

REVIEW ARTICLE

Systemic Kappa Opioid Receptor Agonists in the Treatment of Chronic Pruritus: A Literature ReviewNgoc Quan PHAN¹, Tobias LOTT¹, Attila ANTAL², Jeffrey D. BERNHARD³ and Sonja STÄNDER¹¹Competence Center Chronic Pruritus, Department of Dermatology, University Hospital Münster, Münster; ²Department of Dermatology and Allergology Ludwig-Maximilians-University, München, Germany, and ³Department of Dermatology, University of Massachusetts Medical School, Worcester, Massachusetts, USA

Chronic pruritus is frequently refractory to currently available treatments. Studies suggest that pruritus may arise from an imbalance of the mu- and kappa-opioid receptor system activity in either the skin or the central nervous system. Stimulation of kappa-opioid receptors by their agonists inhibits pruritus in both animals and humans. The antipruritic effect of kappa-opioid receptor agonists can currently be assumed to be related to their binding to kappa-opioid receptors on keratinocytes and cutaneous and/or central itch neurones. To date, several case reports and 2 controlled trials have demonstrated a beneficial effect of systemic kappa-opioid receptor agonists in the treatment of uraemic pruritus, prurigo nodularis, paraneoplastic and cholestatic pruritus. Nalfurafine hydrochloride (Remitch[®]), a selective kappa-opioid receptor agonist, is approved for the treatment of chronic pruritus in Japan. The aim of this review is to provide an overview of the promising role of kappa-opioid receptors and their agonist in the pathophysiology and treatment of pruritus. Key words: itch; therapy; kappa opioid receptor antagonist; mu-opioid receptor.

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Chronic pruritus is frequently refractory to treatment. Accordingly, a symptomatic antipruritic therapy that would inhibit the induction, transmission, or perception of itch is badly needed. During the past 10 years, opioid receptors have been identified as a target in the treatment of pruritus. Mu- and kappa-opioid receptors are expressed in the skin and central nervous system (CNS) (1). Mu-opioid receptors (MOR) antagonists are effective in chronic pruritus of various origins (1). MOR and kappa-opioid receptors (KOR) mediate opposite effects (2). For example, activation of MOR inhibits pain, while activation of KOR inhibits itch. The newly developed KOR agonists have demonstrated in experimental and clinical

studies antipruritic effects in antihistamine-resistant and antihistamine-sensitive pruritus in animals and humans (3, 4). Given that an imbalance of the endogenous opioid system has been considered as a pathomechanism in uraemic pruritus, antipruritic effects of KOR agonists have been investigated in randomized controlled trials (RCT) in this indication (5–8). The major advantage of the KOR agonists over MOR antagonists seems to be the fewer rates of up-to-date reported adverse events. MOR antagonists show a high rate of troublesome side-effects (1), hampering their application mainly in elderly patients. The aim of this paper is to provide an overview of the current knowledge of KOR and their role in pruritus as well as the evidence of antipruritic potency of KOR agonists and their possible use in the treatment of chronic pruritus.

METHODS

A systemic search for reports of KOR and KOR agonist in experimental animal models and studies in humans was carried out. The major electronic databases (PubMed, Ovid and DIMDI) were searched using the free-text key words kappa opioid receptor or kappa opioid receptor agonist, butorphanol, nalfurafine and/or skin, pruritus, itch, and several combinations of these words. Searching was carried out without time and language restriction, and without contacting manufacturers or authors. In addition, information on these two drugs from current data sheets was included.

RESULTS

A total of 3,183 papers (until August 2011) with the key word “kappa opioid receptor agonist” were found, mostly addressing the analgesic properties of KOR agonists. A combination of the key words “kappa opioid receptor agonist” and “itch” or “pruritus” resulted in 28 papers, of which only 7 were case reports, case studies or randomized trials on antipruritic effects of KOR agonists in humans. In addition, we included papers on mechanisms of action, e.g. in animal models and experimental models as well as information from current data sheets of KOR agonists, finally resulting in 74 references.

Kappa opioid receptor expression

Opioid receptors (ORs) are a member of the pertussis toxin-sensitive heterotrimeric G_i/G_o protein-coupled receptor family with a 7 transmembrane domain and belong to the rhodopsin subfamily (9, 10). Three major classes of opioid receptors have been identified: KOR, MOR and delta-opioid receptors (DOR) (11–13). MOR is specific for the ligand beta-endorphin, DOR for enkephalins and KOR for dynorphins (Dyn) (14), but no ligand is completely specific for any receptor (15). It is assumed that 3 different subtypes of KOR (k1, k2 and k3) exist, based on ligand receptor binding studies, but only one has been identified so far (GenBank Acc. No. U11053) (16–22).

KOR is expressed in the CNS as well as in the periphery. In the CNS, KOR are localized in axons in the medial prefrontal cortex (23), in the nucleus accumbens, hypothalamic nuclei, periaqueductal gray (PAG), nucleus of the solitary tract, ventral tegmental area, amygdala, neocortex and supraspinal nucleus (24–26) and in the dorsal horn of the spinal cord (27). Interestingly, in the dorsal horn of the spinal cord, KOR may be linked with the cannabinoid system (28). Systemic application of the cannabinoid receptor agonist delta-9-tetrahydrocannabinol (THC) was demonstrated to inhibit nociceptive reflexes, possibly resulting from an inhibition of dorsal horn neurones through a KOR-dependent mechanism (28). KOR-expressing neurones are also located in the dorsal and trigeminal root ganglia (29), which is an important link to the peripheral nervous system. In the periphery, KOR has been detected in nerve terminals of muscles, joints and viscera (30). Expressed widely in the CNS and peripheral nervous system, the KOR system was shown to play an important role in anti-nociception (31), dysphoria (32, 33) and water diuresis (31, 33, 34).

KOR are expressed in human epidermal keratinocytes (35, 36) as well as dermal fibroblasts (36, 37) and mononuclear cells (37) as demonstrated in cell cultures (e.g. HaCaT, HNK) and skin biopsies on mRNA and protein levels. KOR expression in subepidermal nerve fibres was demonstrated by immunohistochemical staining (36). The corresponding KOR ligands DynA (1–17) and DynA (1–8) were identified in the epidermis (35). Studies suggest that KOR contribute to proliferation and differentiation of keratinocytes (38). For example, KOR knockout mice revealed epidermal hypotrophy and slightly enhanced cutaneous nerve fibre density after induction of dry skin dermatitis (38). The epidermis was significantly thinner than in wild-type mice (38). In addition, real-time polymerase chain reaction (PCR) showed increased KOR expression in epidermal keratinocytes and fibroblasts in hypertrophic scars in comparison with normal skin (36), which may contribute to the increased nociception in scars. Interestingly, a recent paper demonstrated that KOR expression was significantly decreased in the epidermis of itchy psoriatic

patients compared with healthy controls (39). Psoriasis shows an epidermal hyperplasia, but no thinned epidermis. The reduced KOR expression argues against a role of KOR in differentiation of keratinocytes in patients with psoriasis. Further studies need to address the role of KOR in human keratinocyte biology (39). KOR are expressed on blood derived dendritic cells (40). In cell cultures (KOR transfected Jurkat T cells), activation of KOR down-regulates cytokines and chemokines in inflammatory cells, and thus could induce an anti-inflammatory response (41). This is of great interest for inflammatory diseases presenting with pruritus, such as atopic dermatitis (AD).

Role of kappa opioid receptor in pruritus

Like MOR, KOR plays a role in the sensation of itch in animals and humans (34, 42). Systemic administration of the selective and potent KOR antagonist norbinaltorphimine induced scratching in mice (42). In contrast, activation of itch neurones in the superficial layer of the dorsal horn of the spinal cord was shown to be inhibited by the KOR agonist TRK-820 (nalfurafine) in mice (43). Consequently, oral (3, 44) or subcutaneous (45, 46) administration of nalfurafine resulted in significant reduction of substance P (SP) or histamine-induced pruritus in wild-type mice. In addition, spontaneously developing scratching behaviour in NC/Nga mice could be suppressed by nalfurafine (3, 44–46). Scratching behaviour was reduced in KOR knockout mice after dry skin induction in comparison with wild-type mice (38). In a model of autoimmune-induced pruritus in aged MRL/lpr mice, oral nalfurafine also inhibited scratching behaviour (47). In a rat model of cholestatic pruritus, nalfurafine reduced scratching behaviour significantly (48). Intravenous application of TRK-820 suppressed scratching induced by systemic application of morphine in rhesus monkeys (49).

Together, KOR are involved in the pathophysiology of pruritus not only by their expression in the CNS, but also by their presence in the skin. For example, application of the peripherally acting KOR agonist ICI 204,448 inhibited chloroquine-induced pruritus in mice suggesting a peripheral pathway in itch suppression (50). Moreover, it was demonstrated that KOR immunostaining is down-regulated in the epidermis of atopic dermatitis (AD) and itchy psoriasis patients (35, 39). Psoralen plus ultraviolet A (PUVA) therapy did not lead to normal KOR levels in AD, but an increase in the KOR ligand DynA (35). Interestingly, KOR is up-regulated in the skin of patients with painful diseases such as fibromyalgia and painful scars (36, 51).

Kappa opioid receptor agonists in clinical use

The antipruritic effects of several artificial KOR agonists have been studied in rodents and monkeys, including models of histamine-, SP- and morphine-induced itch

Table I. Effect of kappa-opioid receptors (KOR) agonists in chronic pruritus

Diagnosis	KOR agonists in studies (dosage; ref.)	Study design	n	Compared with	Effect
Uraemic pruritus	Nalfurafine (5 µg i.v. 3/week for 2 or 4 weeks; 4)	RCT	144	Placebo	Significant improvement in pruritus ($p < 0.05$)
	Nalfurafine (2.5 and 5 µg p.o. for 14 days; 8)	RCT	337	Placebo	Significant decrease in pruritus intensity on VAS ($p < 0.0001$)
Prurigo nodularis	Butorphanol (1 mg/day; 70)	CR	1	–	Improvement
Primary biliary cirrhosis	Butorphanol (1 mg/day; 70)	CR	1	–	Improvement
Idiopathic pruritus in elderly patients	Butorphanol (1 mg/day; 70)	CR	1	–	Improvement
Non-Hodgkin's lymphoma	Butorphanol (1 mg/day; 70)	CR	1	–	Improvement
Pruritus in chronic renal failure, diabetes (perforating collagenosis)	Butorphanol (1 mg/day; 70)	CR	1	–	Improvement

CR: case report; RCT: randomized controlled trial; VAS: visual analogue scale; i.v.: intravenous; p.o.: per oral.

(43–49). Besides nalfurafine, all KOR agonists currently approved for therapeutic use in humans are mixed KOR agonists/MOR antagonists with similar receptor affinity-dependent side-effects of varying intensity. Nalbuphine, butorphanol and pentazocine are well known for their beneficial effects in acute morphine-induced pruritus (52–54). Only butorphanol and nalfurafine have been applied in chronic pruritus (Table I).

Nalfurafine

Nalfurafine (TRK-820) was developed in 1998 (55) and is a full agonist for the KOR, a partial agonist for the MOR and low-affinity antagonist for the nociceptin receptor (56). Compared with other synthetic KOR agonists, nalfurafine showed higher selectivity for KOR (46, 56). Nalfurafine has anti-nociceptive effects, as demonstrated in mice (e.g. hot plate test, tail flick test, tail pressure test) (57) and monkeys (58). The antipruritic effects of nalfurafine were investigated for the first time in 2002 (3). Pruritus induced by SP- and histamine was significantly inhibited by orally administered nalfurafine in mice, whereas antihistamines did not inhibit SP-induced itching (3). In the first multicentre, randomized, double-blind placebo-controlled trial, Wikström et al. (4) demonstrated significant clinical benefit of nalfurafine in humans with uraemic pruritus ($n = 144$) (Table I). The finding of reduced pruritus intensity was confirmed later in a similar cohort of patients, i.e. patients with uraemic pruritus, ($n = 337$) in a randomized placebo-controlled trial (8). Patients responded quickly to nalfurafine, after the first 7 days of treatment a considerable change in VAS was observed. Interestingly, the change in VAS was larger in treatment days 8–14 than in the first 7 days. This observation was independent of the dosage. In fact, 2.5 µg seemed to be almost equally effective as 5 µg. Uraemic itch is defined as a localized or generalized, chronic pruritus of almost unknown pathophysiology in patients with chronic renal failure and/or undergoing haemodialysis (4, 5). Given that an elevation of endogenous opioids has been postulated as a contributory factor, the antipruritic effects of nalfurafine in this indication may be specifically targeting

the pathophysiology (4, 59–61). Nalfurafine is licensed only in Japan for the therapy of uraemic pruritus. There are studies on the use of nalfurafine in other pruritic diseases in animal models (e.g. atopic dermatitis) (44), but none on humans are available to date.

Evaluation of adverse events demonstrated nalfurafine to be well tolerated in clinical use. Common adverse drug reactions are mediated by the CNS (insomnia, somnolence, vertigo and headache) and the gastrointestinal system (constipation, nausea and vomiting). All events were transient and resolved without therapy discontinuation (4, 8) (Table II). There were no remarkable changes in haematology and blood chemistry or in vital signs/electrocardiography (8). Moderate transient increased prolactin, decreased blood thyroid stimulating hormone (TSH), decreased free testosterone, elevated eosinophils, transient elevation of aspartate aminotransferase and alanine transaminase were some of the adverse events observed (4, 8). Neither addiction nor symptoms of withdrawal were noted in nalfurafine-treated patients. Being a partial agonist for MOR and DOR, nalfurafine significantly reduced physical dependence on morphine in mice and humans (62).

Table II. Side-effects of therapy with the selective kappa-opioid receptor agonist nalfurafine

Adverse drug reactions (ADR) in the phase III study, as occurred in 337 patients (8)	
Incidence of >3%	Insomnia (14%) Constipation (7%) Somnolence (4.5%)
Moderate ADR in individual cases	Anorexia Headache Pruritus Sudden hearing loss Hypertension Vomiting Nausea Transient mood alterations (elevated mood, feeling abnormal)
Laboratory findings	Decreased TSH Increased eosinophils Transient increase in prolactin Decrease in free testosterone

TSH: thyroid stimulating hormone.

Table III. Side-effects of therapy with mixed-action Mu-opioid receptor antagonist/kappa-opioid receptor agonist (butorphanol, nalbuphine and pentazocine)

	Side-effects
General (body as a whole)	Asthenia/lethargy, dizziness ^a , drowsiness, sensation of heat ^a , somnolence ^a
Digestive/urogenital	Anorexia, constipation, dry mouth, impaired urination nausea ^a , stomach pain, vomiting ^a
Cardiovascular	Hypertension, hypotension, palpitations, syncope, tachycardia, vasodilatation
Respiratory	Bronchitis, cough, dyspnoea, epistaxis, oedema, infection, nasal congestion ^a (butorphanol), nasal irritation, pharyngitis, rhinitis, sinus congestion, sinusitis, upper respiratory
Neurologic	Abnormal dreams, agitation, anxiety, confusion, dysphoria, euphoria, floating feeling, hallucinations, hostility, headache, insomnia ^a , nervousness, paraesthesia, tremor, withdrawal symptoms
Special senses	Blurred vision, ear pain, tinnitus, unpleasant taste
Skin/allergic	Flush, hives, pruritus, sweating/clammy

^aFrequent appearance.

Butorphanol

Butorphanol, developed in the 1970s, is an injectable or intranasally applicable mixed KOR agonist/MOR antagonist, with analgesic potency higher than morphine, pethidine or pentazocine, and is administered to patients with acute postoperative pain (63–65). It relieves acute morphine-induced pruritus even in children (66, 67). However, prophylactic application of butorphanol before application of morphine does not prevent induction of pruritus (68). Moreover, butorphanol itself can induce acute pruritus (69) (Table III). An open-label uncontrolled study of butorphanol in single patients reported that the antipruritic effect of this drug sets in 1–4 days after nasal administration in elderly, primary biliary cirrhosis and non-Hodgkin's lymphoma-associated pruritus (70). An impaired balance between MOR and KOR systems is suggested to have a role in cholestatic pruritus (71); furthermore, intranasal butorphanol was recommended in cholestatic pruritus, but not investigated in trials (72). A formulation containing 2 mg butorphanol tartrate in 100 µl purified water encapsulated into multilamellar phospholipid vesicles was topically used in rats and could be shown to penetrate the skin with low plasma levels (73). This formulation could potentially be used in the future to treat circumscribed pruritus and thus avoid systemic side-effects. Adverse effects of butorphanol are, for example, dizziness, sedation and nausea (64, 74). As with other morphine-like agents, respiratory depression can occur that is reversible in healthy subjects with moderate doses (up to 0.8 mg) of naloxone (64). Psychotomimetic reactions have been reported. Butorphanol is not recommended for use in patients dependent on narcotics. It should be used with caution in patients with increased intracranial pressure, disorders of respiratory function or control. In patients with hepatic or renal impairment, the initial dose of butorphanol should generally be half the recommended adult dose (e.g. 0.5 mg i.v.). Reproduction studies in animals (mice, rats and rabbits) did not reveal any teratogenic potential of butorphanol; however, it should be used with caution in pregnant and nursing women. There have been rare reports of infant respiratory distress/apnoea following

the administration of butorphanol injection during labour. Mixed KOR agonists are not recommended for use in patients below 18 years of age.

CONCLUSION

KOR play an important role in pruritus and skin biology. Therefore, application of KOR agonists as systemic, and probably also topical, agents is a promising therapeutic approach to chronic pruritus. Clinical studies have demonstrated the efficacy of the KOR agonist nalfurafine in uraemic pruritus. Evidence from animal models and morphological studies in humans suggests that KOR agonists might also be effective in pruritus of other origin, for example atopic dermatitis.

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