



REVIEW

Advances in understanding itching and scratching: a new era of targeted treatments [version 1; referees: 2 approved]

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v1 **First published:** 22 Aug 2016, 5(F1000 Faculty Rev):2042 (doi: 10.12688/f1000research.8659.1)
Latest published: 22 Aug 2016, 5(F1000 Faculty Rev):2042 (doi: 10.12688/f1000research.8659.1)

Abstract

Chronic itch is a significant health burden with few effective treatments. As such, itch researchers seek to understand the mechanisms behind itch and to find potential targets for treatment. The field of itch research is dynamic, and many advances have been made so far this decade. In particular, major steps forward include the identification of new peripheral and central itch mediators and modulators, the discovery of greater roles for immune cells and glia in itch transmission, and a focus on the brain processing of itching and scratching. Finally, several new therapeutic interventions for itch have shown success in clinical trials.

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Referee Status:

	Invited Referees	
	1	2
version 1 published 22 Aug 2016		

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How to cite this article: Sanders KM, Nattkemper LA and Yosipovitch G. **Advances in understanding itching and scratching: a new era of targeted treatments [version 1; referees: 2 approved]** *F1000Research* 2016, 5(F1000 Faculty Rev):2042 (doi: [10.12688/f1000research.8659.1](https://doi.org/10.12688/f1000research.8659.1))

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Grant information: The author(s) declared that no grants were involved in supporting this work.

Competing interests: The authors declare that they have no competing interests.

First published: 22 Aug 2016, 5(F1000 Faculty Rev):2042 (doi: [10.12688/f1000research.8659.1](https://doi.org/10.12688/f1000research.8659.1))

Introduction

Itch, or pruritus, affects between 8 and 38% of the general population worldwide and is a common feature of diseases such as atopic eczema, psoriasis, and uremia¹. Despite the prevalence of itch and its impact on quality of life, there are still many aspects of itch signal transmission that are unexplained, and treatments for chronic itch are lacking. However, the field of pruritus research is constantly changing and growing, and many areas of discovery have taken root in the six years since our previous F1000 report². There have been many exciting new finds in itch research in both humans and animal models that have both given us insight into the mechanisms of itch signaling and informed advances in treatment.

Peripheral mediators of itch

Many recent studies have worked to define the roles of various itch mediators and receptors in the skin. Of these, the identification of an itch-specific population of neurons represents a major advance in the itch field. Mas-related G protein-coupled receptor A3 (MrgprA3) was previously identified to be a receptor for non-histaminergic itch, as it is activated by chloroquine (and not histamine) administration³. Building on this research, Han *et al.*⁴ identified an itch-specific population of MrgprA3-expressing neurons in the dorsal root ganglion (DRG). These neurons exclusively innervate the epidermis, respond to multiple pruritogens, and form synapses with gastrin-releasing peptide receptor-positive (GRPR⁺) neurons in the dorsal horn of the spinal cord. Crucially, ablation of these neurons reduces scratching in response to pruritogen injection without altering pain responses.

Research into other members of the Mrgpr family in animal models has also been fruitful. The pruritogenic peptide SLIGRL (Ser-Leu-Ile-Gly-Arg-Leu) activates MrgprC11⁵, while β -alanine induces itch through MrgprD⁶. Both MrgprA3⁺ and MrgprD⁺ neurons were found to be hyperexcitable in a mouse model of contact dermatitis, suggesting a role for these neurons in chronic itch as well as acute itch⁷. More importantly, some of these results have been validated in human⁸ and monkey⁹ studies.

Several members of the thermosensitive transient receptor potential (TRP) channel superfamily are expressed in normal human skin and have been implicated in itch. TRP vanilloid 1 (TRPV1) is necessary for histaminergic itch transmission¹⁰, and TRP ankyrin 1 (TRPA1) was found to be a downstream target of MrgprA3 and MrgprC11 necessary for itch signaling through these receptors¹¹. Deletion of TRPA1 also abolished scratching in a dry skin mouse model of chronic itch, further cementing its role in non-histaminergic itch transmission¹².

Another peripheral mediator, endothelin-1 (ET-1), was found to induce both itch and pain behaviors in mice, as distinguished by the cheek injection model¹³. ET-1 iontophoresis also induced itch in human subjects, and ET-1 and its downstream mediators were upregulated in patients with prurigo nodularis and chronic itch¹⁴.

Voltage-gated sodium channel (NaV) 1.7, previously known to be involved in pain transmission, has also been found to mediate itch. A gain-of-function mutation in *SCN9A* (the gene encoding NaV 1.7) in three family members was associated with intense paroxysmal itch triggered mainly by warmth and spicy food¹⁵. Furthermore, a monoclonal antibody targeting NaV 1.7 suppressed inflammatory and neuropathic pain as well as acute and chronic itch in mice, suggesting that this channel may be a target for both pain and itch treatment¹⁶.

Peripheral crosstalk between neurons and immune cells

Immune cells interact directly with nerve fibers in the skin, and this crosstalk has been shown to have important functions in pathological itch. Several pruritic diseases have been associated with increased levels of Th2 cytokines (for review, see 17), and interleukin-31 (IL-31) in particular has been identified as an “itchy” cytokine in atopic eczema. Recently, IL-31 was found to be produced by malignant T cells in cutaneous T cell lymphoma (CTCL), and serum levels of IL-31 correlated to CTCL pruritus severity¹⁸. We examined expression levels of IL-31 and its receptors in the skin and found a correlation between epidermal expression and itch severity¹⁹. Epidermal expression of IL-31 receptors was also found to be increased in the skin of patients with lichen amyloidosis and pruritus²⁰. In mice, both single and repeated intradermal administration of IL-31 caused an increase of scratching behavior, and repeated exposure led to increased expression of IL-31RA in the DRG^{21,22}.

Central itch transmission

Gastrin-releasing peptide (GRP) and its receptor (GRPR) were previously identified as the first itch-specific mediators in the spinal cord²³, and recent research has expanded on this pathway. Mishra and Hoon²⁴ reported that mice lacking natriuretic polypeptide b (Nppb), normally expressed in the DRG, showed almost no scratching in response to a range of intradermally injected pruritogens. These mice retained normal responses to touch, pain, and other stimuli, suggesting that Nppb⁺ neurons are specific to itch transmission. Intrathecal injection of GRP still induced scratching in Nppb knockout animals, leading the authors to propose a model of itch signaling with Nppb and its receptor NPRA upstream of GRP-GRPR.

However, this study sparked controversy in the itch field. Following another school of thought, Liu *et al.*²⁵ rebutted that Nppb signaling does not occur upstream of the GRP-GRPR pathway. They were unable to replicate immunostaining of Nppb and NPRA and, in contrast to Mishra and Hoon, were able to detect *Grp* mRNA in the DRG. Additionally, they reported that blocking GRP-GRPR signaling did not alter Nppb-induced scratching. They argued that the role of Nppb remains to be clarified.

In addition to research into spinal transmission of the itch signal, there has been significant work on the inhibition of itch at the spinal

level. Mice lacking Bhlhb5⁺ inhibitory (B5-I) interneurons in the spinal dorsal horn displayed increased scratching and subsequent skin lesions²⁶. Further experiments revealed that this population of B5-I interneurons is activated downstream of certain TRP channels and releases dynorphin, a kappa opioid receptor ligand, to inhibit itch²⁷. Additionally, a population of spinal interneurons expressing neuropeptide Y has been found to gate itch induced by light mechanical stimuli²⁸.

Central interactions between neurons and glia

Previous studies demonstrated the involvement of glial cells in neuropathic pain, and recent work suggests their involvement in modulating itch. Signal transducer and activator of transcription 3-induced astrogliosis in the spinal dorsal horn was observed in mouse models of both contact dermatitis and atopic dermatitis²⁹. This activation was reduced in mice with clipped toenails but was still present in artificially scratched mice, suggesting that scratching plays a crucial role in this kind of reactive astrogliosis. Another study found that Toll-like receptor 4, part of the innate immune system, induced astrogliosis in the spinal dorsal horn of mice with dry skin itch³⁰. This astrogliosis was also dependent on scratching; preventing scratching with an Elizabethan collar also prevented astrogliosis. Of note, microglial activation was mild and transient in this model.

In contrast, an increase in microglial activation within the spinal cord was seen after intradermal injection of either compound 48/80 (a histaminergic pruritogen) or 5'-guanidinonaltrindole (a kappa opioid receptor antagonist) in mice³¹. In a chronic itch mouse model, spinal microglia were activated after scratching, and suppression of microglia via minocycline treatment in turn reduced the level of scratching³². A similar pattern was observed in a mouse model of atopic dermatitis. These mice displayed increased levels of microglia in the spinal cord, and minocycline treatment reduced scratching and improved dermatitis scores³³.

Chronic itch features not only spontaneous itch but also the dysethesias of allodynia (itch evoked by light, normally non-itchy touch) and hyperknesis (increased itch in response to a normally itchy stimulus). These sensations are thought to be caused by central sensitization. Although these properties have been long reported in patients with chronic itch and in healthy skin injected with histamine, there was a lack of animal models to study them. Such models are especially important because the mechanisms behind this increased sensitivity appear to be related to, but distinct from, those underlying spontaneous itch. To this end, an elegant mouse model of allodynia was developed by using von Frey filaments to stimulate mice with a light touch sensation³⁴. Mice displayed scratching in response to light touch after intradermal injection with several different pruritogens, as well as in a dry skin itch model.

Stress and reward in the itch-scratch cycle

Itch is intrinsically linked with scratching, and the pleasure and relief evoked by scratching have been the focus of several recent studies. The intensity of itch (experimentally induced with

cowhage) and the pleasure of scratching were found to vary according to the area of the body being scratched, and there was greater itch, itch relief, and pleasure during scratching of the back and ankle in comparison with the forearm³⁵. Functional magnetic resonance imaging using arterial spin labeling demonstrated that scratching an itch led to activation in several brain areas involved in reward and perception, including the striatum, midbrain, primary somatosensory cortex, and insula³⁶. We further found a difference in brain activity during active scratching of an itch by the participant compared with passive scratching by an experimenter³⁷. Several reward-associated areas (ventral tegmental area, nucleus accumbens, caudate nucleus, and ventromedial prefrontal cortex) were activated during active scratching and correlated with pleasure, itch relief, or both.

Greater attention is also being paid to the role of stress in itch and possible psychological and educational interventions. These techniques include habit reversal training, relaxation therapy, and cognitive behavioral therapy³⁸. Such interventions represent a unique approach to breaking the itch-scratch cycle and managing chronic itch. They can be helpful both for chronic itch patients and for caretakers of children with chronic itch.

Novel targets for chronic itch

A revolution in the treatment of chronic pruritus is under way. Recently, much effort in treating has been placed on targeting the immune system in pruritic diseases. Agents that target IL-4 and IL-13³⁹ and IL-31⁴⁰, as well as a topical phosphodiesterase 4 inhibitor⁴¹, have been used in patients with atopic eczema, whereas biologics that target IL-17⁴² and oral phosphodiesterase 4 inhibitors⁴³ have shown anti-pruritic efficacy in patients with psoriasis.

Agents targeting the nervous system are also showing promise in clinical trials for itch of different types. Nalfurafine, a kappa opioid agonist, has continued to be a successful anti-itch therapy⁴⁴, and other kappa opioid agonists and combined kappa opioid agonists/mu opioid antagonists are being explored as treatment options⁴⁵. Neurokinin 1 inhibitors have also shown some success in the treatment of itch⁴⁶.

Due to the complexity of the different etiologies, cell types, and mediators involved in chronic itch, a combination of topical and systemic therapies addressing peripheral mediators and top-down approaches targeting the brain and spinal cord may be the best strategy of treatment. The mediators identified in current animal and human studies may prove to be effective targets in future therapies.

Competing interests

The authors declare that they have no competing interests.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Competing Interests: No competing interests were disclosed.
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Competing Interests: No competing interests were disclosed.