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Why do we itch and scratch?

Itch was described in 1660 by Samuel Hafenreffer as 'an unpleasant sensation eliciting urge to scratch', and this definition appears to still hold true[1]. It is a sensation that affects all of us daily. However for some people it is chronic, known as chronic pruritus, when it can be debilitating. The prevalence has proven difficult to quantify but it is very common, potentially affecting up to 27% of people[2]. This essay will describe the mechanisms that produce the sensation from the skin to nerve cells to the brain, where cognitive and emotional processing shape a complex multidimensional signal leading to scratch. It will show how at each level it can be created in normal and pathological conditions. The International Forum for the Study of Itch (IFSI) groups such conditions into dermatological, systemic, neurological, psychiatric, mixed and unknown[3]. Knowledge comes from a rapidly growing body of research; explaining each experiment is unfortunately beyond the scope of this essay, but they involve novel thought in neurology, physiology, genetics, pharmacology and psychology. Research in the past has been lacking, partly because it was assumed that mechanisms were similar to pain, with limited treatments leading to continued itching and scratching. Now many treatments are being developed and hopefully will help patients. Finally, this essay will discuss why itch may have evolved in the past, and also why we continue to itch and scratch in the present when some treatments are available.

Mechanisms

i) Peripheral

Stimuli for itch are known as pruritogens. These are mainly chemicals, but they can also be mechanical, electrical and thermal. Histamine-induced itch has been a focus since Eppinger's discovery in 1933, but we now know that there are many pruritogens produced both outside (exogenous) and inside (endogenous) the body, explaining why anti-histamines do not always help[4]. The physical presence of the stimulus must be converted into an electrical signal in a sensory nerve cell. This process is called sensory transduction. With chemical pruritogens it occurs through their binding to a receptor. The receptors are often specific and have different functional properties: many are G-protein coupled (GPCRs) but there are also ion channels involved (diagram 1)[5]. This process is involved in producing non-pathological itch. For example, an insect bite may lead to an inflammatory response with histamine binding to the histamine-1-receptor (H1R), or a prick from a cowhage plant may introduce a protease that directly binds a protease-receptor (PAR).

This peripheral process is also very important in causing pathological itch; the mechanisms are complex and not fully understood (diagram 1)[4]. Itch is a major diagnostic feature of the common dermatological condition atopic dermatitis (AD)[6]. Many pruritogens here are released by immune cells, including histamine, tryptase and cytokines such as IL-31[7].These may be produced as part of an abnormal immune reaction against environmental substances, known as atopy. This has some genetic factors, with a reduced skin barrier. Anti-inflammatories and emollients are good therapies. AD also illustrates the interactions in itch production between skin cells, immune cells, and nerves[4]. The nerves themselves produce molecules called neuropeptides, such as substance P, that activate immune cells leading to release of

more stimulatory pruritogens – this is called neurogenic inflammation[5]. Also immune cells can release nerve growth factor, leading to neuronal hyperplasia – this could parallel pain sensitisation[8]. Phototherapy may reduce hyperplasia, and tacrolimus targets neuropeptides[9]. New therapies targeting the substance P receptor, neurokinin-1 (NK-1), are promising[10]. One could argue that this constitutes neurological itch, as the response of the nerve is disordered. This process occurs even more in psoriasis. Here atopy and histamine are unimportant, with neurones releasing many inflammatory mediators[4]. The immune cells activated may be different, with some unusually reactive to GABA, releasing IL-2[11]. There may again be some genetic factors behind this[12]. New biological treatments successfully target inflammatory mediators.

With regards to systemic diseases, in chronic kidney disease (CKD) uremic toxins were considered as pruritogens but now research points to micro-inflammation systemically and in the skin with high CRP, Th1 and IL6[4,13]. Cytokines are also thought to be involved in the itch produced by T-cell lymphomas and systemic malignancies, but serotonin and tumour-produced factors may be implicated[,14,15]. In liver disease, bile acids may bind to the TGR5 receptor[16]. Substance P appears to be raised in many systemic conditions, but the implications are not understood[4].

Unfortunately, once scratching damages the skin more inflammatory mediators are made to repair it, creating a vicious itch-scratch circle. This is particularly pathological in lichen simplex chronicus and prurigo nodularis.

There are also some receptors sensitive to mechanical stimuli, called mechanoreceptors[17]. They may become sensitised in AD, which could explain why rubbing of wool causes itching.

There is debate about the nature of the sensory neurones that these receptors are on. Just as there are a range of receptors, there appear to be a range of neurones (diagram 1). These include C fibres and Aο fibres, with different functional properties including the pruritogens they respond to[18,19,20]. Interestingly people have different proportions of fibres[20]. It is unclear if any cells are specific for itch, because so far all also have receptors for noxious stimuli.

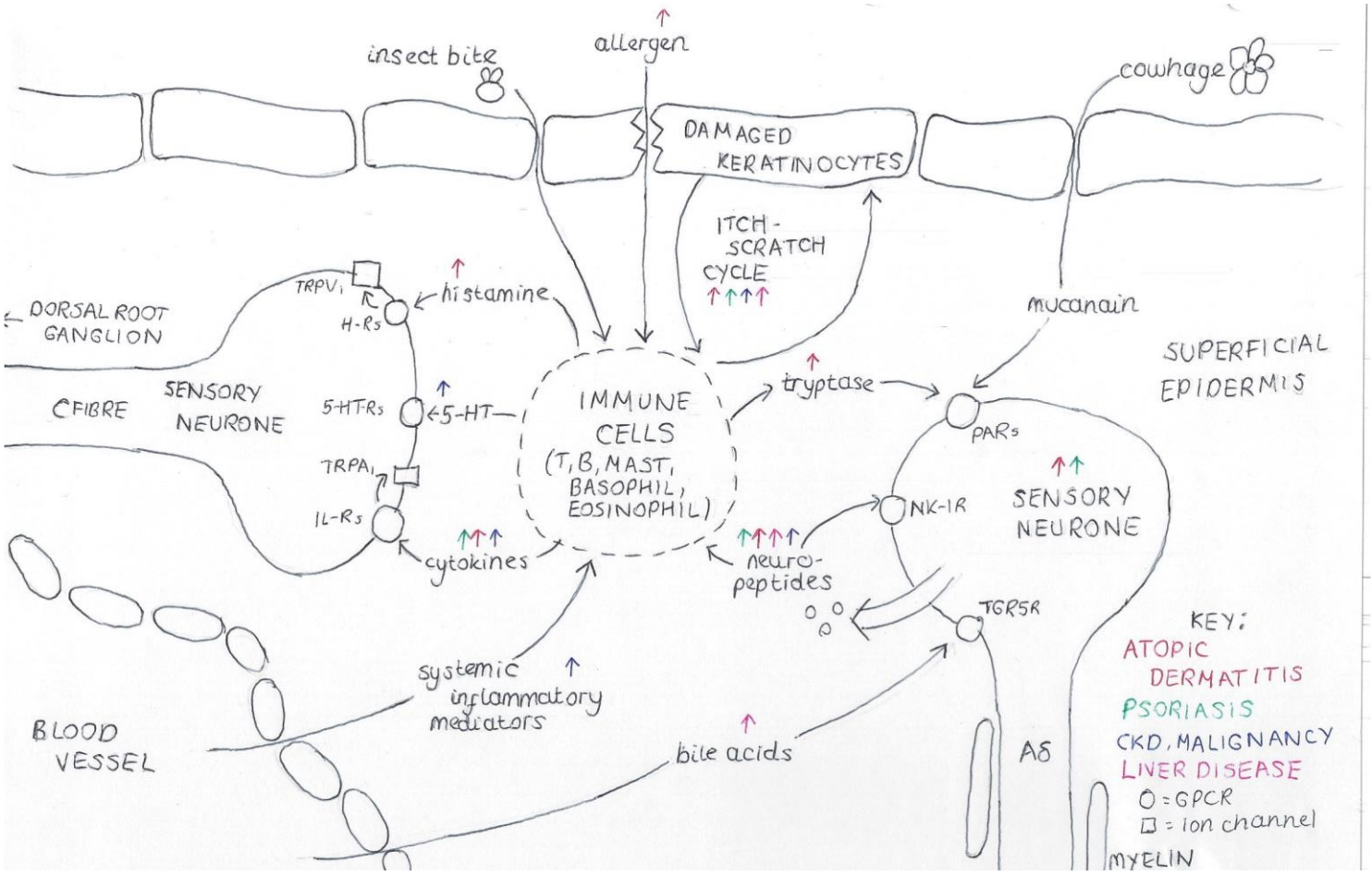

Diagram 1: Peripheral Mechanisms of Itch[4,5,17]. Not to scale and different receptors may be found

ii) Spinal cord

These sensory neurones enter the spinal cord, with cell bodies in the dorsal root ganglia. Here there may be more pruritogenic receptors[17]. The neurones then ascend two levels before synapsing with second-order neurones. A variety of neurotransmitters act here including glutamate, gastrin-releasing-peptide (GRP), substance P and neuropeptide-natriuretic-polypeptide-b (NPPB) (diagram 2) [17,21]. The GRP receptor is co-localised with the u-opioid receptor. This explains why opioids make us itch, and may explain why we itch in systemic conditions: in liver failure there may be excess production of opioids by the liver, stimulating this receptor[22]. Opiate antagonists help and also do in CKD, where the first oral drug against pruritus was used in 2009[23]. There are also spinal interneurons that inhibit the itch signal when scratch occurs, integrating signals from the brain and spinal cord[4].

These secondary neurones decussate and ascend in the lateral spinothalamic tract, which also transmits pain and temperature sensation. There has been much debate as to how the signal for itch is carried in these neurones, with the contrasting theories and their evidence well explained in review articles[4,24]. Current thought is synthesised into the 'population coding theory'. This suggests that there is a specific neural circuit where normal activation generates itch alone, but that different sensory circuits must interact to generate one dominant sensation[25]. Pain and cold can inhibit the itch sensation, explaining why people may try pinching or cooling the skin to stop scratching.

Nerve damage anywhere can cause neurological itch. Defining this can be problematic because arguably some disorder occurs in dermatological conditions. There are some extremely severe cases where patients have scratched through to their skull[26]. The causes are any that can damage nerves including trauma, compression, tumours, stroke and multiple sclerosis (MS)[4]. One named condition is brachioradial pruritus, with itching of the arm after nerve compression in the cervical region. Phantom itch, like phantom pain, can occur after amputation; one study found that it was the most common sensation after mastectomy[27]. Multiple pathological mechanisms may be involved (diagram 2). First, if a nerve is damaged neuropathic inflammation can occur as an attempt to repair, but this is indirectly pruritogenic as previously explained. Second, some damage is directly pruritogenic: shingles and MS are inflammatory, whilst neurofibroma tumours contain mast cells that release histamine[28]. Third, damage may make a nerve more likely to fire action potentials: cavernous haemangiomas cause haemosiderin deposition, which is excitatory[29]. Finally, if a nerve function is lost sometimes there is compensation causing abnormal firing of adjacent neurones, and loss of inhibitory circuits[26]. Such loss occurs after amputation. The itch scratch circle can also become more severe if there is reduced pain sensation[30].

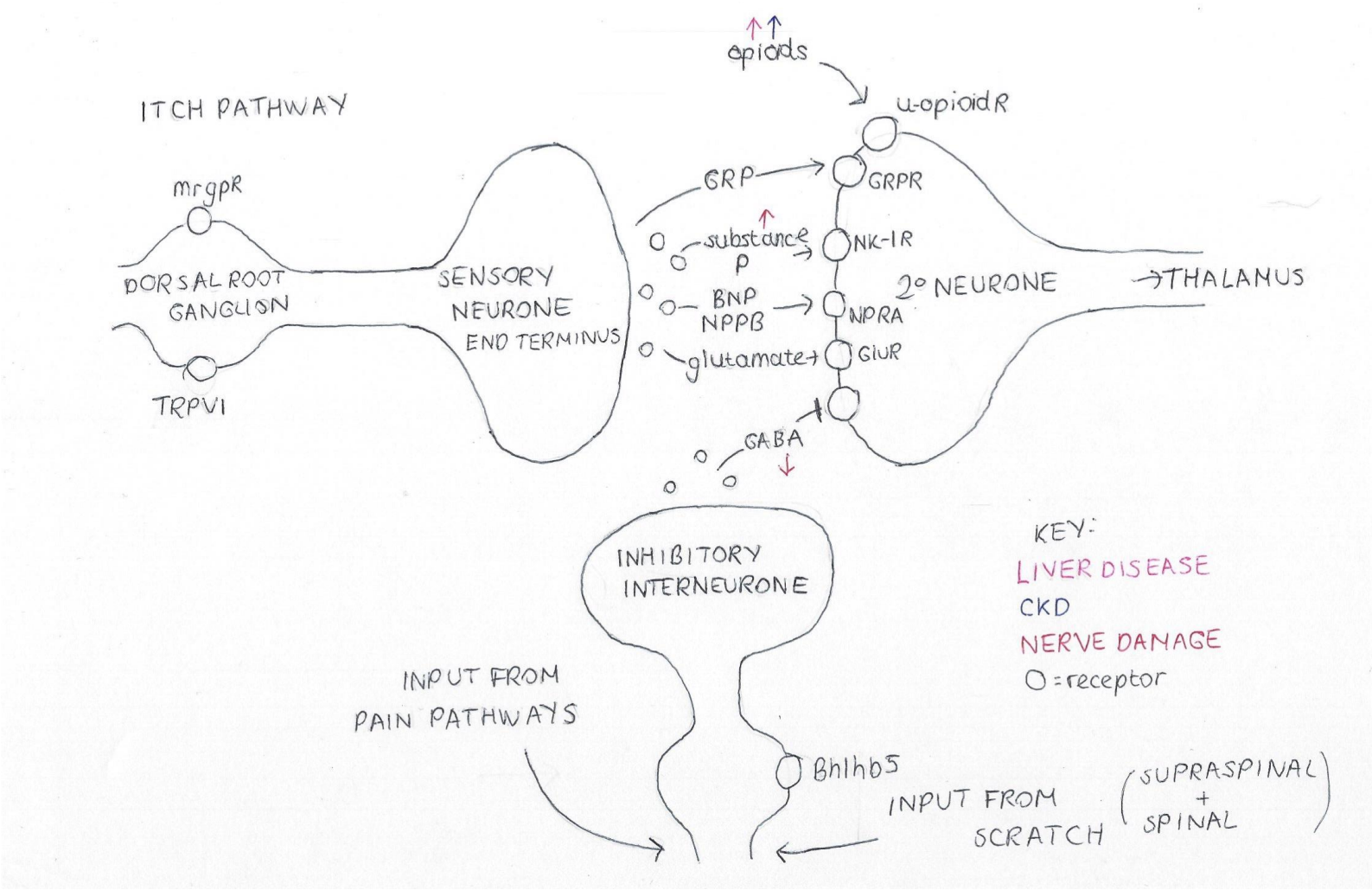

Diagram 2: Population Coding Theory and Neurotransmitters[4,5,17,24,25]. Not to scale and different receptors may be found

iii) Brain

These secondary neurones ascend through the brainstem and synapse in the thalamus. From here third-order neurones project into the brain.

A number of brain regions are involved. Interestingly different pruritogens, namely cowhage and histamine, activate distinct areas[31]. Areas include: somatosensory areas that process the sensory signal; motor areas (premotor cortex, motor cortex,

cerebellum) that focus attention, plan and execute the scratch; interoceptive areas (insular cortex) that give awareness; emotional areas (limbic system, substantia nigra and reward circuits) involved in pleasure and addiction; and areas of memory retrieval[4,16]. Thus there is a complex multidimensional response, more so than occurs to pain. The itch that we perceive comes from the processing in all of these regions, and the scratch is the output back through the motor systems. The fact that the motor side is always activated and that areas of craving and perception are involved shows how intrusive the urge to scratch is.

These areas are involved in all pruritic conditions. The urge to scratch and the resulting pleasant sensation contribute to the itch-scratch cycle[32]. Certain neural circuits are more strongly activated in AD, which could mean scratching is even more addictive[33]. Cognitive areas also show examples of plasticity: after amputation itch may occur because the cortex projects information about the proximal limb onto areas that used to represent the amputated part, which is why wearing a prosthesis to provide visual input and mirror therapy can help[26,34]. Also, patients with severe CKD have been found to have thinning in itch processing areas, though the implications are not understood[35]. Whether this constitutes a neurological contribution to itch could again be argued. Neurological itch does occur in central neurones when they are damaged by stroke. Linking to another of the IFSI's categories, in the past this may have been attributed to a psychiatric cause, known as psychogenic itch. Oaklander believes that we should not diagnose psychogenic itch without the presence of other psychogenic symptoms, and that there is often an underlying neurological cause with delusional explanations[4]. For example, brain

imaging in some patients diagnosed with somatic delusions showed abnormal brain activity[36]. This is not to say that psychogenic itch never occurs: itch is associated with obsessive-compulsive-disorder (OCD) and depression worsens pruritus, possibly due again to neurogenic inflammation[16].

One very interesting feature of itch is its 'contagious' nature. We all know that you can make yourself feel itchy by thinking about it; just imagine realising that your patient has scabies! This is proven in many studies[37,38,39]. This does not occur with most sensations. The central production of pruritus offers interesting therapeutic interventions, such as cognitive behavioural therapy, which is preliminarily reported as helping habit reversal in AD[40]. This phenomenon was used by one sufferer of phantom itch, who found relief in itching the leg of another person[41]!

Evolutionary reasons

A question asking 'why' merits consideration from an evolutionary perspective, although one must remember that evolution is not a purposeful process. There are no reviews or articles fully focused on this.

The main belief is that itch and scratch may have been useful in rapidly removing external threats from the skin such as insects, parasites, and toxins. There is much evidence to support this theory. Insect bites do usually cause itch through inflammation, and plant toxins such as cowhage can stimulate pruriceptors. The fact that cowhage and histamine activate specific pathways could have root in these different scenarios. We have also seen that some itch receptors are sensitive to

mechanical stimuli, with insect legs comparable to stray wool fibres. The scratch action would successfully remove the threat, in the way that a pain response would not, and in a more rapid and guaranteed time frame than a response to touch. The scratch also produces an injury itself that triggers inflammation, furthering protection if anything has already entered. Cranial neuropathies are the most likely to trigger neuropathic itch, which could be because the face was the main location for insect bites[42]. Interestingly, the most common irrational explanation for chronic pruritus is a parasite infestation, known as delusionary parasitosis, which in this light may not be so delusional…

A simple spinal reflex would be able to remove external threats, so more explanation is needed. Contagious itch involves higher processing, and is a phenomenon that could feasibly prevent parasite infestations. This processing is complex because we do not tend to itch the location seen, meaning that it is a shared feeling not a mimic[43]. Nakayama describes this as a primitive form of empathy[44]. This could mean that itch has had major social implications. One could go on to suggest that alongside empathy it could also have promoted social grooming, with further implications for our sociality. However, self-scratching has been shown to be more rewarding[38].

Current reasons

We have seen that treatment is lacking for some pruritic conditions, but is available for others. Despite this many patients continue to itch and scratch, and it is important to consider why. It is thought to often be due to poor optimisation of treatment. For

example, studies suggest that up to 40% of psoriatic patients do not use their medication as directed[45].

Poor optimisation may result from the way in which patients understand their condition and how they perceive their treatment. Understanding a condition can help patients to understand why and how medications are used. The use of a cream is arguably more complex than a tablet, with varying prescribing practices and many non-prescription creams compounding this complexity[46]. One study in a paediatric clinic found that at baseline <5% of the parents remembered receiving a good explanation with 24% of children receiving no emollient. After repeated nurse education there was an 800% increase in emollient usage and an 89% reduction in severity[47]. How a medication is perceived also influences optimisation, and this is well illustrated by steroids. Much poor adherence in AD appears to be due to topical corticosteroid phobia: in one study 80.7% of respondents reported having fears, usually about skin thinning[48,49]. Problems with medications also occur because they are time-consuming and disliked; in one study of psoriasis 57% stated that messiness reduced adherence[45].

Although there are real difficulties with treatment, education and a good rapport can help to minimise this and empower patients to see the benefits. This does require time, but it reaps long-term benefits.

Conclusion

Overall we have seen that there are many mechanisms contributing to itch and scratch. Originally it probably evolved as a useful protective mechanism, and still is on occasion, but now it is often a feature of pathological conditions. Many, but not all, of these conditions share features of inflammatory pruritogens, interaction between nerve and immune cells, and the formation of a vicious itch-scratch circle. The IFSI has grouped these conditions but there appears to be overlap between dermatological and neurological, and between neurological and psychogenic conditions. As understanding of the mechanisms increases, so has the development of new therapies, making it an exciting field. However, as drugs target increasingly complex systems, we need to remember the patient perspective. Then hopefully we can help all patients out of Dante's hell of being left to itch for eternity.

Words: 2500

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