Glial Cells are Involved in Itch Processing

Hjalte H. ANDERSEN, Lars ARENDT-NIELSEN and Parisa GAZERANI
SMI®, Department of Health Science and Technology, School of Medicine, Aalborg University, Denmark

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 chronication 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.

Accepted Feb 10, 2016; Epub ahead of print Feb 11, 2016

Parisa Gazerani, SMI®, Department of Health Science and Technology, School of Medicine, Aalborg University, Fredrik Bajers Vej 7, Bld. A2-208, DK-9220 Aalborg E, Denmark. E-mail: Gazerani@hst.aau.dk

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

<table>
<thead>
<tr>
<th>Glial cell type</th>
<th>Itch model/condition</th>
<th>Mechanism(s)</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>Central glial cells</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Astrocytes</td>
<td>Topical DCP (contact dermatitis) and NC/Nga mouse strain (atopic dermatitis)</td>
<td>Itch and repeated scratching shown to induce STAT3 enhancing central itch transmission via LCN2-signalling with GRPR+ neurons</td>
<td>(11, 46, 47)</td>
</tr>
<tr>
<td>Microglia</td>
<td>Topical DNFB (model of contact dermatitis)</td>
<td>Microglia-maintained pruritus induced by DNFB via activity in the FKN/CX3CR1/P38MAPK</td>
<td>(12, 13)</td>
</tr>
<tr>
<td>Oligo-dendrocytes</td>
<td>N/A for itch (shown to modulate pain)</td>
<td>N/A for itch (shown to modulate pain)</td>
<td>(68, 69)</td>
</tr>
<tr>
<td>Peripheral glial cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satellite glial cells</td>
<td>N/A for itch (shown to modulate pain)</td>
<td>N/A for itch (shown to modulate pain)</td>
<td>(52, 53)</td>
</tr>
<tr>
<td>Schwann cells</td>
<td>HES-related pruritus and prurigo nodularis</td>
<td>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.</td>
<td>(49-51)</td>
</tr>
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</table>

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.

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 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.

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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 the microglial activation marker CD11b (12, 13). While μ-opioid receptor agonists are notably shown to have an anti-itch effect (25, 39). Elaborating on these results, receptor agonists frequently cause severe itch, κ-opioid receptor agonists are known to have an antipruritic effect (26–28). Therefore, Shira-tori-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 astrogliotic activation upon pruritic stimulation and notably observed that intrathecal injection of the astrogliol inhibitor L-α-aminoacapate 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). Palmitoyl-ethanolamide (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 factors 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.

REFERENCES


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