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# The Itchy scalp - scratching for an explanation

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## Abstract

Scalp pruritus is a common complaint that is considered a diagnostically and therapeutically challenging situation. Scalp skin has a unique neural structure that contains densely innervated hair follicles and dermal vasculature. In spite of the recent advances in our understanding of itch pathophysiology, scalp itching has not been studied as yet. In this review, we summarize the current knowledge on the neurobiology of scalp and hair follicles as well as itch mediators and provide a putative mechanism for scalp itch with special emphasis on neuroanatomy and pathophysiology.

### Keywords

Pruritus; Innervation; Scalp; Hair follicle

Scalp pruritus is a common and distressing symptom. It is most commonly associated with seborrheic dermatitis and psoriasis but appears often without any noticeable skin lesion or obvious diagnosis. It is considered a diagnostically and therapeutically challenging situation particularly when no other body part itches and no detectable lesion seen (1). The focus of this review is to describe the putative mechanism of scalp itch with special emphasis on neuroanatomy and pathophysiology.

## Epidemiology of scalp pruritus

Although scalp itch is considered common, there is a paucity of data published on its prevalence (2). In a study conducted on a quantitatively representative sample of the French population, scalp itching was reported in 25% of the population (3). In patients with generalized idiopathic pruritus, 13% showed involvement of the scalp (4).

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## Causes of scalp pruritus

Scalp pruritus can arise from a variety of conditions including dermatologic, systemic, neurologic and psychogenic diseases. Among patients with psychogenic pruritus, the most commonly affected sites are scalp and face (5). Scalp pruritus can be classified based on the potential underlying disease (Table 1).

### Major dermatologic conditions associated with scalp pruritus

**Seborrheic dermatitis—**The most common presentation of scalp pruritus occurs in the setting of seborrheic dermatitis (24). Pathogenesis of seborrheic dermatitis is complex and appears to result from interactions among scalp skin, sebaceous secretions, Malassezia fungi, and the cutaneous immune system (25). In seborrheic dermatitis, yeast fails to possess lipid layer because of alterations in the availability of nutrients on the lipid surface, this may explain the inflammatory nature of this itchy dermatosis (see below malassezia species) (26,27).

Kerr et al. suggested an association between the subjective perception of itch in the scalp of seborrheic dermatitis patients and the level of histamine in the skin. They reported also that the scalp histamine level in subjects with seborrheic dermatitis was more than twice that in those without it. Treatment with a commercial potentiated zinc pyrithione shampoo led to a reduction in histamine in subjects with dandruff to a level that was statistically indistinguishable from those who did not have dandruff. This reduction in histamine was accompanied by a highly significant reduction in the perception of itch intensity (28).

**Scalp Psoriasis—**A recent large survey of 195 psoriatic patients showed that 58% suffer from scalp pruritus (7). Another survey in moderate to severe chronic-plaque psoriasis revealed regional variations in the sites of pruritus; the most affected anatomical site was the scalp (50%). Itching was limited to psoriatic lesions (70% of cases) (29).

**Scarring alopecias—**Scalp itching is commonly encountered in patients with lichen planopilaris when inflammation is present (30). Scalp pruritus is seen in approximately 70% of patients (8,9). Central centrifugal cicatricial alopecia is a common cause of scarring alopecia in African American women and is frequently associated with scalp itching or tenderness, with variable degrees (31).

**Neuropathic itch—**Neuropathic itch in scalp can be seen in association with diabetes mellitus, and herpes zoster (15,32). Scribner observed several patients whose primary complaint of pruritus confined to the scalp proved to be caused by unsuspected diabetes. Complete relief of the pruritus was achieved with control of the underlying diabetes (15).

Post herpetic neuralgia (PHN) has been historically associated with pain. However data emerged that PHN also induces Post herpetic itch (PHI) (32). A large epidemiological study reported PHI in roughly half of PHN patients. PHI can coexist with PHN or occur alone. PHI is more likely after zoster of the head and neck, particularly in the Trigeminal (V1) dermatome (33).

In a patient with PHI on the scalp, quantitation of PGP 9.5-immunoreactive epidermal nerves demonstrated loss of 96% of PGP 9.5 stained epidermal innervation in the itchy area. Concomitantly, quantitative sensory testing indicated severe damage to most sensory modalities except itch. Possible mechanisms include selective preservation of peripheral itch-fibers from neighboring unaffected dermatomes, imbalance between excitation and inhibition of second-order sensory neurons, and/or electrical hyperactivity of hypo-afferented central itch specific neurons (32). Oaklander has suggested that the excessive

scratching observed in some patients with PHI may be due to a reduced sensation of pain (34). Normally, the act of scratching to relieve itch elicits mild pain, which provides a protective negative feedback to halt further scratching. In PHI, scratching the affected skin area elicits no pain, so that scratching persists unabated, sometimes to the point of severe skin damage (34). Ross et al. recently demonstrated the existence of itch inhibitory interneurons within the dorsal horn. Bhlhb5 mutant mice lacking these interneurons had persistent itch (35). Glutamate is one of the major excitatory neurotransmitters in the spinal cord and may have a role in these interneurons. Therefore drugs suppressing presynaptic glutamate-release such as gabapentin and pregabalin may inhibit certain subtypes of itch such as neuropathic itch via this pathway (36).

**Sensitive scalp—**Sensitive skin is characterized by subjective complaints of discomfort without predictable classical visible signs of irritation and without an immunologic response (37,38). It was found that 36% of 400 subjects in 2 hospitals declared that they had sensitive skin on scalp (39). Further epidemiological studies revealed that 44% and 32% subjects declared suffering from sensitive scalp (3,40). Itching affects about 60% of subjects with sensitive scalp (40). In addition, hair loss was significantly associated with scalp sensitivity(3).

## Pathophysiology of itch in the scalp

The pathogenesis of scalp pruritus has rarely been investigated. In order to better understand why the scalp is so itchy it is important to understand the neuroanatomy of the hair follicle in its different cycles.

**The Scalp is a complex neural structure for itch—**The sensory innervation of the scalp conducted through branches from the trigeminal nerve, cervical plexus and dorsal rami of the cervical nerves (Figure 1). The hair follicle (HF) is highly innervated with four types of specific nerve endings (41,42). These are: free nerve endings (nociceptors), lanceolate nerve endings (acceleration detectors), Merkel nerve endings (pressure detectors), and pilo-Ruffini corpuscles (tension detectors) (43). The free nerve endings innervating the HF are from A-delta (thinly myelinated) or C fibers (unmyelinated) that emerge from the superficial nerve plexus. These nerves terminate as free nerve endings in the connective tissue between the sebaceous gland and HF (Figure 2) (44). Furthermore, HF development and cycling do affect the HF innervations. Peters et al. showed that cutaneous and follicular neuropeptide-containing NFs express major hair-cycle-associated changes (45). Initially, epidermal innervation is very dense, while it decreases and gains neuropeptide expression after penetration of HFs through the epidermis. Here, the number of neuropeptide containing NFs increases during the anagen phase of HF, decreases during the catagen phase, and stays low in the telogen phase as do their contacts with mast cells (MCs) (46).

In addition to HF, the scalp has abundant blood vessels more than in any other body region (47,48). There are also cyclic changes of perifollicular vascularization. Yano et al. found a significant increase in perifollicular vascularization during the anagen phase of HF, followed by regression of angiogenic blood vessels during the catagen and telogen phases (49). Pruritus involves different classes of cutaneous unmyelinated, slowly transmitting, sensory C-NFs that are distributed in the epidermis and papillary dermis. They are of two types; mechano-insensitive that are activated by histamine, and mechano--sensitive that cause pruritus with burning when induced activated by cowhage spicules (*Mucuna pruriens*) (50,51). Two systematic quantifications of epidermal NF density in multiple body sites revealed that scalp epidermal NF density was comparable to the back, but less than the cheek, neck and distal limbs (52,53). This variability in NF density may explain the topographical distribution of sensory thresholds in human skin to temperature as well as itch

and pain (54). Informative data, namely distribution of C-fibers at various body sites, is lacking. This data will be the key to better understanding of the topographical distribution of itch sensation in humans.

**Are there differences in sensation between scalp and other skin areas?—** Although the scalp is considered extremely itchy in many cutaneous inflammatory diseases and as mentioned above highly innervated, experimental itch studies in humans were not able to demonstrate lower itch thresholds. Rukwied et al. reported that forearm was more itch-sensitive than the scalp when investigated by histamine intradermal microdialysis, whereas topical application of histamine demonstrated that scalp was more itch-sensitive than the forearm skin (55). Shelly and Arthur had also demonstrated differences in itch perception among various areas of the body by the insertion of cowhage spicules, which activate Proteinase activating receptor 2 (PAR-2), an important non histaminergic itch pathway (see below) (56). In their studies, the scalp showed no response to cowhage spicules (57). Furthermore, hand and ankle were more sensitive to electrically evoked itch as compared to head and neck (58). These data corroborate with Essick et al. findings who studied the thresholds for detection of cooling, warming, cold pain and heat pain. They found that the scalp was notably less sensitive to thermal stimulation compared to other body areas, regardless of specific sensation considered (59). Whether these differences in thermal sensitivity between body sites is related to spatial variation in the density of thermal receptors or to differences in central neural processing is a matter of debate (59-63). Our recent preliminary study performed on scalp thermal and pain thresholds, as well as assessment of scalp itch using both histamine and cowhage revealed comparable result to the data above (unpublished data).

## Cutaneous sensory receptors and mediators involved in itchy scalp (Figure 3)

**MCs and Histamine receptors:** Histamine is the prototype of endogenous itch mediator secreted from MCs and can induce pruritus via H1 and H4 receptors on NFs (64,65), whereas H3 receptors appear to be involved in the suppression of pruritus (66). MC can induce pruritus directly also through the release of other mediators such as chymase, tryptase and cytokines. MC also secrete neurotrophins such as nerve growth factor (NGF) that contribute to hyperplasia of NFs in chronic pruritus forms, as has been observed in Atopic dermatitis (AD) (54,64,65). MCs function also as hair cycle regulators and are involved in the control of HF regression in murine system (67,68). MC number, degranulation activity, histochemical staining characteristics, histamine/heparin skin content, and physical MC-NF contacts all fluctuate significantly during synchronized HF cycling in rodent skin (69,70). MC density in scalp skin does not differ significantly from that in forearm skin (71). MCs number in skin has been reported to increase in AD and in the pruritic lesions of psoriasis (71,72).

**PAR-2:** PAR-2 is a G-protein coupled receptor. PAR-2 plays major role in mediating chronic pruritus. During neurogenic inflammation, various endogenous serine proteases such as trypsins from keratinocytes and tryptase from MCs activate PAR-2 on sensory nerve ending to release calcitonin gene-related peptide (CGRP) and substance P (SP) (73). PAR-2 signaling also stimulates the release of neuropeptides from central nerve endings thereby activating CGRP receptor and SP receptor (NK1R) to transmit itch responses to the central nervous system (74). Recently, it was shown that Cathepsin S which is an endogenous cystein protease evokes itch and activates PAR-2 and 4 (75). Exogenous activators of PAR2 may be serine proteinases generated by bacteria, fungi, and house dust mites (76). PAR-2 interacts synergistically with transient receptor potential vanilloid-type 1 (TRPV1), thereby amplifying itch sensation (see below) (77). In the skin, PAR-2 is expressed by almost all cell types including keratinocytes, HF, sensory neurons, and MCs (78-80). In human HF, PAR-2

is confined to the Inner root sheath (IRS) (79). PAR-2 activation is likely to be involved in pruritus of AD (56,81). In addition, skin exposure to exogenous microbial proteases could also induce itch and inflammation via PAR-2 (81). This could explain why staph folliculitis in the scalp is extremely itchy. Frateschi et al. showed that increased expression of epidermal PAR2 In transgenic mice causes epidermal hyperplasia, ichthyosis and itching (82).

**TRPV1:** TRPV1 receptor is activated by capsaicin, the key ingredient of hot chilli peppers. In addition to capsaicin, TRPV1 can also be activated by heat, acidosis and endogenous endovanilloids such as arachidonic acid derivatives, lipid peroxidation metabolites, and endocannabinoids (83,84). When TRPV1 is activated, it causes burning pain, itching and heat sensation, which is suppressed by continuous activation (51). TRPV1-expressing neurons are required for the behavioral responses to several different pruritic compounds including histamine, serotonin, and endothelin-1. TRPV1-expressing neurons have multiple intracellular mechanisms that generate or mediate itch (85). TRPV1 is highly expressed on sensory NFs, epidermal keratinocytes, HFs, dermal blood vessels, MCs, sebaceous glands and eccrine sweat glands (86,87). In human HF, TRPV1 is confined mainly to the Outer root sheath (ORS) and hair matrix (see Figure 3). TRPV1 has a significant role in human hair growth control. In organ culture, TRPV1 activation by capsaicin resulted in hair shaft elongation, suppression of proliferation, induction of apoptosis, premature HF regression (catagen), and up-regulation of intrafollicular transforming growth factor-B2. Cultured human ORS keratinocytes also expressed functional TRPV1, whose stimulation inhibits proliferation, induces apoptosis, up-regulate known endogenous hair growth inhibitors (interleukin-1B, transforming growth factor-B2), and down-regulate known hair growth promoters (hepatocyte growth factor, insulin-like growth factor-I, stem cell factor) (88). In rat skin, hair growth retardation, along with alopecia and a decrease in hair shaft thickness, follows as a consequence of capsaicin-induced sensory denervation (89). Pirt gene was recently identified as a regulator of TRPV1, in both histaminergic and nonhistaminergic itch (90). Tacrolimus has been reported to have anti-itch property, unrelated to its anti inflammatory property. This was explained possibly by a desensitization of TRPV1 and calcium currents through the phosphatidylinositol 4,5-bisphosphate regulation pathway (91). It would be of great interest to examine the role of TRPV1 receptor and its ligands in itchy scalp. We suspect that there could be significant differences in distribution and activity of TRPVs in itchy scalp.

Another thermosensitive Transient Receptor Potential channel which has been shown to have a role in itch in mice is TRPV3 (92). TRPV3 is abundantly expressed in keratinocytes and scalp HF, mainly the ORS (93-95). Activation of TRPV3 shown recently to inhibit human hair growth. In organ culture, TRPV3 activation resulted in a dose-dependent inhibition of hair shaft elongation, suppression of proliferation, and induction of apoptosis and premature HF regression (catagen) (95).

**Mas-related G protein-coupled receptor (Mrgpr):** Mrgpr family can be activated directly by peptides with common C-terminal motifs like RFamide, -RYamide, -RYG or -RLamide, neuropeptide AF, γ2-melanocyte-stimulating hormone, bovine adrenal medulla8-22 peptide [BAM8-22] and chloroquine (96-100). Recently, direct evidence proved the involvement of some of these peptides in itch sensation. Mouse MrgprA3 and MrgprC11 act as itch receptors in the skin for the pruritogens chloroquine, and bovine adrenal medulla 8-22 peptide (BAM8-22) and synthetic peptide Ser-Leu-Ile-Gly-Arg-Leu (SLIGRL) respectively (96,97,101). Interestingly, human MrgprX1 can respond to both chloroquine and BAM8-22 (97).

In human MrgprXs expression was detected exclusively in DRG neurons (99). MrgprA3 and MrgprC11 are expressed in a subset of TRPV1-positive afferent nerves (97), though TRPA1 is required for Mrgpr-mediated signaling (102).

**Opioid receptors:** Opioids and their receptors in the skin comprise part of the endogenous opioid system. It includes three opioid receptors: Mu (MOR), Delta (DOR) and Kappa (KOR), and the opioid peptides, such as enkephalins, endorphins, dynorphins and endomorphins. It is widely accepted that KOR signaling suppresses itch, while MOR signaling can stimulate itch. MOR seems to be important in chronic forms of pruritus, while KOR agonists are important in acute itching (103). Neuronal communication between pain- and itch-transmitting neurons underlies the role of opioids in pruritus (104). Many painful stimuli shown to inhibit itch by activating specific nociceptive pathways and spinal cord as well as higher CNS structures. On the other hand, opioids that activate spinal opioid receptors which induce analgesia (e.g. MOR agonists like morphine) may reduce the inhibition of itch by pain, thus enhancing pruritus (105-108). Itch and pain neurons in the spinal cord are connected by opioid-sensitive interneurons that can inhibit the pruritus transmission. Suppression of the activity of these interneurons by opioids results in clinically relevant itch sensation (104). Pruritus occurs in about 2-10% of patients treated systemically with opioids. But the risk is higher with intrathecal morphine reaching up to 100% (109-111). Intrathecal or epidural Opioid-induced itch frequently involves trigeminal skin in human and monkey (109,112). This phenomenon could be explained by the high concentration of opioid receptors in the spinal nucleus of the trigeminal nerve innervating facial areas (109).Opioid receptors are located in both peripheral and central nervous system, as well as epidermal keratinocytes, fibroblasts, melanocytes and hair follicles (103). In HF, Follicular dermal papilla (FP) mesenchyme and follicular epithelium consistently shows prominent MOR expression throughout the hair cycle (103). B-endorphin immunoreactivity is detected in the keratinocytes of the HFs in scalp (113). B-endorphin was localized to keratinocytes of the follicular matrix or the outer the ORS of the HF (113). B-endorphin expression is weakly detectable in the hair growth-inductive FP during anagen. However, B-endorphin immunoreactivity becomes more readily detectable in the FP during catagen and telogen, as well as in the HF epithelium (103). Tominaga et al. observed a down regulation of KOR, not MOR, in the epidermis of patients with AD, while ultraviolet treatment of this disease down regulated MOR but restored KOR expression (114). Furthermore, antipruritic efficacy of MOR antagonists has been reported in various dermatologic and systemic diseases including prurigo nodularis, chronic urticaria and cholestatic pruritus (104). Among the MOR antagonists, Naltrexone and Nalmefene achieve a significant antipruritic relief in atopic dermatitis (104,115,116). KOR agonists also exhibit a potent antipruritic activity. Among them, Nalfurafine is a selective KOR agonist that shows a potent antipruritic effects in hemodialysis patients with uremic pruritus (117,118) Moreover, Butorphanol is a KOR agonist and a weak MOR antagonist, shown to be effective in alleviating acute opioid induced itch and intractable pruritus (119).

**Cannabinoid receptors (CBs):** Cannabinoid receptors mediate the psychopharmacological action of marijuana (120). Activation of the cannabinoid receptors CB1 and CB2 leads to inhibition of pruritus. Cannabinoid receptors present in the nervous and immune system. In the skin, CB1 and CB2 were observed in cutaneous NFs, MCs, macrophages, epidermal keratinocytes, and the epithelial cells of HFs, sebocytes and eccrine sweat glands. The expression of CB1 and CB2 on cutaneous nerves was identified in large myelinated NFs of the reticular dermis, in small unmyelinated nerves of the papillary dermis, at the dermal—epidermal junction, and occasionally within the epidermis and small NFs associated with HFs. In skin specimens of different body sites (face, head, trunk and extremities) distribution of CB1 and CB2 immunoreactivity on cutaneous nerves was identical. In HFs, the differentiated epithelial cells of the infundibulum and the IRS stained for CB1. In

contrast to the recorded CB1 staining, undifferentiated cells of the infundibulum, the ORS and the bulb of HFs stained for CB2, but the IRS was negative (121). The abundance of these receptors in the HF may suggest they have endogenous antipruritic role attenuating the itch response. Further studies are required to elucidate their exact role in itchy scalp.

**Neurokinin receptors (NKRs):** The neuropeptide SP is reported to be a putative mediator for itching directly; and indirectly through MC activation. After release from sensory nerve endings, it binds with high affinity to the neurokinin-1 receptor (NK1R) on keratinocytes, endothelial cells and MCs. This attracts proinflammatory cells, degranulates MCs with release of pruritogenic proinflammatory cytokines such as tumor necrosis factor-alpha or leukotriene B4 (51).

SP content in the skin was assessed by radioimmunoassay and high-performance liquid chromatography and found to be moderately high in scalp but less than in face (122). In healthy human scalp NK1R is expressed on epidermal keratinocytes, NFs, sebaceous gland, dermal microvascular cells and sweat glands. NK1R expression in anagen HF is localized to the distal, suprainfundibular ORS, IRS and the nucleated hair shaft but weaker expression in HF matrix, and ORS (123).

The murine HF is richly innervated by sensory NFs expressing the neuropeptide SP that are located in close vicinity to the HF bulge region (45). Cutaneous SP expression and the number of SP-immunoreactive NFs are significantly increased during the early anagen phase of the murine hair cycle (45,124). More recently, SP has been described as being capable of inducing hair growth or inhibiting it in murine system. SP effects on the HF are strictly hair cycle-dependent (45,124,125). Furthermore, SP found to be a central element in the stress-induced threat to HF, resulting in premature onset of catagen accompanied by MC activation in the skin and subsequent release of mediators and secretion of NGF (126). This increase in SP and NGF during psychological stress might explain the stress related aggravation of scalp itch in diseases such as seborrhoeic dermatitis and scalp psoriasis (127).

**CGRP:** CGRP can provoke itch when released as a consequence of C-fiber activity. C-fiber activity leading to the itch sensation in the central nervous system also leads to CGRP release in the periphery where it provokes vasodilatation as one of the features of neurogenic inflammation; however, CGRP may be involved in opioid-mediated mechanism of itch perception (128). In addition, CGRP potently enhances brain-derived neurotrophic factor (BDNF) release from cultured trigeminal neurons in vivo in rats (129). CGRP content in the scalp has been assessed by radioimmunoassay and high-performance liquid chromatography and found to be low compared to other cutaneous regions (122). CGRP has been shown to co-localize with SP in human skin, occurring in the dermal papillae, and free epidermal nerve-endings of glabrous skin (130). In murine skin, the number of CGRP immunoreactive single NFs increased significantly during anagen, compare to telogen (45). CGRP inhibited anagen progression (45).

CGRP is involved in the pruritus of AD and Psoriasis (131-133). Repeated application of capsaicin desensitizes the nerve endings such that they no longer respond to local stimuli, and re-accumulation of CGRP and SP is inhibited. This explains the high efficacy of topical therapy with capsaicin in itch (134).

**Neurotrophins (NTs):** Three members of the NT family have been identified as molecular players in the pathogenesis of itch: NGF, BDNF, NT3, and NT4 (135-138). It has been suggested that the increased production and release of NGF and NT4 from resident skin cells such as Keratinocytes, MC, fibroblasts and eosinophils causes proliferation of unmyelinated afferent nerve terminals (135,138). NGF also leads to an increase in MC and

induces tryptase release from mast cells (108,139). NGF, NT-3 and NT-4 acutely sensitize sensory afferents and up-regulate the expression of neuronal neuropeptides especially SP and CGRP, and certain receptors (e.g TRPV1) which can worsen existing pruritus or cause it to persist (108,140). NGF and its high-affinity NGF receptor (TrkA) proteins are both expressed in human scalp skin and HF. Higher expression was found in anagen as compared with either catagen or telogen HF. In the anagen HF, high expression values were seen in the distal region, followed by upper central, lower central and bulb regions for both NGF and TrkA (141). NGF immunoreactivity was mainly detected in the ORS, IRS, FP, and connective tissue sheath, while TrkA was mainly detected in the ORS and IRS (141). Peters et al. suggest an anagen-promoting or anagen-supporting role for NGF and TrkA, and a catagen-promoting role for proNGF/ pan-neurotrophin-receptor (p75) interactions (142). NGF has recently been described as a stress-associated growth factor (143,144), and is one of the key catagen-inducing factors involved in stress-mediated hair growth inhibition in the mouse (145). In AD, Keratinocytes express high levels of NGF, NT-4 and TrkA, and high plasma levels of NGF are found (138,146-148). Although, recent studies demonstrate low plasma and dermal levels of NGF in AD patients (149,150). BDNF levels were also increased in serum, plasma, and oesinophils of AD patients compared with healthy controls (151). BDNF levels were correlated with the nocturnal scratching activities in AD (137). In addition to the sprouting of epidermal NFs that is initiated by increased NGF in AD (152). It was found also that Anti-NGF is antipruritic in animal models of AD (153-154). Increased fiber density and higher local NGF concentrations were also found in patients with pruritic contact dermatitis (155), and increased NGF, and TrkA immunoreactivities were detected in prurigo nodularis (156), and in pruritic lesions of patients with psoriasis (132).

**Gastrin-related peptide receptor (GRPR):** GRPR is a G protein-coupled receptor for GRP, a bombesin-like peptide. The GRP/GRPR system in the spinal cord of mice has a pivotal role in itch signaling but not pain perception. It is strongly activated by histamine-independent mechanisms such as by PAR-2 agonist and chloroquine (157,158). GRP, its ligand is expressed on nerves, keratinocytes, hair follicle, blood vessels, eccrine sweat glands, sebaceous glands and erector pili muscle; though this morphological data are poorly substantiated as it was studied using only one polyclonal antibody (159,160). GRP is co-localized with TRPV1 in cutaneous NFs (108). GRP NFs found to be more abundant in skin of AD mice, but the role of this receptor in humans remains to be defined (161).

**Endothelin (ET):** ET-1 evokes pruritus/itching sensation in both humans and animals. It is released from endothelium and MCs (135,162,163). Interestingly, an anti-nociceptive effect of endothelin1 was found when injected to hairy skin of the rat (164).

**Cytokines:** Certain interleukins (IL) are implicated in the pathogenesis of pruritus. Among them, IL-2 elicits rapid, low pruritogenic effects using skin-prick testing of healthy volunteers (165). It induces itch by activation of a discrete population of cutaneous C-polymodal nociceptors that are chemosensitive to endogenous inflammatory mediators including histamine and bradykinin (166). IL-2 is considered a possible pruritogenic mediator in AD and Psoriasis (72,167,168). Moreover, recombinant IL-2 was shown to induce pruritus when administered to cancer patients (169). IL-31 has been suggested as a pruritic cytokine. IL-31 ligand is released by Th2 lymphocytes. Its receptor IL-31 RA is expressed by keratinocytes, macrophages, dendritic cells, and probably sensory nerves projecting into the dorsal horn of the spinal cord (170,171). It has a significant role in AD itch (172,173). Another pruritogenic cytokine found in AD is IL-8 (174-177). Furthermore, mice overexpressing IL-4 in the epidermis spontaneously developed a pruritic inflammatory skin disease resembling human AD (178).

**Inflammatory cells other than MCs:** Basophilic granulocytes can release histamine similar to MCs and thus contribute to the induction of pruritus (179). Basophils have a proven role in aquagenic itch and in chronic idiopathic urticaria (180,181).

Eosinophilic granulocytes have a role in inflamed skin pruritus through the release neurotoxic granule proteins such as eosinophil cationic protein (ECP); neurotrophins such as NGF and BDNF; and neuropeptides such as SP. Accumulation of ECP in lesional skin and BDNF correlates with the severity of pruritus and disease activity of AD respectively (51). Eosinophils express histamine receptors including the H4 receptor (184). Furthermore, eosinophils hematopoiesis, activation, survival, and elaboration of mediators can all be regulated by mast cells in tissue. Moreover, because eosinophils can secrete stem cell factor, they can regulate mast cell function in a paracrine manner (183).

## Other non neuronal unique properties of scalp that may play role in scalp itch

**Scalp microflora—**The scalp normally harbors many micro-organisms including in particular Malassezia species, staphylococci and Propionibacterium species (24,76,184).

**A- Malassezia species may have a dual effect on scalp itch- protective in healthy skin and itch inducing in sebum abnormalities:** The highest density of *Malassezia* species is found in scalp (185). In normal condition, Malassezia yeast significantly reduces the production of pro-inflammatory cytokines by keratinocytes, which is related to the presence of lipid-rich microfibrillar layer surrounding yeast cells (186). High quantity of lipid may prevent the yeast cell from inducing inflammation while low lipid content will reverse this protective mechanism (27,187). This was proven when extraction of cell-wall lipids of all species of Malassezia reversed their capacity and increased IL-6, IL-8 and IL-1a production above levels elicited by the capsulated forms. Notably, acapsular viable, stationary phase M. globosa caused a 66-fold increase in IL-8 production (27,187). In the author opinion, this may contribute the etiology of seborrheic dermatitis itch.Furthermore, *Malazzesia* species have lipase activity, which hydrolyze human sebum triglycerides in to free fatty acids (FFAs) (25), consume specific saturated fatty acids, and leave behind the unsaturated lipids. The unsaturated fatty acids are well know irritants and can induce inflammation including elevating IL-la and IL-8 levels (188-191). The unsaturated fatty acids effect on the skin is well controlled by intact stratum corneum barrier function (192,193).

Malassezia species have been identified as a causative organism or aggravating factor in various pruritic skin diseases, including pityrosporum folliculitis, seborrheic dermatitis and AD (194,195). AD patients with sensitivity to P.orbiculare are characterized by severe itch disturbing sleep. They suffer also from a more chronic course, higher total eczema score and more frequent distribution in the head-neck-face regions (196).

**B- Staph aureus has itch inducing mechanism:** Staphylococcal exotoxins can lead to IL-31 expression by T cells (170), which is a known mediator of itch. Staph can also mediate itch through serine protease activation of PAR-2 receptor (197).

**Scalp Sebum has both itch protective and itch inducing mechanisms—**The scalp is a sebum rich zone that is even richer than the face. Human sebaceous glands secrete a lipid mixture (sebum) containing squalene, wax esters, cholesterol esters, triglycerides, and free cholesterol. On the surface of the skin, triglycerides produce FFAs by catalytic reactions in the presence of bacterial hydrolases (198). Some of these FFAs are highly irritating to the skin.

Skin Surface lipid chemical composition can be severely altered in different skin diseases. This is the case of AD, seborrheic dermatitis and psoriasis (199-202).

On the contrary, Sebum content was significantly lower in people with sensitive scalp to hair dyes compared to non-sensitive group (203). FFAs in the skin surface lipids function as a barrier to diseases caused by bacteria and fungi and keep the surface acidity constant an important factor in inhibiting proteases and cathepsins (204,205).

There is marked individual and anatomical variability in the amount and composition of sebum in human skin (198,206,207). The total amounts of FFAs were greatest in the scalp (198).

**Scalp Stratum corneum has itch protective measures—**Stratum corneum of the scalp skin is functionally distinct from that of the face and extremities. The water barrier function of the scalp stratum corneum was almost comparable to that of the volar forearm, but was far better than that of facial skin. Hydration of the scalp skin surface was markedly higher than that of facial skin and volar forearm. These characteristics seem to be dependent, at least to some extent, on the amount of sebum-derived skin surface lipids because these were abundant on the scalp skin (208). This may have a protective measure to reduce scalp itch in healthy skin as good barrier function prevents signaling of exogenous factors such as soaps, bacterial infections and other irritants from inducing itch.

### Conclusion

Scalp itch continues to be a major symptom for dermatologic patients. The scalp has a complex neuroanatomy with abundance of sensory neural end organs in the pilosebacous unit. Because ‘itchy scalp’ is a common complaint with disparate origins; namely dermatologic, neuropathic, systemic and psychogenic; dissecting these neural circuits, their anatomical and physiologic role in itch is of prime importance. Understanding the unique features of itch circuit in the scalp is key to development of effective therapies. Table 2 summarizes future therapeutic targets for interventions for scalp itch. A highly focused hypothesis-driven approach must be applied when trying to parse out mechanisms of scalp pruritus

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## ABBREVIATIONS

| | |
|---|---|
| **AD** | Atopic dermatitis |
| **BDNF** | Brain-derived neurotrophic factor |
| **CB** | Cannabinoid receptor |
| **CGRP** | Calcitonin gene-related peptide |
| **DOR** | Delta-opioid receptor |
| **DP** | Follicular dermal papillae |
| **eCB** | Endogenous cannibinoids |
| **ECP** | Eosinophil cationic protein |

| | |
|---|---|
| **ET** | Endothelin |
| **FFA** | Free fatty acids |
| **GRPR** | Gastrin-related peptide receptor |
| **HF** | Hair follicle |
| **IL** | Interleukin |
| **IRS** | Inner root sheath |
| **KOR** | Kappa-opioid receptor |
| **MC** | Mast cell |
| **MOR** | Mu-opioid receptor |
| **Mrgpr** | Mas-related G protein-coupled receptor |
| **NF** | Nerve fiber |
| **NGF** | Nerve growth factor |
| **NK1R** | Neurokinin-1 receptor |
| **NT-3** | Neurotrophin 3 |
| **NT-4** | Neurotrophin 4 |
| **ORS** | Outer root sheath |
| **PAR-2** | Proteinase activating receptor 2 |
| **PGD2** | Prostaglandin D2 |
| **PHI** | Post herpetic neuralgic itch |
| **PHN** | Post herpetic neuralgia |
| **SP** | Substance P |
| **TrkA** | High-affinity NGF receptor |
| **TRPV1** | Transient receptor potential vanilloid-type 1 |
| **TXA2** | Thromboxane A2 |

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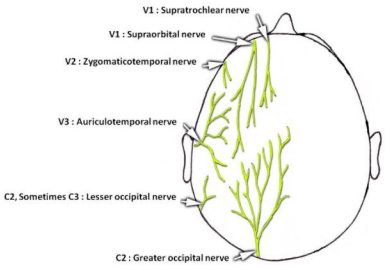


**Figure 1. Sensory innervations of the scalp**

V1: Ophthalmic division of trigeminal nerve; V2: Maxillary division of the trigeminal nerve; V3: Mandibular division of the trigeminal nerve; C2: Second cervical nerve; C3: Third cervical nerve.

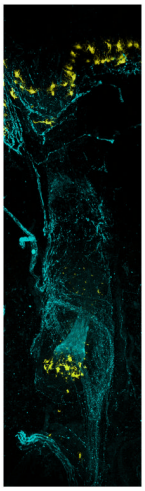

**Figure 2. Innervation around a human scalp hair and melanocytes of the dermal papilla and epidermis**

Projection of 55 one-micron optical sections of human scalp hair follicle captured using laser scanning confocal microscopy.

4-mm punch biopsy from human scalp, was cryo-sectioned into 180-micron, vertical section. Sample was immunostained with antibodies to a pan-neuronal marker PGP9.5 (pseudo-colored aqua), and Mel5 (pseudo-colored yellow). 100XMAG

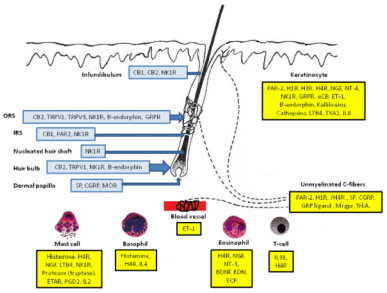


**Figure 3. Itch mediators in the scalp**

Scalp pruritus involves a complex interaction between different cells, mediators and receptors, most of them are shown above.

PAR-2, proteinase-activated receptor 2; H1R, Histamine 1 receptor; H3R, Histamine 3 receptor; H4R, Histamine 4 receptor; NGF, nerve growth factor; ET-1; TrkA, high-affinity NGF receptor; endothelin-1; ETAR, endothelin receptor A; eCB, endogenous cannibinoids; NT-3, neurotrophin 3; NT-4, neurotrophin 4; LTB4, leukotriene B4; TXA2, thromboxane A2; GRP, gastrin-related peptide; SP, substance P; CGRP, calcitonin gene related peptide; Mrgpr, mas-related G protein-coupled receptor; IL-2, interleukin-2; IL-4, interleukin-4; IL-8, interleukin-8; IL-31, interleukin-31; BDNF: brain-derived neurotrophic factor; EDN, eosinophil-derived neurotoxin; ECP, eosinophil cationic protein; PGD2, prostaglandin D2; ORS, outer root sheath; IRS, inner root sheath; CB1, cannabinoid receptor1; CB2, cannabinoid receptor2; NK1R, neurokinin-1 receptor; TRPV, transient receptor potential vanilloid; MOR, Mu-opioid receptor.

## Table 1

proposed clinical classification of scalp pruritus According to potential underlying disease*

**Dermatologic**: (*arising from diseases of the skin in order of frequency*)

*Inflammatory dermatoses*: seborrheic dermatitis, psoriasis, advanced aging itch and skin xerosis

atopic dermatitis [7], contact dermatitis, sensitive scalp [3], lichen planopilaris [8, 9], Frontal fibrosing alopecia [10], central centrifugal cicatricia alopecia [11], Pityriasis amiantacea [12], xerosis, active phase of alopecia areata, urticaria, scars, insect bite, lichen simplex chronicus, lichen nuchae, discoid lupus erythematosus, acne necrotica, folliculitis decalvans [13], Angiolymphoid hyperplasia with eosinophilia [14].

*Infectious dermatoses*: folliculitis, mycotic, bacterial and viral infections, scabies, pediculosis capitis, cutaneous larva migrans.

*Autoimmune dermatosis*: dermatitis herpetiformis.

*Neoplasms*: lymphoma, leukemic infiltrates of the skin.

**Neuropathic**: (*arising from diseases or disorders of afferent nerve fibers*)

Diabetes mellitus [15], Post herpetic neuralgia, migraine headache, atypical facial neuralgia, scalp dysesthesia [16], brain and spinal cord injury[17], Narrowing of the bony foramina from osteoarthritis[17], Wallenberg syndrome [18], brain tumors [19] .

**Systemic**: (*arising from diseases of organ*)

Chronic renal failure, cholestatic liver disease, Lymphoma- Hodgkins and non hodgkins, dermatomyositis [20, 21], drug induced pruritus (e.g dobutamine) [22], Eosinophilic arteritis of the scalp [23].

**Psychogenic/psychosomatic**: (*somatoform pruritus with co-morbidity of psychiatric and psychosomatic diseases*)

Obsessive compulsive disorders, anxiety disorders, Somatoform and dissociative disorders, tactile hallucinations, delusional parasitosis, schizophrenia, depression

*Source: with modification from (1,6).

## Table 2

Novel therapeutic targets in scalp pruritus*

| Pruritic mediator | Scalp itch target | Therapy |
|---|---|---|
| Proteinase-activated receptor 2 | AD, chronic dry skin, pruritus of elderly, chronic folliculitis, and acne-form related itch in scalp. | Tetracycline and its derivatives: doxycycline, minocycline.<br>PAR-2 antibodies [such as SAM-11 (Santa Cruz) and P2pal-2135]<br>PAR-2 antagonists [such as FSLLRY (Peptides International), ENMD-106836] |
| Endogenous proteases: | | |
| - Serine proteases (mast cell tryptase and kallikreins). | -chronic folliculitis, and pruritus of elderly. | - Nafamostat mesilate and camostat mesilate |
| - Cysteine proteases (Cathepsin S) | -AD, and pruritus of elderly. | - Cathepsin S inhibitor (E-64) |
| Transient receptor potential vanilloid- type 1 | neuropathic itch, AD, prurigo nodularis, lichen simplex chronicus, and psoriasis. | Topical capsaicin, Topical tacrolimus |
| Histamine 1 and 4 receptors | AD, psoriasis, and seborrhoeic dermatitis. | Anti-histamines |
| Mu-opioid receptor | systemic pruritus, intractable pruritus, AD, and prurigo nodularis. | Mu-opioid receptor antagonists such as naloxone, naltrexone, 1% naltrexone cream, nalmefene, Butorphanol, methylnaltrexone |
| Kappa-opioid receptor | systemic pruritus, intractable pruritus, and acute opioid induced pruritus. | Kappa-opioid receptor agonists such as Nalfurafine, bremazocine, GR 89696, Butorphanol, topical liposomal butorphanol preparation, ICI 204,448 (Tocris Bioscience), Asimadoline (EMD-61753), SA14867 (Santen Pharmaceutical Co.) |
| Interleukin-31 | AD, prurigo nodularis, lichen simplex chronicus, staph folliculitis, and lichen amyloidosis in scalp. | IL-31 antibody |
| Neurokinin Receptor | AD, prurigo nodularis, pruritus of malignancy, and chronic refractory pruritus. | NK1R-antagonist (Aprepitant) |
| Cannabinoids | AD, and neuropathic itch. | Topical cannabinoid receptor agonists |

* Source: with modification from (209)