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Kappa opioid agonists in the treatment of itch: just scratching the surface?

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Abstract

Chronic pruritus is a debilitating condition affecting 23–44 million Americans. Recently, kappa opioid agonists (KOAs) have emerged as a novel class of potent antipruritic agents. In 2021, the Food and Drug Administration approved difelikefalin (Korsuva) for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adults undergoing hemodialysis. Difelikefalin is a potent, peripherally restricted KOA that is intravenously available. Although promising, difelikefalin is currently available as an intravenous composition only, limiting the scope of use. Oral formulations of difelikefalin did not meet the primary endpoint criteria in recent phase 2 clinical trials; however, additional clinical studies are ongoing. The future for KOAs in the treatment of pruritus is encouraging. Orally active pathway-biased KOAs, such as triazole 1.1, may serve as viable alternatives with broader applications. Extended-release compositions, such as the TP-2021 ProNeura subdermal implant, may circumvent the pharmacokinetic issues associated with peptide-based KOAs. Lastly, dual-acting kappa opioid receptor agonist/mu opioid receptor antagonists are orally bioavailable and may be useful in the treatment of various forms of chronic itch. In this review, we summarize the results of KOAs in clinical and preclinical trials and discuss future directions of drug development.

Keywords

Itch; Pruritus; Kappa; Opioid; Agonist; Difelikefalin; TP-2021; Triazole 1.1

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Introduction

Chronic pruritus is a debilitating condition defined as itching lasting longer than 6 weeks[1]. An estimated 23–44 million Americans suffer from chronic pruritus in the setting of both cutaneous and systemic conditions[2,3]. Itch can be stratified into 4 major clinical categories: neurogenic, neuropathic, psychogenic, and pruritoceptive[4]. Neurogenic itch is generated by the central nervous system (CNS) in response to itch-promoting substances, or pruritogens, without evidence of neural disease. Neuropathic itch results from pathology of the central and peripheral nervous system along the afferent pathway. In psychogenic pruritus, psychological factors, such as anxiety, depression, obsessive-compulsive disorder, mania, delusional disorders, such as parasitophobia, and substance abuse play a role in eliciting symptoms. Pruritoceptive itch involves pruritogenic signals generated within the skin, commonly relating to inflammation and immune-system-driven cutaneous pathologies.

The sensation of itch can be transmitted by 2 main pathways: histamine-dependent and histamine-independent pathways[4]. Acute itch is commonly histamine-driven (histaminergic), whereas chronic itch is predominantly mediated by nonhistamine pruritogens (nonhistaminergic)[4,5]. The histamine-dependent pathway involves the activation of histamine-sensitive unmyelinated C-fibers[4,5]. Histamine is a chemical substance that is released by certain immune cells in response to an allergic reaction or an inflammatory process. When histamine binds to its receptors on the C-fibers, it triggers a series of events that result in the transmission of the itch signal to the spinal cord[5]. The histamine-independent pathway, in contrast, involves alternative pruritogens and similar signals through unmyelinated C-fibers. It is important to note that the 2 pathways can interact and influence each other. For example, histamine can enhance the response of the histamine-independent pathway, making the sensation of itch more intense. In addition, certain drugs that block histamine receptors can also reduce the activity of the histamine-independent pathway, providing relief from itch.

There are several pruritogens that are thought to be involved in chronic itch. Common examples include proteases, serotonin, endothelin-1, substance-P, and nerve growth factor[5]. Proteases are enzymes produced by bacteria, fungi, and other micro-organisms, that can trigger chronic itch by activating specific receptors on nerve fibers in the skin[6]. Serotonin is a neurotransmitter involved in many biological processes, including the regulation of mood, appetite, and sleep[7]. It is also believed to play a role in chronic itch, as high levels of serotonin in the skin have been associated with persistent itch. Endothelin-1 is a peptide that is produced by endothelial cells in blood vessels. It is known to cause itching by binding to endothelin receptors on nerve fibers in the skin[8]. Substance-P is a neuropeptide that is involved in pain and inflammation and is also believed to play a role in chronic itch by activating nerve fibers in the skin. Nerve growth factor is a protein that is involved in the growth and survival of nerve cells. It has been shown to be elevated in the skin of patients with chronic itch and is believed to contribute to the development and maintenance of chronic itch by sensitizing nerve fibers in the skin[9]. It is important to note that the specific pruritogens responsible for chronic itch may vary depending on the underlying cause of the itch. For example, in patients with atopic dermatitis (AD), certain cytokines and

chemokines may play a more prominent role in chronic itch. A more comprehensive review of pruritogens responsible for chronic itch is reviewed extensively elsewhere[5].

The most common chronic conditions causing pruritus include chronic kidney disease (CKD), chronic liver disease, AD, xerosis (dry skin), and psoriasis[1,3]. Additional causes of itch include dermatological conditions, such as contact dermatitis, hand eczema, lichen planus, lichen simplex chronicus, prurigo nodularis, urticaria, mastocytosis, dermatitis herpetiformis, and pemphigoid; infections, such as human immune deficiency virus, mites, and parasites; malignancy, including polycythemia vera, leukemia, and lymphoma; medications, such as mu opioid agonists and immune checkpoint inhibitors; neurological conditions, including shingles, disc herniation, and notalgia paresthetica; mast cell activation syndrome, and idiopathic causes[10]. Chronic pruritus is often refractory to conventional treatments, which include antihistamines, corticosteroids, and over-the-counter topicals[1,3,10,11]. Prescription topical medications may be used, such as corticosteroids, calcineurin inhibitors, capsaicin, PDE4 inhibitors, and local anesthetics[11]. Prescription topical medications are often unsuccessful and cause burning, stinging, irritation, and drying of the skin[12–28]. Systemic medications include mirtazapine, cyclosporin, methotrexate, dupilumab, gabapentin, pregabalin, mycophenolate mofetil, and azathioprine. These medications, except for dupilumab, gabapentin, and pregabalin, have the potential for significant side effects and thus should be used conservatively[29–36]. More recently, topical and oral Janus kinase inhibitors, such as abrocitinib (oral), upadacitinib (oral), and ruxolitinib (topical), have been approved to treat moderate to severe AD. These drugs have demonstrated impressive results in treating AD and preventing itch; however, oral compositions are immunosuppressive, putting patients at risk for infection and cancer, and are associated with an increased risk of serious heart-related events, blood clots, and death[37,38]. Although promising, consideration of adverse drug events and patient contraindications must be weighed heavily before prescribing these medications. Lastly, patients are advised on proper skin hydration and elimination of itch-aggravating triggers[11]. This approach is challenging, as triggers are commonly broad, unavoidable, and unknown. Thus, there is a significant need for an efficacious antipruritic drug with a limited side-effect profile. In this review, we provide a brief overview of the mechanisms of kappa opioid agonist (KOA) itch attenuation; summarize the current clinical and preclinical efforts to develop optimized drug candidates, and discuss important future directions pertaining to drug development of KOAs.

Kappa opioid receptor in itch

The kappa opioid receptor (KOR) participates in itch neurotransmission within the peripheral and CNS[4,39–41]. The KOR, a target expressed postsynaptically by spinal interneurons along this pathway, has emerged as an attractive target in the treatment of itch[42–44]. The KOR is a G protein–coupled receptor (GPCR) that in humans is encoded by the *OPRK1* gene. The KOR system, and its endogenous agonist ligands, the dynorphins, have widespread distribution and activity in the central and peripheral nervous system[45–49]. The KOR modulates itch at the level of the spinal cord, blocking upstream pruriceptor signals that most commonly originate from macrophages, keratinocytes, mast cells, and T cells within the skin (Fig. 1A). The KOR and gastrin-releasing peptide receptor (GRPR) are

coexpressed in the spinal cord and activation of the KOR attenuates GRPR-mediated itch signaling through the KOR-PLC-PKCd-GRPR signaling pathway (Fig. 1B, C). The KOR is also expressed on primary afferents and keratinocytes. Activation of these peripheral targets is thought to contribute to the antipruritic effect of KOAs, but the extent of the contribution is still unknown. Cytokines, such as interleukin (IL)-4, IL-13, IL-31, and IL-33, are involved in itch promotion at the neuronal level[5]. KOAs have significant anti-inflammatory effects, leading to cytokine downregulation. KOA-mediated suppression of inflammation is thought to also contribute to the antipruritic effects of these compounds[50].

Kappa opioid receptor agonists

KOAs are efficacious in itch and pain models but suffer from CNS-mediated effects, such as dysphoria, sedation, hallucinations, and psychosis[50,51]. KOR agonist xenobiotics exist as small molecules and peptides. Traditional small molecule derivatives include nalfurafine (TRK-820), salvinorin A, spiradoline (U62,066E), U50,488H, ICI 204,448, BRL 52537, and U69,593[50]. These small molecule candidates exhibit potent nanomolar range activity but cross the blood-brain barrier, leading to untoward CNS-mediated side effects. More specifically, nalfurafine (Remitch) is a centrally active partial agonist at both the kappa and MORs. Although it has a higher affinity for the kappa receptor, it can also activate the mu receptor to some extent. However, its mu-opioid activity is weaker than its kappa opioid activity, and it has been shown to have a lower potential for abuse and dependence compared with other mu-opioid agonists. Nalfurafine is approved in Japan for use in patients with uremic pruritus indicated for hemodialysis; however, nalfurafine failed phase 1 safety trials in the United States due to the induction of CNS-mediated side effects[52,53]. Recent clinical trials exploring alternative doses and compositions of nalfurafine will be discussed below. Efforts to derivatize peripherally restricted small molecule KOAs have been unsuccessful.

Peptides derived from dynorphin have emerged as high-affinity, selective agonists of the KOR. Furthermore, difelikefalin (Korsuva), HSK21542, and TP-2021 (also known as JT09) activate the KOR in the picomolar range, with agonist selectivity for kappa over other peripheral opioid receptors > 10,000-fold[50,51,54,55]. The use of peptidic KOAs is limited due to poor pharmacokinetics. Difelikefalin and HSK21542 are exclusively intravenously available in humans, whereas TP-2021 possesses moderate oral activity in rodents[51]. TP-2021 is currently in investigative new drug–enabling studies and is yet to be studied in humans. Efforts to optimize oral and sustained-release compositions of peptidic KOAs are ongoing and will be discussed in this commentary. Of added value, preclinical and clinical studies have established a reasonable side-effect profile associated with peripherally restricted KOAs[50]. The safety profile of these compounds would allow for broad application in the treatment of itch should new formulations with optimized pharmacokinetic properties emerge.

Clinically studied kappa opioid receptor agonists for pruritus

Three clinical-stage KOAs exist: difelikefalin (Korsuva), nalfurafine, and HSK21542. Of the 3 drug entities mentioned, difelikefalin remains the only KOA with Food and Drug Administration (FDA) approval for the treatment of pruritus. Specifically, in 2021, the FDA-

approved difelikefalin for the treatment of moderate-to-severe pruritus associated with CKD in adults undergoing hemodialysis[56]. The approval was based on the new drug application filing that was supported by positive efficacy and safety data from 2 critical phase 2 trials and 32 clinical studies in total. In a randomized, double-blind, placebo-controlled phase 3 study (NCT03422653), difelikefalin 0.5 μg/kg through an intravenous (IV) bolus thrice weekly after hemodialysis treatments for 12 weeks led to a ≥ 3 point itch reduction on the Worst Itching Intensity Numerical Rating Scale when compared with placebo (49.1% vs 27.9% reduction for difelikefalin and placebo, respectively)[57]. In addition, difelikefalin led to improved scores on health-related quality of life assessments relative to placebo. The most common side effects of difelikefalin at 0.5 μg/kg were dizziness (6.9%–7.9%), nausea (6.6%–11.3%), and diarrhea (9.5%–12.1%)[58,59]. Additional reported adverse events include constipation (3.0%–7.0%), gait disturbance (6.6%–11.5%), hyperkalemia (4.7%–8.4%), headache (4.5%–6.0%), somnolence (2.0%–6.0%), mental status change (3.3%–4.4%), nasal congestion (3.0%–8.0%), insomnia (1.0%–4.0%), increased urine output (5.0%), and hypotension (1.0%–4.0%). Reported adverse events during clinical trials were mild and short-lived. Difelikefalin is a peptide and likely participates in many nonspecific interactions with alternative targets. Off-target interactions may contribute to the side-effect profile of difelikefalin. In addition, patients receiving difelikefalin were mostly elderly patients with poor renal function. Of importance, difelikefalin is predominantly renally eliminated. As such, patients with CKD-related pruritus may be at higher risk for adverse events. In addition, blood barrier barrier disruption associated with uremia and advanced age may have contributed to the development of adverse events.

The small molecule nalfurafine was assessed in a phase 3 randomized, double-blind, placebo-controlled study conducted at 73 centers throughout Japan (NCT01513161)[60]. The study examined 407 patients undergoing hemodialysis with severe uremic pruritus. Patients were treated with either 2.5 or 5 μg of oral nalfurafine for 14 days. Nalfurafine promoted a statistically significant reduction in itch scores, with common side effects, including nasopharyngitis, insomnia, somnolence, and constipation. Despite demonstrating impressive antipruritic activity, nalfurafine has not received FDA approval over concerns for CNS-mediated side effects. Phase 3 clinical trials to assess the efficacy, safety, and plasma concentration of nalfurafine for the treatment of refractor pruritus are ongoing in the United States at 5 μg taken once daily with dinner[61]. Prior clinical trials assessing nalfurafine at 5 μg doses demonstrated a modest antipruritic effect with an unfavorable side-effect profile due to a lack of peripheral selectivity.

The tetrapeptide HSK21542 is a selective KOA with higher potency and peripheral selectivity than CR845[62]. There are 2 ongoing clinical trials studying HSK21542 in the United States. A multicenter, randomized, double-blind, placebo-controlled phase 2 study involving 90 liver disease subjects with moderate or above pruritus is ongoing (NCT04999787). Patients are randomized to 2 dose groups (0.3 μg/kg, IV and 0.6 μg/kg, IV) and a placebo control group at a 1:1:1 ratio, including 30 subjects per group. In addition, a multicenter, randomized, double-blind, placebo-controlled study involving 310 maintenance hemodialysis patients with moderate or above CKD-associated pruritus was enrolled (NCT05135390). Patients were randomized into either the treatment group

(HSK21542, 0.3 μg/kg, IV) or the control group (placebo) at a 1:1 ratio. Clinical trials are ongoing.

Future directions

Oral formulations of difelikefalin (Korsuva)

In 2019, Cara Therapeutics entered a definitive licensing agreement with Enteris BioPharma to develop an oral formulation of difelikefalin using the Peptilligence technology[63]. Oral difelikefalin has been studied in 3 separate phase 2 clinical trials in patients with AD (KARE), hepatic impairment due to primary biliary cholangitis, and stage III–V CKD. In the KARE trial (NCT04018027), 401 patients with moderate-to-severe pruritus associated with AD were randomized to difelikefalin [0.25 mg, 0.5 mg, 1.0 mg, twice daily (BID)] or matching placebo for 12 weeks, followed by a 4-week active extension phase. The primary endpoint of the study was a statistically significant change from baseline in the weekly mean of the daily 24-hour itch Numerical Rating Scale score at week 12 of the treatment period[64]. While oral difelikefalin demonstrated statistically significant itch reduction in earlier time points, such as week 1, no dose group met the primary endpoint at 12 weeks. In a prespecified analysis, a statistically significant change in the primary efficacy endpoint was observed in patients with mild-to-moderate AD at week 1 that was sustained through the treatment period. Oral difelikefalin reduced the presence of itch and inflammatory biomarkers. Further studies on dosing and timing of drug administration are warranted. Phase 2 clinical trials in patients with CKD and primary biliary cholangitis are ongoing. Of note, difelikefalin is a tetrapeptide with unstable pharmacokinetics. Single daily oral doses of difelikefalin were up to 12 times the dosage given to patients intravenously in previous phase 2 and 3 clinical studies[56,65]. The initial high dose was administered due to the rapid plasma clearance of the peptide after oral absorption. Similar to the trials involving IV difelikefalin administration, dose-dependent increases in adverse side effects were noted. These side effects include dizziness, somnolence, mental status changes, paresthesia, fatigue, hypertension, and vomiting. In a more recent study, patients with notalgia paresthetica who received difelikefalin orally experienced slightly more significant reductions in itch intensity scores over an 8-week period than those who received a placebo[66]. However, adverse events were associated with this treatment. Further studies, both larger and longer in duration, are required to evaluate the effectiveness and safety of difelikefalin therapy for this condition. The development of an extended-release (ER) oral formulation of difelikefalin would expand the potential use of KOAs in the outpatient management of chronic pruritus. Controlled drug release would help reduce peak and trough plasma concentrations, potentially reducing the risk of adverse drug events.

Orally active pathway–biased kappa opioid agonists

Pathway-biased KOR agonists represent an exciting avenue of development of orally active small molecules with limited CNS-mediated side effects. The KOR signals through 2 independent signaling pathways: the GPCR and β-arrestin pathways[67]. Activation of the GPCR pathway attenuates pain and itch signals, whereas CNS activation of β-arrestin promotes untoward adverse effects. The small molecule triazole 1.1 is a pathway-biased KOA with low nanomolar activity for the GPCR pathway and negligible activity for the

β-arrestin pathway. Triazole 1.1 is as efficacious in attenuating itch and pain as conventional KOAs but is devoid of negative CNS-mediated side effects. Specifically, triazole 1.1 did not induce sedation or reductions in dopamine release in mice, nor did it produce dysphoria as determined by intracranial self-stimulation in rats[68]. Further study of triazole 1.1 has revealed limited CNS permeability of the small molecule, suggesting the activity of the compound is primarily peripherally mediated[67]. Given most KOR neurons responsible for the inhibition of itch and pain signals are present in the medulla of the brain, a CNS-permeable pathway–biased KOA may possess improved activity in the treatment of neurogenic, neuropathic, and psychogenic itch. As such, optimization of the physiochemical properties of triazole 1.1 in the development of CNS-permeable KOA may be of significant value.

TP-2021 subdermal kappa opioid agonist implant

The peripherally-selective tetrapeptide TP-2021 (formerly known as compound 9 or JT09) is a highly potent and selective KOR agonist. In vitro studies assessing drug binding kinetics demonstrated a KOR EC_{50} of 52.2 picomolar; roughly twice as potent as dynorphin, the endogenous KOR ligand[69]. Unlike difelikefalin and derivatives, TP-2021 does not interact with the mu or delta-opioid receptors. TP-2021 is devoid of CNS-mediated side effects, including sedation, dysphoria, and abuse liability[50,51,54,55]. TP-2021 is currently under development by Titan Pharmaceuticals, Inc. Titan Pharmaceuticals has incorporated TP-2021 into their FDA-approved subdermal implant, ProNeura. The ProNeura delivery system is a semirigid ethylene vinyl acetate implant that supports continuous drug release and nonfluctuating medication levels over a period of 6 months or longer, depending on drug characteristics[70]. Preliminary studies demonstrated potent antipruritic activity in a mouse model of acute itch. TP-2021 was as efficacious as difelikefalin in promoting itch attenuation. Results from a murine model of chronic pruritus demonstrated a significant reduction in scratching behavior in animals who received TP-2021 implants at both day 28 and day 56 postimplantation in comparison to placebo implants. No safety issues or evidence of tolerance were observed. Release pharmacokinetic studies demonstrated supra-therapeutic plasma levels of TP-2021 through day 84. Efficacy assessment at later time points, as well as investigative new drug–enabling studies, are required.

Dual kappa opioid agonist/Mu opioid antagonists

Dual-acting KOR agonist/mu opioid receptor (MOR) antagonists, such as nalbuphine, have been used in pain management since the 1980s[71]. Nalbuphine is FDA-approved for use in the treatment of refractory moderate to severe pain and is used off-label for pruritus associated with neuraxial opioid use[72]. Currently, an oral ER formulation of nalbuphine is being studied in clinical trials for the treatment of itch in patients with uremic pruritus and prurigo nodularis[57]. The efficacy of nalbuphine in hemodialysis patients with uremic pruritus was assessed in a double-blind, placebo-controlled phase 2/3 study (NCT02143648). Patients were assigned to nalbuphine ER 60 mg, nalbuphine ER 120 mg, or placebo twice daily for 8 weeks. Results indicated a statistically significant reduction in itch severity scores in those treated with nalbuphine ER 120 mg relative to placebo controls. Similarly, the antipruritic efficacy of nalbuphine in patients with prurigo nodularis was assessed in a double-blind, placebo-controlled phase 2 clinical study (NCT02174419).

Patients were assigned to nalbuphine ER 81 mg, nalbuphine ER 162 mg, or placebo twice daily for 8 weeks. In this trial, nalbuphine failed to meet the primary endpoint of itch reduction, despite a statistically higher proportion of patients receiving nalbuphine ER 162 mg having achieved reductions in the 7-day average itch intensity relative to placebo control. Patients on nalbuphine ER 162 mg demonstrated a reduction in excoriations and had evidence of improved healing of their skin lesions. Most reported side effects were nausea, dizziness, diarrhea, and somnolence. Of note, although nalbuphine is no longer a controlled substance, preclinical and clinical studies have demonstrated evidence of abuse potential[73]. The abuse liability of nalbuphine is thought to be due to CNS-mediated partial agonist activity of the MOR at high doses. As such, dosing of nalbuphine should be considered with caution in the context of chronic pruritus. Clinical studies involving pediatric opioid-induced pruritus are ongoing.

Future kappa opioid agonist drug discovery

Although efficacious, the development of KOAs has been limited by their side effects, such as dysphoria, sedation, and hallucinations. Therefore, future directions of KOA drug discovery are focused on identifying compounds that have reduced side effects with retained therapeutic efficacy. One approach is to develop biased KOAs that selectively activate certain downstream signaling pathways, such as the G protein pathway. This can potentially improve the therapeutic efficacy of KOAs while reducing their side effects. Another approach is to develop KOR agonists that are more selective for certain subtypes of KOR, such as KOR1 or KOR2[74]. This can potentially improve the therapeutic efficacy of KOR agonists while reducing their side effects. Finally, there is a need to develop better animal models for studying the effects of KOR agonists, as many of the existing animal models do not fully recapitulate the effects of KOR agonists in humans. Improving animal models will help to better understand the pharmacological effects of KOR agonists and to develop more effective and safe drugs. Lastly, to gain a better understanding of the interactions between ligands and receptors, it would be beneficial to conduct cheminformatics studies to evaluate potential off-target interactions of difelikefalin, butorphanol, nalbuphine, nalfurafine, HSK21452, and triazole 1.1. In addition, the use of pharmacokinetic prediction tools can aid in the development of optimized compounds and should be used in future drug discovery efforts.

Alternative antipruritic compounds

Although promising, KOAs should be used judiciously in patients with significant comorbidities that may affect blood-brain barrier integrity. Alternative medications with an acceptable side-effect profile include gabapentin, pregabalin, and dupilumab (Dupixent). Gabapentin and pregabalin are medications that were initially developed to treat seizures but have also been used off-label to treat various types of chronic itch, including neuropathic itch[75]. They work by binding to voltage-gated calcium channels in the nervous system, which reduces the release of certain neurotransmitters that are involved in the sensation of itch. Dupilumab is a monoclonal antibody that targets IL-4 and IL-13, which are cytokines that play a role in the development of AD (eczema) and other allergic diseases[76]. It is FDA-approved for the treatment of moderate-to-severe AD and has been shown to significantly

reduce itch in clinical trials. In terms of side effects, gabapentin and pregabalin may cause dizziness, drowsiness, and peripheral edema. Dupilumab may cause injection site reactions, conjunctivitis, and other types of infections. In terms of efficacy, clinical studies have shown that gabapentin and pregabalin can provide relief from chronic itch in some patients, but their efficacy varies and may depend on the underlying cause of the itch. For example, they have been shown to be effective in treating neuropathic itch, but less effective in treating itch caused by other conditions. Dupilumab has been shown to be highly effective in reducing both the severity and frequency of itch in patients with moderate-to-severe AD and is considered a first-line treatment option for this condition. However, it is not effective in all patients, and its long-term safety and efficacy are still being studied. It's important to note that the use of alternative therapies to KOAs for itch depends on the underlying cause of the itch, and the decision to use these treatments should be made in consultation with a health care provider who specializes in itch and related conditions.

Conclusions

KOR agonists (KOAs) have received attention as novel drug candidates in the treatment of pruritus. Recently, the peripherally restricted tetrapeptide KOA difelikefalin (Korsuva) was approved by the FDA for the treatment of moderate to severe uremic pruritus in patients undergoing hemodialysis. Although encouraging, difelikefalin is currently available as an IV composition only, limiting the scope of use. Oral formulations of difelikefalin did not meet the primary endpoint criteria in recent phase 2 clinical trials; however, additional clinical studies are ongoing. Development of an oral ER formulation of difelikefalin is warranted. New technologies, such as the TP-2021 ProNeura implant, may circumvent the pharmacokinetic issues associated with KOA peptides and expand the use of KOAs in chronic pruritus. Orally active pathway–biased KOAs, such as triazole 1.1, pose an avenue for future development. Pathway-biased KOAs may prove, especially, beneficial in the treatment of centrally mediated forms of itch. Dual-acting KOR agonist/MOR antagonists are orally bioavailable and may be useful in the treatment of various forms of chronic itch.

Although KOAs, such as difelikefalin, have shown potential in the treatment of itch, they have not fully met therapeutic expectations. While KORs play a role in modulating itch sensation, the clinical efficacy of kappa agonists in relieving itch has been variable and inconsistent. Despite initial promise, challenges, such as pharmacokinetics, potential side effects, and variability, in individual response have hindered their widespread success as itch-relieving agents. The development of optimized KOAs may address these issues and represent a potential future direction in the treatment of chronic itch.

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T.C.B. is a coinventor of TP-2021 and a consultant to Titan Pharmaceuticals, Inc. L.W.L. has funding and consulting roles with Sanofi and Regeneron who comarket dupilumab. Also, participates in prurigo nodularis studies with Trevi. The remaining authors declare that they have no financial conflict of interest with regard to the content of this report.

References

[1]. Rajagopalan M, Saraswat A, Godse K, et al. Diagnosis and management of chronic pruritus: an expert consensus review. Indian J Dermatol 2017; 62:7–17. [PubMed: 28216719]

[2]. Mollanazar N. Epidemiology of chronic pruritus: where have we been and where are we going? Curr Dermatol Rep 2015;4:20–9.

[3]. Fourzali KM, Yosipovitch G. Management of itch in the elderly: a review. Dermatol Ther (Heidelb) 2019;9:639–53. [PubMed: 31549284]

[4]. Garibyan L, Rheingold CG, Lerner EA. Understanding the pathophysiology of itch. Dermatol Ther 2013;26:84–91. [PubMed: 23551365]

[5]. Kim BS, Inan S, Stander S, et al. Role of kappa-opioid and mu-opioid receptors in pruritus: Peripheral and central itch circuits. Exp Dermatol 2022;31:1900–7. [PubMed: 36054458]

[6]. Akiyama T, Lerner EA, Carstens E. Protease-activated receptors and itch. Handb Exp Pharmacol 2015;226:219–35. [PubMed: 25861783]

[7]. Haddadi NS, Foroutan A, Shakiba S, et al. Attenuation of serotonin-induced itch by sumatriptan: possible involvement of endogenous opioids. Arch Dermatol Res 2018;310:165–72. [PubMed: 29352328]

[8]. Akiyama T, Carstens E. Neural processing of itch. Neuroscience 2013; 250:697–714. [PubMed: 23891755]

[9]. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out. Clin Rev Allergy Immunol 2016; 51:263–92. [PubMed: 25931325]

[10]. Mayo Clinic Staff. 2023. Itchy skin (pruritus). (January 2023). Accessed: February 17, 2023. https://www.mayoclinic.org/diseases-conditions/itchy-skin/symptoms-causes/syc-20355006

[11]. Lipman ZM, Labib A, Yosipovitch G. Current clinical options for the management of itch in atopic dermatitis. Clin Cosmet Investig Dermatol 2021;14:959–69.

[12]. Pavlis J, Yosipovitch G. Management of itch in atopic dermatitis. Am J Clin Dermatol 2018;19:319–2. [PubMed: 29285724]

[13]. Weisshaar E, Heyer G, Forster C, et al. Effect of topical capsaicin on the cutaneous reactions and itching to histamine in atopic eczema compared to healthy skin. Arch Dermatol Res 1998;290:306–11. [PubMed: 9705161]

[14]. Ference JD, Last AR. Choosing topical corticosteroids. Am Fam Physician 2009;79:135–40. [PubMed: 19178066]

[15]. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: Section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol 2014;71: 116–32. [PubMed: 24813302]

[16]. Tanei R Atopic dermatitis in older adults: a review of treatment options. Drugs Aging 2020;37:149–60. [PubMed: 32086792]

[17]. Senba E, Katanosaka K, Yajima H, et al. The immunosuppressant FK506 activates capsaicin- and bradykinin-sensitive DRG neurons and cutaneous C-fibers. Neurosci Res 2004;50:257–62. [PubMed: 15488288]

[18]. Kaufmann R, Bieber T, Helgesen AL, et al. Onset of pruritus relief with pimecrolimus cream 1% in adult patients with atopic dermatitis: a randomized trial. Allergy 2006;61:375–81. [PubMed: 16436149]

[19]. Pereira U, Boulais N, Lebonvallet N, et al. Mechanisms of the sensory effects of tacrolimus on the skin. Br J Dermatol 2010;163:70–7. [PubMed: 20302583]

[20]. Siegfried EC, Jaworski JC, Hebert AA. Topical calcineurin inhibitors and lymphoma risk: evidence update with implications for daily practice. Am J Clin Dermatol 2013;14:163–78. [PubMed: 23703374]

[21]. Remitz A, Harper J, Rustin M, et al. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. Acta Derm Venereol 2007;87:54–61. [PubMed: 17225017]

[22]. Tom WL, Van Syoc M, Chanda S, et al. Pharmacokinetic profile, safety, and tolerability of crisaborole topical ointment, 2% in adolescents with atopic dermatitis: an open-label phase 2a study. Pediatr Dermatol 2016; 33:150–9. [PubMed: 26777394]

[23]. Nazarian RWJ. AN-2728, a PDE4 inhibitor for the potential topical treatment of psoriasis and atopic dermatitis. Curr Opin Investig Drugs 2009;10:1236–42.

[24]. Draelos ZD, Stein Gold LF, Murrell DF, et al. Post hoc analyses of the effect of crisaborole topical ointment, 2% on atopic dermatitis: associated pruritus from phase 1 and 2 clinical studies. J Drugs Dermatol 2016;15:172–6. [PubMed: 26885784]

[25]. Zane LT, Kircik L, Call R, et al. Crisaborole topical ointment, 2% in patients ages 2 to 17 years with atopic dermatitis: a phase 1b, open-label, maximal-use systemic exposure study. Pediatr Dermatol 2016;33: 380–7. [PubMed: 27193740]

[26]. Yosipovitch G, Gold LF, Lebwohl MG, et al. Early relief of pruritus in atopic dermatitis with crisaborole ointment, a non-steroidal, phosphor-diesterase 4 inhibitor. Acta Derm Venereol 2018;98:484–9. [PubMed: 29363715]

[27]. Simpson EL, Yosipovitch G, Bushmakin AG, et al. Direct and indirect effects of crisaborole ointment on quality of life in patients with atopic dermatitis: a mediation analysis. Acta Derm Venereol 2019;99:756–61. [PubMed: 30896779]

[28]. Lee HG, Grossman SK, Valdes-Rodriguez R, et al. Topical ketamine-amitriptyline-lidocaine for chronic pruritus: a retrospective study assessing efficacy and tolerability. J Am Acad Dermatol 2017;76:760–1. [PubMed: 28325395]

[29]. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2016;375: 2335–48. [PubMed: 27690741]

[30]. Han Y, Chen Y, Liu X, et al. Efficacy and safety of dupilumab for the treatment of adult atopic dermatitis: a meta-analysis of randomized clinical trials. J Allergy Clin Immunol 2017;140:888–91.e886. [PubMed: 28479326]

[31]. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet 2017;389:2287–303. [PubMed: 28478972]

[32]. Wahlgren CF, Scheynius A, Hagermark O. Antipruritic effect of oral cyclosporin A in atopic dermatitis. Acta Derm Venereol 1990;70:323–9. [PubMed: 1977258]

[33]. Schram ME, Roekevisch E, Leeflang MM, et al. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. J Allergy Clin Immunol 2011;128:353–9. [PubMed: 21514637]

[34]. Roekevisch E, Spuls PI, Kuester D, et al. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. J Allergy Clin Immunol 2014;133:429–38. [PubMed: 24269258]

[35]. Herman SM, Vender RB. Antihistamines in the treatment of dermatitis. J Cutan Med Surg 2003;7:467–73. [PubMed: 15926215]

[36]. Khanna R, Boozalis E, Belzberg M, et al. Mirtazapine for the treatment of chronic pruritus. Medicines (Basel) 2019;6:73. [PubMed: 31284577]

[37]. Levy G, Guglielmelli P, Langmuir P, et al. JAK inhibitors and COVID-19. J Immunother Cancer 2022;10:e002838. [PubMed: 35459733]

[38]. Schwartz DM, Kanno Y, Villarino A, et al. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nat Rev Drug Discov 2017;17:78.

[39]. Huang J, Polgar E, Solinski HJ, et al. Circuit dissection of the role of somatostatin in itch and pain. Nat Neurosci 2018;21:707–16. [PubMed: 29556030]

[40]. Potenzieri C, Undem BJ. Basic mechanisms of itch. Clin Exp Allergy 2012;42:8–19. [PubMed: 21645138]

[41]. Arvidsson U, Riedl M, Chakrabarti S, et al. The kappa-opioid receptor is primarily postsynaptic: combined immunohistochemical localization of the receptor and endogenous opioids. Proc Natl Acad Sci USA 1995;92: 5062–6. [PubMed: 7539141]

[42]. Brust TF, Morgenweck J, Kim SA, et al. Biased agonists of the kappa opioid receptor suppress pain and itch without causing sedation or dysphoria. Sci Signal 2016;9:ra117.

[43]. Wikstrom B, Gellert R, Ladefoged SD, et al. Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. J Am Soc Nephrol 2005;16:3742–7. [PubMed: 16251241]

[44]. Butelman ER, Yuferov V, Kreek MJ. Kappa-opioid receptor/dynorphin system: genetic and pharmacotherapeutic implications for addiction. Trends Neurosci 2012;35:587–96. [PubMed: 22709632]

[45]. Goldstein A, Tachibana S, Lowney LI, et al. Dynorphin-(1–13), an extraordinarily potent opioid peptide. Proc Natl Acad Sci USA 1979;76:6666–70. [PubMed: 230519]

[46]. Mansour A, Fox CA, Meng F, et al. Kappa 1 receptor mRNA distribution in the rat CNS: comparison to kappa receptor binding and prodynorphin mRNA. Mol Cell Neurosci 1994;5:124–44. [PubMed: 8032682]

[47]. Machelska H, Celik MO. Opioid receptors in immune and glial cells-implications for pain control. Front Immunol 2020;11:300. [PubMed: 32194554]

[48]. Yuferov V, Fussell D, LaForge KS, et al. Redefinition of the human kappa opioid receptor gene (OPRK1) structure and association of haplotypes with opiate addiction. Pharmacogenetics 2004;14:793–804. [PubMed: 15608558]

[49]. Galligan JJ, Sternini C. Insights into the role of opioid receptors in the GI tract: experimental evidence and therapeutic relevance. Handb Exp Pharmacol 2017;239:363–78. [PubMed: 28204957]

[50]. Beck TC, Hapstack MA, Beck KR, et al. Therapeutic potential of kappa opioid agonists. Pharmaceuticals (Basel) 2019;12:95. [PubMed: 31226764]

[51]. Beck TC, Reichel CM, Helke KL, et al. Non-addictive orally-active kappa opioid agonists for the treatment of peripheral pain in rats. Eur J Pharmacol 2019;856:172396. [PubMed: 31103632]

[52]. Inui S Nalfurafine hydrochloride to treat pruritus: a review. Clin Cosmet Investig Dermatol 2015;8:249–55.

[53]. Riviere PJ. Peripheral kappa-opioid agonists for visceral pain. Br J Pharmacol 2004;141:1331–4. [PubMed: 15051626]

[54]. Beck TC, Hapstack MA, Ghatnekar GS, et al. Diuretic activity of a novel peripherally-restricted orally-active kappa opioid receptor agonist. Med Sci (Basel) 2019;7:93. [PubMed: 31480425]

[55]. Beck TC, Dix TA, Reichel CM. Targeting peripheral kappa opioid receptors for the treatment of chronic pain: review article. Adv Nanomed Nanotechnol Res 2019;1:16–9. [PubMed: 35494408]

[56]. Anon. FDA approves KORSUVATM Injection for the Treatment of Pruritus in Hemodialysis Patients. Retrieved February 17, 2023. from https://fmcna.com/insights/articles/fda-korsuva-pruritus/.

[57]. Elmariah S, Chisolm S, Sciascia T, et al. Modulation of the kappa and mu opioid axis for the treatment of chronic pruritus: a review of basic science and clinical implications. JAAD Int 2022;7:156–63. [PubMed: 35497636]

[58]. Narita I, Tsubakihara Y, Uchiyama T, et al. Efficacy and Safety of difelikefalin in Japanese patients with moderate to severe pruritus receiving hemodialysis: a randomized clinical trial. JAMA Netw Open 2022;5:e2210339. [PubMed: 35511180]

[59]. Fishbane S, Jamal A, Munera C, et al. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. N Engl J Med 2020;382:222–32. [PubMed: 31702883]

[60]. Kumagai H, Ebata T, Takamori K, et al. Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: a Phase III, randomized, double-blind, placebo-controlled study. Nephrol Dial Transplant 2010;25:1251–7. [PubMed: 19926718]

[61]. A multi-site bridging study of nalfurafine hydrochloride orally disintegrating tablet. 2021. Shenyang Sunshine Pharmaceutical Co., LTD Accessed: February 17, 2023. https://clinicaltrials.gov/ct2/show/NCT04728984.

[62]. Wang X, Gou X, Yu X, et al. Antinociceptive and Antipruritic effects of HSK21542, a peripherally-restricted kappa opioid receptor agonist, in animal models of pain and itch. Front Pharmacol 2021;12:773204. [PubMed: 34867403]

[63]. Inc. Enteris BioPharma. 2019. Enteris biopharma and Cara Therapeutics enter into licensing agreement for Peptelligence® to advance development of Oral KorsuvaTM. (August 2019). Accessed: February 17, 2023. https://www.prnewswire.com/news-releases/enteris-biopharma-

and-cara-therapeutics-enter-into-licensing-agreement-for-peptelligence-to-advance-development-of-oral-korsuva-300905076.html

[64]. Anon. 2021. Cara Therapeutics announces topline results from KARE Phase 2 dose-ranging trial of Oral KorsuvaTM in atopic dermatitis patients with moderate-to-severe pruritus. (April 2021). Accessed: February 17, 2023. https://ir.caratherapeutics.com/news-releases/news-release-details/cara-therapeutics-announces-topline-results-kare-phase-2-dose.

[65]. Deeks ED. Difelikefalin: First Approval. PMID 2021;81:1937–44 doi:10.1007/s40265-021-01619-6.

[66]. Kim BS, Bissonnette R, Nograles K, et al. Investigators, K.T. Phase 2 trial of difelikefalin in notalgia paresthetica. N Engl J Med 2023;388:511–7. [PubMed: 36780675]

[67]. Beck TC, Dix TA, Norris RA. Biased opioid receptor ligands: gain without pain. Trends Endocrinol Metab 2020;31:801–2. [PubMed: 32943311]

[68]. Dalefield ML, Scouller B, Bibi R, et al. The kappa opioid receptor: a promising therapeutic target for multiple pathologies. Front Pharmacol 2022;13:837671. [PubMed: 35795569]

[69]. Anon. 2021b. Titan announces upcoming TP-2021 implant data presentation at Neuroscience 2021. (November 2021). Accessed: February 17, 2023. https://www.titanpharm.com/news/press-releases/detail/260/titan-announces-upcoming-tp-2021-implant-data-presentation.

[70]. Anon. Titan Pharmaceuticals, Inc Accessed: February 17, 2023. https://www.titanpharm.com/.

[71]. Inan S, Dun NJ, Cowan A. Nalfurafine prevents 5'-guanidinonaltrindole- and compound 48/80-induced spinal C-fos expression and attenuates 5'-guanidinonaltrindole-elicited scratching behavior in mice. Neuroscience 2009;163:23–33. [PubMed: 19524022]

[72]. Larsen D, Maani CV. Nalbuphine. [Updated 2023 May 1]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK534283/

[73]. Davis MP, Fernandez C, Regel S, et al. Does nalbuphine have a niche in managing pain. J Opioid Manag 2018;14:143–51. [PubMed: 29733100]

[74]. Aceves M, Mathai BB, Hook MA. Evaluation of the effects of specific opioid receptor agonists in a rodent model of spinal cord injury. Spinal Cord 2016;54:767–7. [PubMed: 26927293]

[75]. Sreekantaswamy SA, Mollanazar N, Butler DC. Gabapentinoids for pruritus in older adults: a narrative review. Dermatol Ther (Heidelb) 2021;11:669–79. [PubMed: 33721214]

[76]. Harb H, Chatila TA. Mechanisms of dupilumab. Clin Exp Allergy 2020; 50:5–14. [PubMed: 31505066]

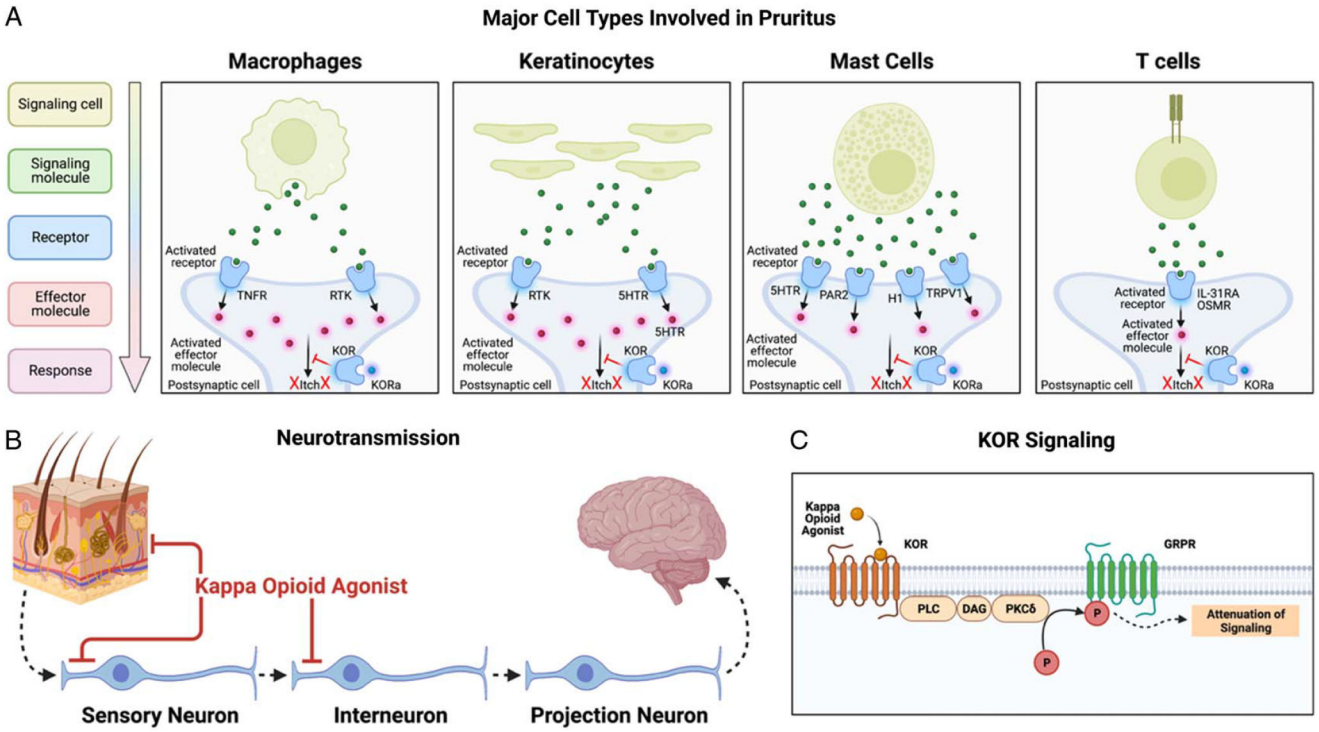

Figure 1.

Mechanisms of itch and KOR itch-neuromodulation. A, Pruritogenic signals originate from various cell types, such as macrophages, keratinocytes, mast cells, and T cells. Various receptors participate in itch neurotransmission, including TNFR, RTK, 5-HTR, PAR2, H1 receptor, TRPV1, OSMR, and IL-31RA. The KOR is located downstream of these receptors and can block itch neurotransmission signals. B, Itch signals originating within the skin travel to spinal interneurons through sensory afferent neurons. Projection neurons receive signals from spinal interneurons and transmit pain and itch-relevant information to the brain. C, Activation of the KOR attenuates GRPR-mediated itch signaling through the KOR-PLC-PKCd-GRPR signaling pathway. Figure made using BioRender. GRPR indicates gastrin-releasing peptide receptor; H1, histamine 1; 5-HTR, 5-hydroxytryptamine receptor; IL-31RA, interleukin-31 receptor alpha; KOR, kappa opioid receptor; OSMR, oncostatin M receptor; PAR2, protease-activated receptor 2; RTK, receptor tyrosine kinase; TNFR, tumor necrosis factor receptor; TRPV1, transient receptor potential vanilloid 1.