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REVIEW ARTICLE

Glial Cells are Involved in Itch Processing

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Recent discoveries in itch neurophysiology include itch-selective neuronal pathways, the clinically relevant non-histaminergic pathway, and elucidation of the notable similarities and differences between itch and pain. Potential involvement of glial cells in itch processing and the possibility of glial modulation of chronic itch have recently been identified, similarly to the established glial modulation of pain processing. This review outlines the similarities and differences between itch and pain, and how different types of central and peripheral glial cells may be differentially involved in the development of chronic itch akin to their more investigated role in chronic pain. Improvements are needed in the management of chronic itch, and future basic and interventional studies on glial activity modulation would both enhance our understanding of mechanisms underlying the chronification of itch and provide novel opportunities for the prevention or treatment of this debilitating and common condition. ***Key words: itch; glia; glial cells; astrocytes; microglia; neurophysiology; satellite glial cells; Schwann cells; pain; surrogate models of itch.***

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Itch is a sensory modality defined as the "unpleasant somatosensation that evokes a desire to scratch" (1). In its acute form, itch carries a protective purpose by prompting a scratch response in the affected area. In cases of pathologically associated itch, e.g. in conditions such as psoriasis, prurigo nodularis, uraemic pruritus, drug-induced pruritus, or atopic dermatitis (AD), however, itch often turns into a chronic or frequently recurring debilitation. Chronic itch affects millions of individuals (2), imposes a significant burden on the quality of life of the afflicted patients, and interferes with vital functions such as sleep, attention, and sexual activity (3, 4). Similar to the events leading to chronification of pain conditions, certain pathological predispositions, such as inflammatory skin disorders, frequently lead to the intensification and chronification of pruritus. This, in turn, leads to excessive, recurrent scratching, typically worsening the skin lesions and leading to more or prolonged pruritus (5, 6). This phenomenon, known as the itch–scratch–itch vicious cycle, is physiologically complex and is likely to involve: local inflammatory mediators and structural changes, reward components, and the autonomic nervous system (5, 7). In most conditions associated with chronic itch, very limited or ambiguous evidence is found for the effectiveness of pharmaceutical interventions, and the evidence is often characterized by off-label small-scale trials or case series. Histamine is now widely accepted not to have a key role in evoking itch in most of the clinical conditions characterized by chronic pruritus (for an overview of itch neurobiology and mechanisms, see recent reviews in the field [8, 9]). This is in agreement with the fact that these conditions are often largely or entirely resistant to treatment with topical as well as systemic antihistamines (3, 10). Hence, the current treatment regimens for relieving itch, beyond targeting the underlying disorder, are suboptimal (3). Preclinical studies have recently shown that glial cells may also play an important role in the development of pathological chronic itch (11–13). This review aims to recapitulate on these novel findings and highlights the similarities and differences between pain and itch in relation to neuron-glial interactions. Finally, this paper provides an overview of the currently elucidated molecular mechanisms of glial involvement in itch, and future interventional opportunities are discussed, in order to stimulate further investigation within this novel area.

ITCH AND PAIN

Itch and pain, although distinct, are highly entwined sensory modalities with numerous similarities, but also distinct differences. In chronic conditions, both itch and pain tend to generalize anatomically, decrease quality of life, and precipitate secondary reactive depression (14). Notably, mild cutaneous pain is commonly found to co-exist with chronic itch, for instance in patients with AD and psoriasis, who nonetheless typically report itch as their primary sensory complaint (15). Itch and pain are also pathophysiologically grouped in a similar way; often presenting as inflammatory or neuropathic (16). Moreover, itch causes the central sensitization-associated signs termed "alloknesis" and "hyperknesis", similar to those produced by painful stimuli, "allodynia" and "hyperalgesia", respectively

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(14). Alloknesis describes the dysesthetic state, in which otherwise non-pruritic stimuli, e.g. light touch, provoke a sensation of itch (17, 18), and hyperknesis is an exaggerated itch response elicited after a normally pruritic or prickling stimulus (16, 19). A study by van Laarhoven et al. (20) compared somatosensory processing of itch and pain using quantitative sensory testing (QST) and itch provocations between patients with rheumatoid arthritis and psoriasis. The patients with psoriasis had an increased itch response to histamine iontophoresis (visual analogue scale (VAS)=3, 0–10 scale), but not electrical itch stimulation, while the patients with rheumatoid arthritis displayed decreased tolerance to painful stimuli (cold pressor test and mechanical stimulation) indicative of pathway-specific pruriceptive and nociceptive sensitization, respectively (20). At the same time, a few studies using QST indicate that sensory aberrations, particularly associated with thermal parameters and conditioned pain modulation, are present in patients with itch, as have also been thoroughly established and utilized for a number of pain conditions. However, some studies are notably in disagreement with the concept of central sensitization as a significant feature in relation to chronic itch (21–24). Finally, several treatment opportunities represent commonalities; as with chronic pain, itch occasionally responds to, for example, topical capsaicin, anticonvulsants, local anaesthetics, and homotopic cold counter-stimulation (3, 14). Interestingly, and in complete contrast to the aforementioned, a frequent side-effect of μ-opioid analgesics is induction of severe itch, which is thought to be, at least in part, a consequence of decreased activity in the dorsal horn neurons of the nociceptive system, thereby causing spinal disinhibition of itch-signalling (25). The paradoxical itch response to opioids underlines the notion of separate neuronal pathways and central processing of itch and pain. In relation to pain processing, non-neuronal glial cells are widely accepted to play a significant role in the initiation or maintenance of pain. Central glia, foremost astrocytes and microglia, have been extensively implicated in pain processing, and more recently a number of studies have emerged focusing on the role of peripheral glia, e.g. satellite glial cells (SGCs) in relation to pain. Recent accumulating evidence reviewed here proposes a possible interaction between glial cells and pruriceptive neurons that might play a role in the chronification of itch.

NEURON-GLIA INTERACTIONS IN PAIN – AND ITCH?

A large amount of strong evidence supports a role of glial cells in relation to both neuropathic and inflammatory pain (26–28). The neuron-glia interactions are shown to be crucial in modulating several induced pathological pain conditions particularly associated with sub-acute and chronic pain (29, 30). Neuronal excitability of nociceptive circuits can be extensively augmented by neurotransmitters, but also by immune mediators directly released from, or modulated by, glial cells, such as microglia, astrocytes and, to a lesser extent, oligodendrocytes (28). The notion of neuro-inflammation as a maintainer of pain-induced hyperexcitability and pain chronification has prompted similar research related to the role of glial cells in prolongation or chronification of itch (11, 12). New strategies considered promising in glial modulation of some pathological pain states, which could be equally applicable and important for itch modulation and treatment. Table I highlights recent and important findings on the contribution of glial cells in itch processing.

Drawing on these parallels between itch and pain opens up the possibility of understanding the underlying mechanisms of chronification and potential modulation of itch (26, 29). Considering the fact that itch and pain are mediated mostly by primary afferent C-fibres with their cell bodies located in the dorsal root ganglia (DRG) or the trigeminal ganglia (TG), the interactions between neuronal tissue conveying itch and the non-neuronal component (e.g. SGCs) at the level of the sensory ganglia, are hypothesized to be similar to the established interactions between SGCs and nociceptive

Table I. *Summation of the current knowledge on glial cells contribution to modulation of itch*

Glial cell type	Itch model/condition	Mechanism(s)	Ref.
Central glial cells			
Astrocytes	Topical DCP (contact dermatitis) and NC/Nga mouse strain (atopic dermatitis)	Itch and repeated scratching shown to induce STAT3 enhancing central itch transmission via LCN2-signalling with GRPR$^+$ neurons	(11, 46, 47)
Microglia	Topical DNFB (model of contact dermatitis)	Microglia-maintained pruritus induced by DNFB via activity in the FKN/CX3CR1/p38MAPK. The itch was reversible by minocycline, a microglial inhibitor	(12, 13)
Oligo-dendrocytes	N/A for itch (shown to modulate pain)	N/A for itch (shown to modulate pain)	(68, 69)
Peripheral glial cells			
Satellite glial cells	N/A for itch (shown to modulate pain)	N/A for itch (shown to modulate pain)	(52, 53)
Schwann cells	HES-related pruritus and prurigo nodularis	HES-infusing therapy frequently causes persistent itch, which is probably a consequence of long-term HES-storage in Schwann cells. Schwann-cell morphological alterations have been observed in prurigo nodularis.	(49–51)

DCP: diphenylcyclopropenone; DNFB: 2,4-dinitrofluorobenzene; GRPR$^+$: gastrin-releasing peptide receptor (positive); HES: hydroxyethyl starch; LCN2: lipocalin-2; N/A: not applicable; STAT3: signal transducer and activator of transcription 3.

afferents (31, 32). If peripheral glial cells are capable of inducing or maintaining hyperexcitability in the sensory neurons under inflammatory or neuropathic pain conditions, a possible explanation of pain chronification, similar processes would probably occur in relation to itch chronification (which is also frequently associated with neuropathy or inflammation). A recent study has highlighted the role of CXCL10/CXCR3 signalling within the DRG after the development of squaric acid dibutylester (SADBE)-induced allergic contact dermatitis (ACD) as a model of skin inflammation and itch (33). The study did not exclude a glial or leukocyte origin of the CXCL10/CXCR3-overexpression, and since the receptor is established to be intricately involved in aberrant glial signalling during painful states (34), non-neuronal cells were probably contributing to the mediation of allergic itch. The following section aims at comparatively describing the current knowledge on the role of central and peripheral glial cells in relation to itch, while drawing parallels with available and more abundant knowledge established in relation to the contribution of activated glial cells in pain processing.

Microglia and itch

Microglia are central nervous system (CNS)-residing macrophages of erythro-myeloid origin (35) known to carry out immune-regulatory tasks within the CNS. Spinal microglia are well known to be activated in chronic pain and neuroinflammatory models, a process known as "microgliosis" (36, 37). Activation of microglia leads to the release of inflammatory substances, including interleukin (IL)-1b, IL-6, and tumour necrosis factor (TNF) α, which are known to contribute to pain maintenance and chronification (38). To test whether scratching activated spinal microglia, Zhang et al. (13) deployed an itch model by application of 5'-guanidinonaltrindole (GNTI; a κ-opioid antagonist) and compound 48/80 in mice to induce itch and subsequent scratching. The group demonstrated that spinal microglia were highly activated by prolonged itch and scratching, reflected in an elevated expression of p-p38, and the microglial activation marker CD11b (12, 13). However, since scratching is usually associated with pain and tissue-damage it remains to be elucidated to what extent scratching *per se* provokes microgliosis. Nalfurafine, a κ-opioid receptor agonist, reversed these expressions and reduced the scratching. While μ-opioid receptor agonists frequently cause severe itch, κ-opioid receptor agonists are notably shown to have an antipruritic effect (25, 39). Elaborating on these results, a recent study induced chronic contact dermatitis-like pruritus in mice by repeated topical administration of 2,4-dinitrofluorobenzene (DNFB) and showed that scratching was associated with activation of spinal microglia via the p38 MAPK pathway (12, 13). In addition, the group used intrathecally delivered p38 inhibitor and minocycline (a microglial inhibitor) to significantly reduce severe scratching in the DNFB-treated mice. They also applied antiserum against both CX3CR1 and fractalkine (FKN) to examine the effect on scratching and highlighted a role of fractalkine/CX3CR1 signalling in the development of pruritus. The FKN/CX3CR1/p38MAPK pathways are also well-established to be involved in the development of neuropathic pain (40). Interestingly, minocycline administration has also occasionally been associated with an antipruritic effect in humans, particularly in patients with prurigo pigmentosa. However, the mechanism behind this effect is unclear and could be unrelated to the glial modulatory function of minocycline (41, 42).

Astrocytes and itch

Astrocytes also play a critical role in chronic pain (26–28). Astrocyte activation, known as "astrogliosis", includes up-regulation of the astrocytic markers, most prominently glial fibrillary acidic protein (GFAP) and is generally a longer lasting phenomenon than microgliosis (43–45).

In one study, mice with chronic atopic itch underwent resiniferatoxin-induced TRPV1-ablation, resulting in a decreased expression of GFAP and reduced scratching behaviour, showing that a link may exist between pruritus, cutaneous pain caused by scratching and central astrocytic dysregulation (11, 46). Furthermore, Shiratori-Hayashi et al. (11) demonstrated that the signalling pathway involved in itch-induced astrogliosis in chronic itch includes increased STAT3-signalling since the expression of this marker was highly augmented in two mice models of itch (AD; NC/Nga mice and contact dermatitis; diphenylcyclopropenone (DCP)-induced) (11, 46). Furthermore, the subsequent injection of the JAK-inhibitor AG490 blocked both the STAT3 expression and reversed the scratching behaviour. The protein, LCN2 secreted from active astrocytes, was found to be highly expressed in the spinal cord after the itch induction and declared to be a likely mediator of the enhancement of spinal itch signalling in the applied surrogate models (11, 46). Hence, LCN2 could be a potential pharmacological target for future treatment of chronic itch. Very recently, Liu et al. (47) observed marked astrogliosis in male mice in response to an acetone, diethyl ether and water-induced (AEW) model of chronic xerotic pruritus and alloknesis. The study showed a distinct role of Toll-like receptor 4 (TLR4)-signalling in astrocytic activation upon pruritic stimulation and notably observed that intrathecal injection of the astroglial inhibitor L-α-aminoadipate reduced AEW-induced chronic itch and associated alloknesis without affecting responses to acute models of itch induced by compound 48/80 and chloroquine. Lastly, it was shown that scratching in response to AEW application was essential to the induction of spinal astrogliosis, since it was nearly abolished by

the use of Elizabethan collars. Astrogliosis has, until recently, been described primarily as a phenomenon found in models of chronic pain following a nerve injury (48).

Peripheral glial cells and itch

Glial cells in the periphery include Schwann cells ensheathing peripheral nerve fibres and providing myelination to certain fibre types and SGCs surrounding the neuronal somata in the DRG and sharing several functional commonalities with the astrocytes. Coincidentally, Schwann cell dysfunction has been implicated in prolonged itch. After hydroxyethyl starch (HES)-infusion therapy, typically in response to blood loss, a common adverse effect is severe protracted itch. Exploratory studies indicate that this is a consequence of HES-accumulation in myelinating and unmyelinating Schwann cells inducing functional disturbances (49, 50). This phenomenon has also been described in prurigo nodularis, a chronic dermatological itch condition, but the specific molecular mechanism(s) remains to be elucidated (51). Our group has focused on glial cells in the periphery and has shown that glial cells of TG are intricately involved in trigeminal pain processing (52, 53) and that SGCs of the DRG are potential contributors in cisplatin-induced neuropathic pain (54), a sensory condition also frequently associated with itch (55). Several groups have also shown the activation and involvement of peripheral glia in different models of inflammatory or neuropathic pain (26, 31). Therefore, there might also be a potential contribution of peripheral glia including SGCs and Schwann cells in the pathogenesis of chronic itch. See Fig. 1 for an illustration of potential mechanisms, in which central and peripheral glial cells are shown or hypothesized to modulate itch.

Interventional opportunities for modulation of neuro-glial interactions

Besides neuron-glial cross-talk, mast cell–glia communication has also been proposed as a mechanism contributing to neuro-inflammation, both at the level of the peripheral system and in the CNS (56). Palmitoylethanolamide (PEA), a fatty acid amide known to regulate neurogenic pain, inflammation, and pruritus, is produced and hydrolysed by microglia and can attenuate activation of mast cells (57–59). Abbramo et al. (60) have shown that the endogenous production of PEA is elevated in the lesional skin of dogs with AD compared with healthy controls, indicating a protective role in an experimental model of canine AD.

Another therapeutic opportunity is low-dose naltrexone (LDN), which has been found to reduce symptoms of pain in a number of pathological conditions, such as fibromyalgia and complex regional pain syndrome, and additionally to significantly reduce itch associated with systemic sclerosis in a case series (61, 62). Naltrexone has two distinct mechanisms. It is a well-known antagonist of μ-opioid receptors, but also an antagonist of the non-opioid receptor TLR4, which is expressed on macrophages and microglia. Via this signalling pathway, the LDN yields anti-inflammatory effects. Given the wide variety of inflammatory factors produced by activated microglia (e.g. pro-inflammatory cytokines, substance P, nitric oxide, and excitatory amino acids), application of LDN suppresses microglial activation.

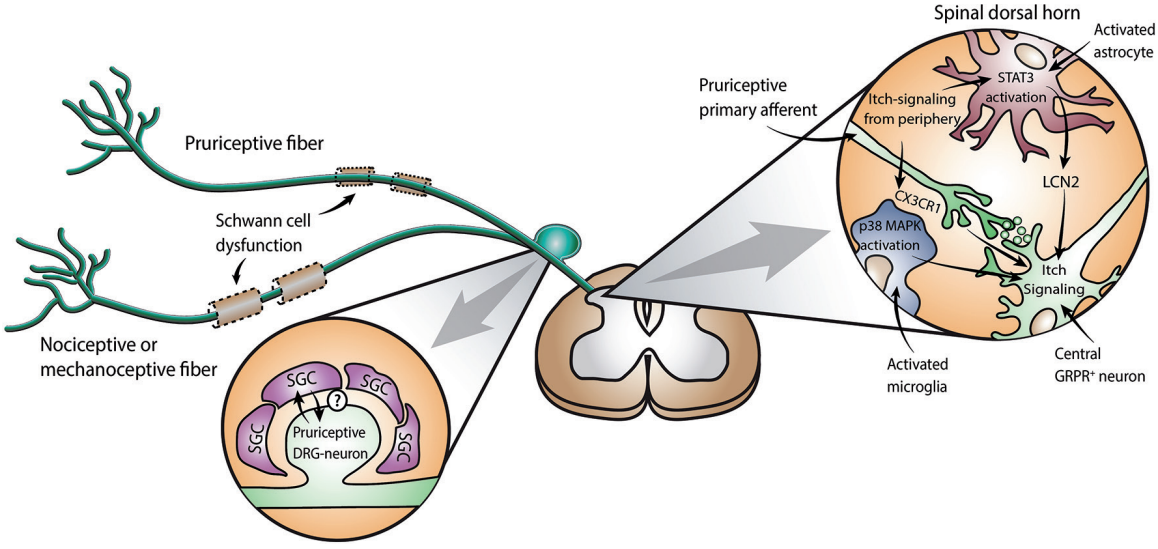

Fig. 1. Recently explored and theoretically hypothesized neuro-glial interactions, which could modulate itch signalling from the periphery to the central nervous system. Schwann cell dysfunction could result in increased signalling, either directly by, e.g. induction of ectopic firing, or indirectly by disinhibition of stimuli (nociceptive, thermal, and mechanical fibres), which normally inhibit pruritic stimuli at the spinal cord level. Note that, contrary to popular belief, C-fibre axons are invaginated in Schwann cells, but not myelinated (70). SGCs of the DRG (marked "?") could interact with the pruriceptive fibres to modulate itch signalling. Similarly, inside the central nervous system, astrocytes and microglial cells have been shown to increase pruritic signalling of central afferent pruriceptive neurons through separate molecular mechanisms. SGC: satellite glial cells; DRG: dorsal root ganglia.

This effect is not limited to the CNS and occurs in the periphery, as supported by findings showing diminished levels of TNF-α, IL-6, monocyte chemotactic protein 1 (MCP-1), and other inflammatory agents from peripheral macrophages. It is possible that naltrexone (mainly used in human studies) and naloxone (mainly used in animal models) act partly via glial cells to exert their analgesic, anti-inflammatory, and perhaps anti-pruritic effects partly independent of opioid receptors (61–63).

CONCLUSION AND FUTURE DIRECTIONS

Recent research has unveiled a number of non-neuronal cells, including glial cells, which are involved in acute as well as chronic itch processing. Mechanisms have, until now, been described for astrocytes, microglia, and indirectly for Schwann cells (13, 46, 49, 50, 64). Whether glial cells, such as SGCs and oligodendrocytes, also contribute in modulation of itch and to what extent, remains to be explored. Moreover, future research is necessary to assess whether pathway-specific histaminergic vs. non-histaminergic itch would prompt different patterns of glial activation, and thus potentially require different targeted interventions. Presently, specific glial modulators for human use are lacking. However, a number of compounds with a glial modulatory effect (e.g. fluorocitrate, minocycline, ibudilast, and even vitamin D) are available. The anti-nociceptive effects of some of these agents have been reported in animal models of pain and some human studies (27, 65, 66). Attempts so far have been quite limited and yielded mixed results. Proof-of-concept studies and randomized controlled trials are needed in order to evaluate the efficacy of these and other potential agents that may prove beneficial in treatment of painful and pruritic conditions. For therapeutic glial modulation, it should be considered that complete attenuation of glial function is not advantageous and is probably associated with significant adverse effects, because these cells, e.g. astrocytes and microglia, exert vital housekeeping and surveillance functions in the nervous system (67). The selectivity of future potential candidates needs to be tested in proper experimental models, since most preclinical studies have focused on early time-points in pain and/or itch models, whereas the equivalent clinical problems are usually chronic. Glial modulation of itch is a field in its very infancy, and significant bench-to-bedside hindrances necessitate additional studies before glial modulation therapy can be clinically utilized.

The authors declare no conflicts of interest.

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