
  - (b) Cold receptors (TRPM8).

### Itch and sensitization

In pain, the phenomena of peripheral and central sensitization are well described. Does a similar process occur with chronic pruritus?. Circumstantial evidence indicates that it does.

#### Peripheral sensitization

Peripheral sensitization is characterized by a decreased threshold and increased responsiveness to stimulation.

There is a good evidence for the existence of a phenomenon of peripheral sensitization in pruritus. The threshold for electrically invoked itch was lower in skin from patients with atopic dermatitis compared to normal healthy control skin.<sup>94</sup> Pruritogen-sensitive C fibers exhibit high levels of spontaneous firing.<sup>95</sup> The dose of pruritogen required to evoke itch in the lesional skin of patients with atopic dermatitis was lower than in normal healthy skin.<sup>96</sup>

In terms of peripheral sensitization, chronic itch is associated with an increase in NGF activity and, as a result, the number of nerve endings in the skin.<sup>97</sup> In the epidermis, there is a natural balance between the stimulation and inhibition of nerve growth. NGF stimulates and Semaphorin 3A inhibits nerve growth. In peripheral sensitization, there is a profound imbalance between these factors leading to heightened NGF activity and hyperinnervation of nerve fibres locally. In addition to the stimulation of nerve growth, NGF also upregulates neuropeptides such as SP and CGRP. Finally, NGF is conveyed via retrograde axonal transport to the dorsal root ganglia where the gene expression of neuropeptides and receptor molecules such as TRPV-1 is increased.<sup>98</sup> In peripherally mediated hyperalgesia, one mechanism is the activation of PAR-2 receptors which, in turn, sensitize TRPV-1 channels. A similar phenomenon may occur in pruritus.

#### Central sensitization

In terms of central sensitization, chronic pruritus causes an increasing sensitization of spinothalamic neurons and two phenomena occur in the skin:

1. *Punctate hyperknesis:* This is an intense feeling of itch with usual itch stimulation.
2. *Alloknesis:* This is the experience of itch with the simplest touch of the skin including dressing, undressing, light touch, and sweating.

These phenomena are analogous to two manifestations of central sensitization in pain – hyperalgesia and allodynia. Alloknesis is probably elicited by A-beta fibres. The precise mechanism of central sensitization of itch generally and in specific pruritic conditions has yet to be elucidated.<sup>98</sup>

### Summary

The symptom of pruritus manifests in many dermatological, systemic, and psychogenic conditions. Over time, myths that surround this symptom have been dispelled. Itch is not a form of low-intensity pain. Itch is a separate symptom. Itch is transmitted by C- and A-delta fibres dedicated to the transmission of itch. There is a mutually exclusive histaminergic and non-histaminergic transmission of itch. In the former, histamine activates histamine receptors via

the activation of the TRPV-1 receptors. In histamine-independent pruritus, a wide variety of pruritogens stimulate multiple itch receptors. There is a complex 'cross-talking' between skin cells and sensory nerve afferents regulating itch. The itch signal is communicated to the dorsal root ganglion and trigeminal ganglia and then onto, respectively, the superficial dorsal horn of the spinal cord and to the trigeminal subnucleus caudalis of the brainstem. The ultimate itch signal to spinothalamic neurons is a combination of a positive signal from the periphery and inhibitory signalling from an intrinsic inhibitory pathway. From the thalamus, multiple areas of the brain are co-activated to delineate the location and intensity of the itch, to respond to the emotional dimension of itch and to plan and carry out the scratch response. The symptom of pruritus, like pain, can trigger both peripheral and central sensitization.

### The future – a mechanistic approach to pruritus and its management

A clear understanding of the pathogenesis of pruritus provides a coherent rationale for the efficacy of current pruritus management and a better foundation for novel treatments. For instance, the mechanism of pruritus reveals the reason that anti-histamines have little effect in many forms of pruritus. It also begins to reveal the reason that alpha 2-delta calcium channel blockers such as the gabapentinoids, KOR agonists, and neurokinin-1 antagonists have been found, in various pathological states, to relieve chronic pruritus. Other therapies where evidence is emerging of efficacy in pruritus of different pathologies include H4 antagonists, cannabinoid agonists, calcineurin inhibitors, IL-31 receptor antagonists, and leukotriene receptor antagonists. A critical aspect in the targeting of therapeutic agents is a precise understanding of the exact mechanisms of pruritus in each pathological condition. Knowledge of one will inform the other. Much work needs to be carried out to gain such an understanding.

This paper has attempted to synthesize the spectacular recent developments in the understanding of the pathophysiology of pruritus. Most of this literature has emerged in neurobiology, immunology, and experimental dermatology. Little has permeated those areas of internal medicine, including palliative medicine, that are most challenged by this often disabling symptom. When our patients suffer with a symptom, including pruritus, it is our responsibility to manage them in a timely manner and in an informed fashion. Significant work needs to be carried out to map out the precise interactions of skin cells, pruritogens, and afferent nerve fibres in specific pathological conditions and the central signaling of pruritus. Logically, future attempts to propose and test different forms of therapy

for pruritus should adopt a mechanistic approach, fully informed by and responsive to an understanding of the basic pathophysiology of pruritus. Management divorced from mechanism reveals only part of a complex story. An alliance between mechanism and management will, ultimately, yield greater dividends for basic scientists, clinicians, and patients alike.

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