Review

Understanding itch in systemic sclerosis in order to improve patient quality of life

T.M. Frech[1], M. Baron[2]

[1]*University of Utah, University of Utah and Veterans Affair Medical Center, Salt Lake City, UT, USA;*
[2]*Jewish General Hospital, McGill University, Montreal, Quebec, Canada.*

Tracy M. Frech, MD, MS
Murray Baron, MD

Please address correspondence to:
Tracy M. Frech, MD, MS,
4B200 SOM 30 N 1900 E,
Salt Lake City, UT 84132, USA.
E-mail: tracy.frech@hsc.utah.edu

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ABSTRACT

Pruritus is a common complaint in systemic sclerosis (SSc) and impairs patients' quality of life. Little is known about the pathogenesis of itch in SSc, but complex and multi-factorial mechanisms of itch are appreciated in many chronic diseases. This review discusses the putative mechanisms of the pathogenesis of itch to better understand the mechanisms that may be relevant to pruritus in SSc. It discusses possible therapeutics in the context of this complex pathogenesis.

Introduction

Systemic sclerosis (SSc, scleroderma) is a chronic, multisystem disease characterised by vasculopathy, fibrosis, and autoimmunity. Pruritus has not been extensively studied in SSc. We have demonstrated that 45% of patients complain of pruritus on most days and that patients complaining of itch have more significant skin involvement, worse respiratory symptoms, and a greater number of gastrointestinal tract complaints (1). SSc patients with pruritus have significantly worse mental and physical function and greater disability than patients without pruritus (2). The origin of itch in SSc, whether systemic- or dermis-derived, and its relationship to vasculopathy and fibrosis is unclear. Nonetheless, an understanding the mechanism of itch in SSc is important to improving patient quality of life.

Complex and multifactorial mechanisms of itch are appreciated in many chronic diseases. Little is known about the pathogenesis of itch in SSc, we undertook this review of the putative mechanisms of the pathogenesis of itch and its treatment in other diseases to better understand the mechanisms that may be relevant to itch in SSc.

Mechanisms of pruritus

The pathophysiology of pruritus has been recently reviewed (3-8). These reviews broadly suggest that itch may originate from interplay between skin inflammation and the nervous system. Pruritogens, which may be mechanical, electrical, thermal, or low pH stimuli in origin, can directly stimulate nerve fibre endings, or may do so via mediators released from resident cells in the skin, particularly mast cells (9, 10). The perception of itch depends on the neurotransmission/neuromodulation of signal from the skin to brain and thus can be modulated at multiple levels throughout the nervous system, including the level of the skin, spinal cord, or brain (Fig. 1). As such, the goal of pruritus treatment is to remove the source of pruritogen, prevent or block the effect of local mediator release, and/or interrupt the perception of itch at various points along nervous system conduction.

Pruritogens

Pruritogens are chemical mediators that activate or sensitise nociceptor terminals to elicit or exacerbate pruritus. They can be generated within the skin or outside the skin (11). Although we commonly think of pruritogens as acting peripherally, in fact they may also act centrally. Their receptors have been found in various intracutaneous cell types, peripheral and central nerves, as well as sensory neurons (12). As such, pruritus is associated with many inflammatory, dermatologic, and systemic conditions.

Histamine

Although a multitude of mediators capable of stimulating afferent nerves leading to itch exist, the classic inflammatory pruritogen is histamine, a prod-

uct of mast cells. In atopic dermatitis (AD) an increase in plasma histamine has been demonstrated, presumably generated by antigen/IgE-stimulated degranulation of mast cells in the gut and/or skin (10). Importantly, similar abnormalities have been noted in SSc. Elevated levels of histamine were found in 18/32 (56%) patients with SSc and was more common in patients with diffuse disease (74%), in contrast to limited disease (31%) (13). In AD anti-histamine therapy is often not effective in relieving itch, suggesting that although there may be an excess histamine release, there are also likely to be other mediators in skin equally important in itch generation (11). The complexity of management required for AD suggests that there may be many altered neurophysiological mediators of itch in this condition, which are important to consider in management of SSc-pruritus (14).

Preformed histamine is present in large amounts in mast cell granules. Thus, after cell activation, can be immediately released into the surrounding area in which it induces itch via H1R (histamine 1 receptors) on nerve fibres (8). Experiments in mice demonstrated that the decreased threshold in response to H3R antagonism activates H1R and H4R on sensory neurons, which in turn results in the excitation of histamine-sensitive afferents and elicits the sensation of itch (15). Thus, H3R and H4R may be of particular interest in SSc since H3R can suppress itch, whereas H4R not only induces the sensation of itch, but also modulates dendritic cell migration through skin and can influence T cell reactions (15, 16); possibly linking itch to immune mediated fibrosis.

Histamine acts on a specific subgroup of mechano-insensitive C-fibres, which are also sensitive to other mediators (17). An 'intensity theory' suggests that both itching and pain result from the activation of nociceptors, but to a different extent, with a weak one leading to itching and a stronger one to pain (18). As such, the sensitivity profile of human cutaneous C-nociceptors determine perception; histamine tends to provoke pruritus and rarely pain; prostaglandin E(2) (PGE2) causes preferentially mod-

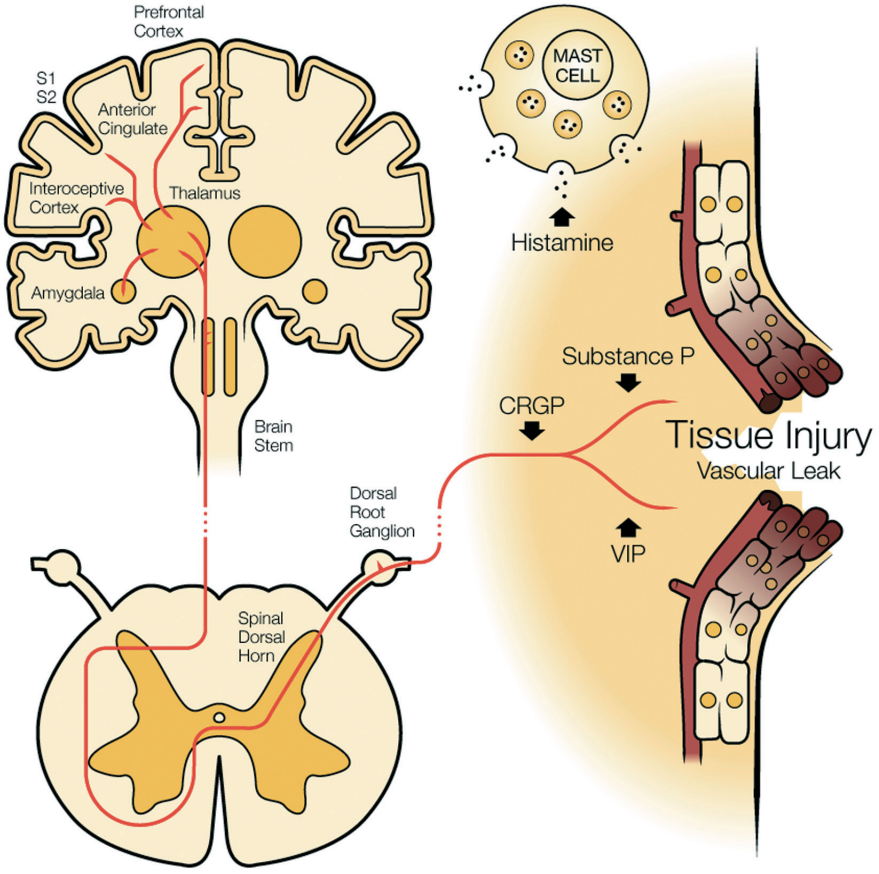

Fig 1. The neurology of itch.

erate itching; capsaicin always induces pain but never pruritus; and serotonin, acetylcholine, and bradykinin induced pain more often than pruritus (19). Thus, a better understanding of cutaneous mechano-insensitive C-fibres in SSc may help clarify the painful and pruritic aspects of this disease.

Non-histamine mast cell-derived pruritogens:

Due to the central role of histamine in certain forms of pruritus, attention has been paid to the role of mast cells in various conditions associated with pruritus. The mast cell may be relevant to itch but not necessarily via histamine release.

Mast cell-derived mediators are of three basic types and include: (1) preformed mediators, such as histamine and heparin, stored in secretory granules, (2) newly-synthesised lipid mediators, and (3) chemokines and cytokines (20). Mast cells produce and secrete these substances in order to influence the innate immune system and the adaptive immune response in an attempt to restore connective tissue homeostasis (21, 22). Local production of cytokine in damaged skin can induce itch and immune dysregulation (23). Modulation of lipid mediators, produced by mast cells have been studied in the treatment of pruritus and may be of interest in SSc (5).

One lipid mediator, lysophosphatidic acid (LPA) may be of particular interest in SSc. LPA is a potent signalling phospholipid that can activate mast cell LPA receptors, which when in the perivascular location results in vascular inflammation (24). Of interest, serum samples from cholestatic patients complaining of pruritus contain higher amounts of LPA (25). This study hypothesised that the LPA accumulation in the circulation of cholestatic patients activated sensory neurons. LPA has also been reported to be elevated in SSc , but secreted from activated platelets (26). Studies suggest that increased local formation of LPA near unmyelinated nerve endings can cause itch

(25). The role of LPA/LPA_1 pathway inhibition as a potential effective new therapeutic strategy for SSc dermal fibrosis was suggested in a mouse model (27). Thus, in addition to fibrosis the LPA/LPA_1 axis may be important in the pruritus of SSc.

Prostaglandin E (2)

PGE2 is a proinflammatory cytokine, which is reported to be a potent vasodilator and a weak pruritic agent in normal skin and in patients with AD (28). PGE2 production and the expression of cytosolic phospholipase A2 (cPLA2), cyclooxygenase (COX)-1, and COX-2 (enzymes that regulate PGE2 production) were found to be upregulated in fibroblasts from SSc skin. PGE2 production and COX-2 expression were inhibited by combined therapy using 8-methoxypsoralen and long wave ultraviolet light (PUVA therapy) (29). The beneficial effect of PUVA on itch in SSc has been suggested and warrants further study (30).

Endothelin

Endothelin-1 (ET-1) is generated by a variety of cell types, including endothelial cells, vascular smooth muscle cells, and leukocytes (31). In a study of the effect of ET-1 in human skin, the vasodilator response to ET-1 was found to be neurogenic in origin (defined as that by mediated nociceptive fibres) and was in part mediated by the local release of nitric oxide (32). In this study, ET-1 was classified as a neuropeptide and itch was found to be independent of mast cell-derived histamine (32). While it is recognised that ET-1 signalling is through specific G-protein-coupled ET_A and ET_B receptors, the downstream signalling mediators for itch in humans are unknown. ET-1 may induce itch by acting directly on nerve endings, or through indirect actions via release of endogenous mediators such as histamine from mast cells (33). In mice, data supports that ET-1 may signal through the ET (A) receptor to induce pruritus sensation, while ET (B) receptor may antagonise the pruritus evoked by ET-1 (33). As endothelin antagonists such as bosentan, a non-selective ET(A)/ET(B) antagonist and ambrisentan, an ET(A) antagonist, are both used for treatment of pulmonary arterial hypertension in SSc, the study of the effect of these medications on itch in SSc is indicated.

Neuropeptides

Neuropeptides from unmyelinated nerve ending may be responsible for itch. The mast cell-nerve functional units at sites near unmyelinated nerve fibres have been associated with differential secretion and degranulation which may explain varying responsiveness to therapeutics used for itch and account for some of the challenge in studying itch (34). As discussed above, once a mast cell degranulates, in addition to histamine, many other substances, such as proteases, lipid mediators, and cytokines are released. These substances subsequently activate and may cause further release of neuropeptides, which enhances tissue damage. Since mast cells can behave as an immune cell, endocrine cell, or even as sensorial neurons based on the microenvironment of damage and mast cells exhibit a flexibility and reciprocity with neuropeptide signaling, which induce and sustain pruritus (5, 35). Thus, the study of neuropeptide induced pruritus, especially as it relates to the mast cell, may prove challenging in SSc.

Nonetheless, an understanding of the neuropeptide influence on itch may also have implications for understanding SSc pathogenesis as the skin may be the source of both itch and disease progression. CRGP is a particularly interesting neuropeptide in its relationship to both itch and the vasculopathy of SSc. Calcitonin related gene peptide (CRGP) is composed of two separate peptides (CRGPα and CRGPβ), which are nearly identical at an amino acid level. CRGPα is known to cause vasodilatation and relaxes smooth muscle cells (36). It can be administered as a therapeutic agent in SSc for digital vasculopathy (37). Both substance P (sP) and CGRP can cause mast cell degranulation (38), which can induce and sustain itch. Vasoactive intestinal peptide (VIP) is another neuropeptide that is recognised to contribute to itch (5) and is upregulated in SSc skin (39, 40). There is a direct correlation between decrease in nerve fibre density stains, including VIP immunostaining and microvascular abnormalities in SSc skin (41). Since itch is most significant in early SSc with significant skin involvement (42), neuropeptides may have a role as a biomarker in SSc or for studies of pruritus therapeutic responsiveness. In sum, neuropeptides can induce the release histamine from skin mast cells and can also directly act as pruritogens. Neuropeptides, such as CGRP, VIP, sP, and ET-1, play an important role in the maintenance of tissue integrity in the skin and may serve as potential biomarker of itch, as their levels vary with itch perception (43, 44).

Temperature mediated itch, through thermosensitive transient receptor potential (TRP) channels nociceptive neurons are another skin-originating itch mechanism that is independent of mast cell activation (45) (46, 47). Direct mechanical nerve fibre activation in the skin, possibly due to a lack of moisture in the skin, is also implicated in pruritus associated with aging (48). Thus, understanding the neurology of itch as it relates to neuropeptides, temperature, and mechanical stimuli, in SSc is important.

Opioid receptors

Exogenous opioids are recognised pruritogens (49). Itch or pruritus is evoked by direct activation of opioid receptors, which have recently been identified in the skin (50). These receptors synapse with the spinal cord, thus are also considered a part of neurogenic itch (12). Although the sources of itch in SSc are unknown, some clues may derive from the information available regarding itch related to opioid receptors in other similar skin diseases, such as hypertrophic scaring (50). Since proinflammatory and profibrogenic cytokines are known to play an important role in the itch seen in hypertrophic scars and may be modified through modulation of opioid receptors, understanding the role of opioid receptors in itch may have relevance to SSc (51).

The nervous system and itch in SSc

In addition to the role of peripherally released neuropeptides in itch, the

nervous system plays an important role in transmission of these stimuli and in their modulation. As discussed above, the unpleasant sensation that provokes a desire to scratch can originate from stimulation of unmyelinated nerve fibres in the skin by locally released pruritogens. Subsequently, the stimulated pathway acts through synapses that pass through the dorsal horn of the spinal cord, the contralateral spinothalamic tract, the posterolateral ventral thalamic nucleus and then to the somatosensory cortex of the post-central cingulated gyrus (Fig. 1) (52). As such, skin pathology, peripheral neuropathy, central nervous system sensitisation, and the cognito-affective aspects of itch must be understood in order to treat it effectively (12). The complexity of the transmission of itch is highlighted by systemic medical conditions, such as end-stage renal disease, chronic liver disease, and malignancy. These conditions are associated with itch, which may be influenced at various points in this transmission pathway and have proven difficult to study (53, 54).

Itch could result form a normal level of pruritogen acting on abnormal peripheral sensors. Thus, pruritus in SSc could arise either from abnormalities of nerve fibre endings in SSc skin, from the presence of an excess of mast cells, and/or from the release of local mediators in skin. Like other chronic inflammatory medical conditions, the role of chemokines (derived not only from mast cells, but possibly also from other peri-vascular immune cells) on SSc itch is also of interest. Serum studies have suggested the association of certain chemokines with the severity of skin involvement in SSc (55).

As discussed above, understanding the role of cutaneous C fibre nerves in SSc is an interesting target. Since nociceptors are present in the skin, muscle, joints, and gastrointestinal tract and respond to potentially damaging stimuli by sending nerve signals to the spinal cord and brain, understanding the activation of itch pathways in this multi-organ disease may prove challenging. Nonetheless, the initiation of the sensation of itch and its modulation can occur at various sites of origin in response to thermal, mechanical, or chemical noxious stimuli, providing several possible therapeutic options (56).

SSc may reduce the number of nerve endings or make them more sensitive. This hypothesis raises the possibility that SSc-itch may be peripherally neurogenic in nature and may change over time and with disease severity. A reduction of sensory and autonomic innervation in both sclerotic and apparently uninvolved skin has been reported in SSc (41) with mast cell association early in the pathologic process (57). Of particular interest, nerve abnormalities in SSc can improve with improved oxygenation of tissue (58). Ultrasound, computed tomography, and magnetic resonance have detected nerve abnormalities in 70% of SSc patients complaining of neurologic disturbances in the hands (59). Interestingly, a subset of cutaneous pruritogen sensitive C-fibres, which originate superficially in the skin and are insensitive to histamine, highlight that identifying the origin of itch initiation may be critical for choice of therapy for itch modulation in SSc (48, 60).

Independent of skin changes, peripheral nerve endings, dorsal root ganglia, the spinal cord and CNS can amplify or suppress pruritus over time (61). Upon stimulation, cells of the dorsal horn of the spinal cord can release sP and CGRP into peripheral tissues, causing the degranulation of mast cells and influencing vascular endothelial cell characteristics in the skin (56). This stimulation could be one central mechanism of itch generation. Similarly, neuropeptides can act in the spinal cord to increase synaptic strength between nociceptors and spinal neurons, which enhances symptoms (62). This synaptic strength has been suggested as important more central mechanism of itch in chronic disease (63), and may highlight the importance of understanding disease duration when studying SSc itch.

Lastly, cognitive factors may modulate the perception of itch. Not surprisingly, psychiatric or psychosomatic conditions are thought to significantly contribute to pruritus and highlight the complexity of itch perception (64). While pruritogens are not well defined in psychiatric itch, mental stress and depression increase pruritus perception (65) and anti-depressants have a role in pruritus management (66). The ability to modulate itch away from the cutaneous nociception is evidenced by the use of psychosomatic counseling and food allergen dietary therapy for refractory pruritus in certain AD individuals (67-69). Therapeutics that act centrally may have implications in SSc-pruritus therapy. Nocturnal pruritus may have a strong psychological component (70). Thus, studies of pruritus should consider the effects of itch on mental health and sleep in SSc as well as the distress of chronic disease on the perception of itch.

Therapy of itch

Anti-histamine

The first line therapy for itch is anti-histamines because of their well known effect of on urticaria. Anti-histamine studies yielded disappointing results for many systemic itch conditions such as uremic pruritus, post-burn pruritus, and cholestatic pruritus (71). Anti-histamines do not block the synthesis of histamine or its release from mast cells, but work at the histamine receptor level, which may account for this disappointing result. It is possible that transduction of chronic itch is through non-histaminergic receptors (60). If anti-histamines are ineffective for interrupting nociception, then both transmission and perception of itch occurs. The most plausible explanation for chronic itch is that one or more of the many other mast cell mediators released after various stimuli may also be responsible for itch and are not affected by anti-histamines (5, 72, 73).

Neuropeptides may be responsible for the perception of itch in patients that are nonresponsive to anti-histamines. Neuropeptide levels of VIP, CRGP, and sP correlate with mast cell load (74). Further, support of the possibility that mediators other than histamine released from mast cells may be important in the itch of SSc, comes from a study of ketotifen. The mast cell-stabilising drug ketotifen was studied in a randomised, prospective, double blind, placebo-controlled trial in 24 SSc patients. While no significant improve-

ments in the clinical parameters, pulmonary function, global assessments, and mast cell release were noted, pruritus tended to improve in the group taking the active drug. These results were based on a small sample size therefore they are suggestive not definitive.

Gabapentin

As conventional treatment modalities such as antihistamines lack efficacy, new therapeutic strategies, which affect the neuronal mechanisms underlying chronic pruritus, have been suggested (8). Gabapentin, an anticonvulsant and gamma-aminobutyric acid agonist, has both central and peripheral effects on pruritus. It impedes transmitting nociceptive sensations to the brain, thus suppressing pruritus. Its effect on pruritus is mediated through inhibition of CRGP, modulation of μ-opioid receptors (MOR), and it has an acute inhibitory effect on sP (76). Gabapentin is safe and found to be effective in uremic pruritus, cancer/haematologic causes, opioid-induced itch, post-burn pruritus, as well as pruritus of unknown origin (77). Further research may be warranted to establish whether gabapentin influences mast cell-induced pruritus and its potential utility in SSc.

Phototherapy

Phototherapy with ultraviolet (UV) light on the skin has proven useful for treating a number of chronic inflammatory, sclerosing, and neoplastic skin diseases. Research suggests that this effect is via its immunomodulating actions, including apoptosis of infiltrating T-cells, suppression of cytokine levels, and reduction in Langerhans and mast cell numbers (78). The therapeutic effect is related to the dose (low, medium, high), wavelength (UVA: 320–400 nm; UVB 320–290 nm) penetration of the skin, and use with concurrent therapies (*i.e.* psoralen or PUVA). Pertinent to SSc, is that phototherapy may modulate endothelial dysfunction (vasculopathy) (79). Furthermore, UVA1 phototherapy reduces the density of dermal mast cells and pruritus (80). Chemical modifications of pruritogens in the skin or altered skin sensitivity to pruritogens are proposed as another potential mechanism of action (81). Phototherapy has been shown to reduce the number of CGRP-immunoreactive nerve fibres (82). Since the modulation effect is thought to be peripheral without untoward central nervous system effects, it is an attractive therapeutic option to study in SSc. Additionally, the effects of phototherapy on VIP and gastrointestinal tract symptoms have been reported (83). The potential effect of phototherapy on neurogenic inflammation in SSc warrants further research.

Opioid modulation

– μ-opioid antagonists

A number of skin cell types, including dermal mast cells, keratinocytes, fibroblasts and macrophages express MOR as well as other opioid receptors (84). Activation of MOR in the skin elicits pruritus and inflammation, while activation of cutaneous κ-opioid receptors has an anti-pruritic effect (84). Central versus peripheral site activation is proposed as a potential mechanism for opioid induced itch and its modulation, with μ- and κ-opioid receptor agonists acting synergistically for analgesia, but inversely in terms of pruritic properties (85). Thus, central MOR act to reduce primary nocireceptor activity (85). Unlike anti-histamines, which act at the tissue level, MOR may influence a central perception of the effect caused by mast cell degranulation. This highlights that identification of both the duration as well as the source of itch in SSc is important to understand its proper treatment.

This mechanism of MOR antagonism is of interest in SSc because MOR antagonists have been studied in primary biliary cirrhosis (PBC), another disease that can occur in SSc patients and is characterised by pruritus. (86-88). The therapeutic effects of MOR antagonists, naloxone, naltrexone, and nalmefene have been studied in PBC and cholestatic pruritus (89-93). In general, agreement exists that MOR is effective. Unlike antihistamines, which act on a single component of mast cells degranulation and are targeted at a peripheral level, MOR antagonists may influence additional neuropeptide perception both at the dorsal horn and more centrally. Double blind, placebo controlled trials are needed to determine optimal dosing of MOR antagonists in SSc, as low dose naltrexone has virtually no reported adverse effects.

Naltrexone is a MOR antagonist primarily used in management of alcohol and opioid dependence. It has also been used off-label to treat cancer and autoimmune disease (94). Low dose naltrexone (LDN), 4.5 mg or less taken at night may inhibit cell proliferation, reduces inducible nitric oxide synthase activity, decrease apoptosis of oligodendrocytes, and inhibits activation of mast cells (95, 96). Through these mechanisms it is hypothesised that LDN may modulate neuropathic and/or neurogenic itch (54, 97). Pilot trials of LDN for pruritus, pain, and quality of life (QOL) in gastrointestinal tract diseases have also been successful (98, 99). However, the site of action, minimal effective dosing, and preferable route of LDN administration are yet to be confirmed (100, 101).

– κ-opioid agonists

Nalfurafine hydrochloride is a selective kappa-opioid receptor agonist and has a potent antipruritic effect on uremic pruritus through central kappa-opioid receptor activation in non-clinical pharmacological studies (102). Nalfurafine (a potent κ-receptor agonist) reduced itch in a meta-analysis of two randomised, double blind, placebo- controlled studies of uremic pruritus (103, 104). While statistical significance was shown, clinical efficacy on pruritus was only modest (103). More research in SSc and PBC is needed to evaluate dosing and the long-term safety and efficacy of nalfurafine, as well as to define its role on mast cells (105). As κ-receptor agonists have been shown to produce peripheral antinociceptive effects in inflamed subcutaneous tissues (106), these agents may be particularly appropriate for SSc whose itch is associated with erythematous or warm skin.

– Mixed κ-opioid agonistic and μ-antagonistic

Butorphanol is a drug that exhibits both κ-agonistic and μ-antagonistic properties, thus combining the beneficial ef-

fects of the previous mentioned drug classes. A study of CRGP and vasodilation has suggested a potential effect on the neuro-vascular axis (107). Butorphanol appeared to be effective in 5 patients with intractable itch associated with various systemic or inflammatory skin diseases (108). This study had limitations including a small sample size and open-label design; consequently, further larger-scale, randomised, controlled trials are needed. Importantly, its effect is primarily through the central nervous system, thus it has the potential untoward side effects of respiratory depression and stimulation of the emetic center, which are not ideal for SSc patients. Thus, like MOR antagonist, optimal dosing clarification is critical. It has low oral and nasal bioavailability due to extensive first-pass metabolism, however intramuscular and intravenous dosing is not practical for outpatient management of pruritus. Topical formulations have been studied in rats, and may hold promise for humans (109). Nonetheless, due to its potential modulation of both central and peripheral itch perception, influence on mast cells, and purported effects on both pruritus and gastrointestinal symptoms, it is of interest in treatment of pruritus in SSc.

Treatment of pruritus in SSc

To our knowledge there has been only one publication reporting the results of treatment of pruritus in SSc exists. In our case series, three SSc patients that had failed anti-histamines, had a significant improvement with LDN in pruritus as measured by the 10-point faces (110). This small case series suggests LDN may potentially be an effective, highly tolerable, and inexpensive treatment for pruritus in SSc. In the one patient in this small case series who was re-biopsied after 6 months of therapy, the decrease in perivascular mast cells was the most significant feature found by microscopic evaluation. Thus, while the etiology of pruritus in SSc is unclear, the role of opioid influence on mast cells is intriguing. Furthermore, this pilot study suggested its effects on GIT symptoms might warrant further investigation.

Conclusion

Pruritus is a common but under-recognised symptom in SSc. It has an important influence on quality of life. The close physical relationship of mast cells to both vessels and nerves that is reported in SSc may play a role in disease pathogenesis and pruritus (57, 111, 112). In other systemic diseases characterised by neurogenic itch, such as post-burn, cholestatic liver disease and uremia, anti-histamines are usually ineffective, possibly due to other mediators besides histamine which are released from mast cells and modulate perception of itch.

In these anti-histamine refractory diseases, neuropeptides may be important and a neuropathic/neurogenic approach is often necessary for pruritus relief. While gabapentin, μ-opioid antagonists, κ-opioid agonists, mixed κ-opioid agonistic and μ-antagonistic, and phototherapy are under investigation in many of these conditions, the use of these agents in SSc is an attractive concept. Nonetheless the use of these agents for treatment of itch in SSc is unaccompanied by clear dosing guidelines, particularly with regards to LDN. Additionally, central nervous system effects of opioid antagonists must be taken seriously particularly as they relate to the respiratory and gastrointestinal tract (113). These potential side effects are particularly important as the main goal for pruritus management is improving patient quality of life. Clinical trial design for pruritus in SSc should focus on quality of life outcomes and should include mechanistic studies to better clarify the pathogenesis of SSc related pruritus as it relates to the vasculopathy and fibrosis and the complex interplay of pruritogens, their receptors, and neural pathways.

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