Dermatol Ther (Heidelb) (2019) 9:613–622
https://doi.org/10.1007/s13555-019-00321-6

REVIEW

The Neuromodulatory Effect of Antipruritic Treatment of Chronic Prurigo

Claudia Zeidler · Manuel Pereira · Sonja Ständer

Received: July 12, 2019 / Published online: September 11, 2019

ABSTRACT

Chronic prurigo is an extremely severe pruritic skin disease which presents with multiple, hyperkeratotic and erosive papules, nodules and/or plaques. Patients with this high-burden disease require effective therapies, but effective treatments with regulatory agency approval are currently lacking. Deeper understanding of the pathophysiology suggests that hypersensitive nerves play an important role in the development of chronic prurigo. Accordingly, a treatment with neuroactive substances which modulate hypersensitivity seems promising. Here, we review antipruritic therapies with a neuromodulative effect. Current treatment options, such as topical capsaicin or opioid-receptor modulators, and also novel and future treatment regimens, such as, for example, interleukin-31 antibodies and neurokinin-1 receptor antagonists, are discussed.

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C. Zeidler (✉) · M. Pereira · S. Ständer
Department of Dermatology and Center for Chronic Pruritus, University Hospital of Münster, Münster, Germany
e-mail: Claudia.Zeidler@ukmuenster.de

Keywords: Chronic prurigo; Nerves; Prurigo nodularis; Treatment; Therapy

INTRODUCTION

Chronic prurigo (CPG) presents clinically with multiple, typically symmetrically distributed, hyperkeratotic and erosive papules, nodules and/or plaques due to prolonged scratching and is an exceptionally severe chronic pruritic disease [1]. It significantly affects the quality of life of those affected and is often refractory to therapy [2]. Understanding the pathophysiology underlying CPG, especially the neuromodulatory mechanisms, is essential for the development of novel and more efficacious therapies than are currently available.

Itch is mediated by histamine-dependent, mechano-insensitive C-fibers (CMi-fibers) and histamine-independent, mechano- and heat-sensitive C-fibers (CMH-fibers) as well as by thinly myelinated Aδ-fibers [3]. Peripheral sensitization of the CMH-fiber population, but not of CMi-fibers, has been demonstrated in patients with CPG compared to controls, arguing for the relevance of non-histaminergic pathways in CPG. Morphological neuronal changes have been recorded in CPG lesions, with neuronal hypertrophy in the dermis [4] and a rarefication of peripheral nerves in the epidermis [5]. Despite these morphological changes, however, no functional impairment of

peripheral nerves could be shown in these patients [6]. Crosstalk between keratinocytes, immunological and inflammatory cells and nerve fibers plays a pivotal role in CPG. In particular, neuropeptide substance P (SP) and calcitonin gene-related peptides (CGRP) released by sensory nerves are important for the growth and differentiation of keratinocytes [7] as well as for neurogenic inflammation caused by vasodilatation, attraction of inflammatory cells and release of neurotrophic factors such as nerve growth factor (NGF) [8]. In turn, neurogenic inflammation leads to an increased neuropeptide release from afferent C-fibers and—over the long term—to increased sensitivity and spontaneous activity of nerve fibers and, ultimately, to chronic pruritus [9].

In addition to peripheral factors, central mechanisms, especially disinhibition expressed as impairment of central pain inhibitory mechanisms, may also contribute to the perpetuation and augmentation of itch in CPG.

In this review we discuss the drugs used for the antipruritic treatment of CPG that target its neuromodulatory mechanisms based on a systematic literature search of the PubMed database. The search items included combinations of the following terms: "pruritus," "itch," "chronic prurigo," "prurigo nodularis," "neuromodulation," "hypersensitivity," "nerves," "therapy" and "treatment."

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

CURRENT TREATMENT OPTIONS WITH ANTIPRURICEPTIVE EFFECTS

Topical Capsaicin

Unmyelinated C-fibers and keratinocytes express pruriceptors, which are peripheral sensory neurons that play an important role in the transduction of itch signals. The signals of these pruriceptors downstream activate the transient receptor potential vanilloid-1 (TRPV1) and 3 (TRPV3) ion channels, which modulate itch, heat and pain [10]. TRPV1 is a non-selective cation channel that can be activated by an increase of temperature to > 42 °C, protons, UV radiation and capsaicin. Once activated, structural changes in TRPV1 allow the influx of calcium, leading to the generation of action potentials and to the release of neuropeptides, such as SP and CGRP, into the surrounding tissue [11]. With continuous stimulation of the TRPV1, the receptor is ultimately desensitized and the transmission of nociceptive stimuli is inhibited [12].

Topical application of capsaicin acts by depleting neurotransmitters such as SP [12], and it is assumed to work by destroying sensory nerve endings in the epidermis [13]. Topical capsaicin has shown efficacy in the treatment of both localized neuropathic pain or pruritus [14, 15] and chronic nodular prurigo (CNPG). In a case series involving 33 patients, the application of topical capsaicin at a concentration of 0.025–0.1% four to six times daily led to the relief of itch within 12 days in all patients [16]. In another study, after treatment with topical capsaicin, the increased expression of TRPV1 in the epidermal keratinocytes and nerve fibers in pruritic skin of patients with CNPG was normalized and a reduction in the levels of neuropeptides (SP, CGRP) was observed [17]. However, the exact mechanism by which topical capsaicin achieves this effect remains unclear. In addition, due to the temporary effect of capsaicin and the intense side effect of burning, it is only recommended for localized forms of itch and CNPG [18]. At the present time, commercial topical capsaicin creams are available, while TRPV1 antagonist use for the treatment CPG remains to be explored.

Transient Receptor Potential Melastatin-8 Modulation by Menthol and its Derivates

Activation of the cold-sensitive transient receptor potential melastatin-8 (TRPM8) ion channel can alleviate pruritus. Itching relief is most likely due to the activation of cutaneous Aδ fibers and spinal B5-I inhibitory interneurons, which produce a stable antipruritic effect without tachyphylaxis [19]. Since the use of topical menthol-containing creams usually

reduces the itching only briefly and lowers the intensity of the itch for only a few minutes [20], an oil-in-water solution was developed which contains two TRPM8 agonists, CHC [(1R, 2S, 5R)-*N*-(2 pyridinyl) ethyl-2-isopropyl-5-methyl-cyclohexane carboxamide] and menthoxypropanediol (MPD), with strong and long-lasting cooling effects [21]. The antipruritic efficacy of this solution in treating in chronic pruritus was demonstrated in an randomized controlled trial (RCT) [19]. In contrast to vehicle, the point difference on the numerical rating scale for the two-components group was 1.0 higher: CHC and MPD Δ2.4; placebo Δ1.4 [19].

Topical Calcineurin Inhibitors

Approved for the treatment of atopic dermatitis, topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, have shown good effectiveness in the treatment of various pruritic dermatoses, including CNPG [22–24]. These substances are anti-inflammatory agents that predominantly act by inducing calcineurin inhibition that interrupts cytokine gene expression and the downregulation of T-cell activity. They also directly influence nerve fiber function by binding to and activating TRPV1 on small, unmyelinated sensory nerve fibers [25, 26]. This mode of action may explain the observed calcineurin inhibitor-related side effects, such as initial burning and pruritus, as well as the subsequent rapid reduction of pruritus. The effect of calcineurin inhibitors on the sensory nerves of the skin was tested in a murine model of contact hypersensitivity to picryl chloride [27]. Following the application of topical tacrolimus there was not only a decrease in inflammatory cells but also a decrease in the expression of SP and CGRP [27]. In another study which used a contact hypersensitivity model to dinitrofluorobenzene, the authors demonstrated that topical tacrolimus significantly inhibited scratching, sensory nerve elongation, NGF mRNA expression and preprotachykinin mRNA expression [28]. The improvement in scratching behavior with the use of topical tacrolimus has been attributed to its inhibitory effect on sensory nerve activation (Table 1). Immunohistological studies of skin biopsies from patients with atopic dermatitis before and after treatment with topical tacrolimus revealed a significant decrease in the expression levels of SP, NGF and neurotrophin-

Table 1 Overview of the drugs discussed in the text and their neuromodulatory mechanisms

Drug	Neuromodulatory mechanisms
Capsaicin[a]	Activation of TRPV1 and TRPV3 ion channels
Menthol[a] and its derivates[a]	Activation of TRPM8 ion channel
Calcineurin inhibitors[a]	Activation of TRPV1
Anesthetics[a]	Stopping the transmission along the sensory nerve fiber
Gabapentinoids	Binding to the α2-δ subunit of calcium channels of nociceptive neurons in both the peripheral and central nervous systems
Cyclosporine	Inhibition of IL-31 and NK1R gene expression and IL-31 and TSLP
Dupilumab	Anti-IL-4 and IL-13 monoclonal antibody
Janus kinase inhibitors	Inhibition of TRPV1 receptors
Naloxone or orally administered naltrexone	Mu-opioid receptor antagonists
Serlopitant	Neurokinin 1 receptor antagonists
Nemolizumab	Interleukin-31 receptor antagonist

IL Interleukin, *NKR1* neurokinin 1 receptor, *TRPM8* transient receptor potential melastatin-8, *TRPV1*, *TRPV3* transient receptor potential vanilloid-1 and -3, respectively, ion channels, *TSLP* thymic stromal lymphopoietin

[a] Topical treatment

3, which is caused by inhibitory calcium influx during TRPV1 phosphorylation [29]. These observations suggest that tacrolimus as a calcineurin inhibitor has direct effects on cutaneous nerve endings [30]. Topical tacrolimus also acts on the regulation of interleukin (IL)-31.

In summary, the antipruritic effect of topical calcineurin inhibitors can not solely be explained by sensory nerve desensitization; a decrease in IL-31 levels also plays a role [31]. The antipruritic effect of pimecrolimus was confirmed in a RCT involving 30 patients with CNPG; after 10 days of treatment, not only was there a significant decrease in pruritus intensity, but there was also a significant reduction in scratch lesions and a significant improvement in quality of life [23].

Topical Anesthetics

Topical anesthetics are commonly used to control pain during superficial surgery. However, they have also proven to be successful in the treatment of chronic pruritus, especially neuropathic pruritus [32]. Many topical anesthetics are believed to work by interfering with the transmission of the itching impulse along the sensory nerve fiber [33]. A number of RCTs, prospective and retrospective studies and case series have shown that several topical anesthetics, such as lidocaine, prilocaine and an amitriptyline hydrochloride/ketamine mixture, are potentially effective in the treatment of a variety of chronic pruritus disorders, including pruritus ani [34], uremic pruritus [35] and neuropathic pruritus (e.g. brachioradial pruritus [36] and itch related to postzoster neuralgia [37]).

Systemic Gabapentinoids

Chronic pruritus can also be treated with gabapentinoids, which have a structure analogous to that of the neurotransmitter γ-aminobutyric acid (GABA), which affect CNPG via neuromodulation of the central nervous system (CNS). The gabapentoinoids gabapentin and pregabalin bind to the α2-δ subunit of the calcium channels of nociceptive neurons in both the peripheral and central nervous systems. The resulting inhibition of glutamate synthesis and calcium influx into neurons leads first the inhibition of depolarization and then to a reduced release of neurotransmitters, such as glutamate, CGRP and SP [38, 39]. Gabapentin not only suppresses the release of SP, but it also inhibits SP-induced activation of the transcription factor NF-κB which is an essential pathway for the cytokine synthesis [38]. RCTs have shown that gabapentinoids can successfully treat not only neuropathic pain but also chronic pruritus of different origin [40]. The successful use of gabapentinoids in CNPG has thus far only been reported in case series [41, 42]. However, it is recommended as a treatment option [43]. Because of the common side effects of gabapentinoids, such as fatigue, drowsiness, dizziness, blurred vision, peripheral edema, weight gain and sexual dysfunction, a topical formula for the treatment of neuropathic pain is currently under development [44]. If this topical preparation is successful, it may also attract interest for the treatment of CNPG.

Immunosuppressive agents

Cyclosporine as an immunosuppressive treatment has not only anti-inflammatory but also neuromodulatory effects [45]. Since inflammatory cells, such as CD4+ T cells, mast cells and eosinophils, interact directly with nerve fibers and eosinophils additionally release itch mediators (e.g. NGF, cytokines and proteases [46]), cyclosporine can reduce the intensity of pruritus [45]. In one study, cyclosporine was able to inhibit increased levels of IL-31 receptor antagonists (IL-31RA) and neurokinin-1 receptor (NK1R) expression in a dose-dependent manner, especially at a dose of 5 mg/kg body weight [47]. Data suggest that cyclosporin reduces the intensity of itch via inhibition of IL-31RA and NK1R gene expression and via IL-31 and thymic stromal lymphopoietin [48, 49]. The success of cyclosporine in the treatment of CNPG has been documented in several case series [50].

Interleukin-4 Receptor Antagonist

The monoclonal antibodies dupilumab, anti-IL-4 and IL-13 have been recently developed for the treatment of atopic dermatitis. Treatment with these agents have led to a substantial reduction in pruritus scores [51]. IL-4 plays an important role in the signaling pathway of chronic pruritus via sensitization of neuronal IL-4Rα sensory neurons [52]. Case series have shown a significant pruritus reduction in patients with CNPG following treatment with monoclonal antibodies [53, 54]. In one of these case series [53], within 12 weeks of treatment with dupilumab the prurigo lesions flattened, pruritus intensity as measured by the numerical rating scale decreased drastically and the quality of life of the patient improved.

Janus Kinase Inhibitors

Janus kinase inhibitors have an antipruritic effect by reducing signal transduction after pruritogenic binding and by inhibiting the action of TRPV1 receptors [55]. In one study involving patients with atopic dermatitis, a topical formulation of tofacitinib applied twice daily improved both disease activity and itching within 1 day of treatment initiation [56]. Tofacitinib is also available as an oral drug, and its use has been reported to have led to a marked and rapid improvement in pruritus in patients with psoriasis [57]. Other Janus kinase inhibitors are currently being tested for the efficacy of atopic itch (ClinicalTrials.gov Identifier: NCT03575871), but not yet in patients with CNPG.

Opioid Receptor Modulation

Agents acting on opioid receptors are of interest for the treatment of chronic pruritus in general and CNPG in particular. Mu-opioid receptor (MOR) antagonists, namely intravenous naloxone or orally administered naltrexone, have shown antipruritic effects for various indications, including CNPG [58, 59]. However, robust RCTs are still lacking. The antipruritic mechanism of action of these drugs is not fully understood. Opioid receptors are ubiquitously distributed throughout the peripheral and central nervous system. Opioid receptors modulate neuronal activation via the suppression of voltage-dependent calcium channels and activation of potassium channels [60]. They likely act at both the peripheral and central nervous system levels, although it is believed that a major factor in their mechanism of action is the activation of interneurons at the spinal level, which induces a suppression of nerve fiber activity. Clinically, in addition to MOR antagonists, kappa-opioid receptor (KOR) agonists have also been used in the treatment of chronic pruritus. For example, treatment with nalfurafine, a KOR agonist, led to a significant decrease in itch in patients with end-stage kidney disease undergoing hemodialysis [61] as well as in patients with cholestatic pruritus [62]. Trials enrolling CNPG patients treated with pure KOR agonists are still lacking. However, nalbuphine, an opioid receptor modulator with dual function (MOR antagonist and KOR agonist), has been tested in patients with CNPG. A phase II clinical trial showed positive results, with nalbuphine reducing itch as well as other efficacy endpoints compared to placebo (ClinicalTrials.gov Identifier: NCT02174419). An additional study with a duration of 14 weeks and a 1-year open label extension to assess long-term effects of nalbuphine in the treatment of itch arising from CNPG is currently ongoing (ClinicalTrials.gov Identifier: NCT03497975).

NOVEL AND FUTURE TREATMENT OPTIONS

Based on our current understanding of the pathomechanism of CNPG, increased levels of IL-31 and receptors for SP play a very important role in the pathogenesis of the disease. Directly blocking IL-31 or SP could therefore represent a new area for research on the treatment of CNPG. A potential additional target could be the tropomyosin receptor kinase A receptor, which is activated by the neurotrophic NGF secreted by mast cells and eosinophils [46] and triggers pruritus via phosphorylating TRPV1 receptors. Another target may be the

cannabinoid receptor. An antipruritic effect was observed in a mouse model by antagonizing spinal cannabinoid receptors [63].

The NK1R Antagonists

The NK1R belongs to the family of G-protein-coupled receptors and is expressed in a variety of tissue types, including keratinocytes, mast cells, neuronal cells, fibroblasts, endothelial cells and epidermal dendritic cells [64]. NK1R is a main receptor for tachykinins. Among the tachykinin peptides, SP is the most prominent ligand, being involved in an extensive array of biological processes, including neurogenic inflammation [65]. Upon activation of peripheral nerve fibers, such as following exposure to a pruritic stimulus, several mediators, including SP, are released, promoting vasodilation, mast cell degranulation and neurogenic inflammation [66]. SP facilitates the release of a plethora of pro-inflammatory substances (e.g. histamine, interleukins, prostaglandins) by the mast cells and keratinocytes [66, 67] and notably promotes the release of NGF, which is involved in neuroplasticity and may be a contributing factor to the dermal neuronal hyperplasia observed in CNPG lesions [68]. NK1R is also present in the CNS, being expressed in neurons of the superficial lamina 1 of the dorsal horns [69] and thus contributing to the central processing of itch.

NK1R antagonists are thus promising agents for the treatment of chronic itch in general and of CNPG in particular [70]. Serlopitant, an orally administered NK1R antagonist, induced a higher reduction of pruritus compared to placebo in an 8-week Phase II clinical trial (ClinicalTrials.gov Identifier: NCT02196324). Phase III RCTs with serlopitant targeting patients with CNPG are currently underway in Europe and the USA (ClinicalTrials.gov Identifier: NCT03677401, NCT03546816). A topical formulation of aprepitant, another NK1R antagonist, has also been tested in CNPG patients in a split-sided, cross-over design, but it showed no higher antipruritic effect compared to placebo [71]. In another trial, oral aprepitant given to patients daily for 4 weeks did not show antipruritic efficacy compared to placebo [72].

IL-31 Receptor Antagonist

Interleukin-31 is overexpressed in inflammatory pruritic skin diseases, which is especially prominent in CNPG lesions [73]. A link between IL-31 expression and itch has been established based on the absence of IL-31 upregulation under nonpruritic inflammatory cutaneous conditions, such as nonpruritic psoriatic lesions [73]. IL-31, which is released by inflammatory cells in general and by Th2 cells in particular, binds to a receptor composed of an IL-31 A subunit (IL-31 RA) and an oncostatin M subunit. Interestingly, dorsal root ganglion neurons co-express IL-31RA and TRPV1 [48], suggesting neurogenic modulation by IL-31. Thus, the targeting of this receptor seems to be a promising antipruritic treatment strategy in CNPG. Nemolizumab, an IL-31 receptor A monoclonal antibody, has shown promising antipruritic effects in atopic dermatitis through a dose-dependent reduction of itch in atopic patients [74, 75]. These positive findings were confirmed in a subsequent long-term extension study, in which a good safety profile was reported [76]. Regarding CNPG, results from an ongoing clinical trial are pending (ClinicalTrials.gov Identifier: NCT03181503).

ACKNOWLEDGEMENTS

Funding. Funding Source: For 2690, DFG (Deutsche Forschungsgemeinschaft; grant number: STA1159/4-1). No funding was received for the journal's Rapid Service Fee.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Claudia Zeidler, Manuel Pereira and Sonja Ständer have nothing to disclose.

Sonja Ständer is a member of the Editorial Board of *Dematology and Therapy*.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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