The Role of Kappa- and Mu-Opioid Receptors in Pruritus

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Introduction

Background

- Itch perception is transmitted from sensory neurons innervating the skin to the spinal cord; from there, spinal projection neurons relay signals to the brain, where itch sensation is perceived (**Figure 1**)
- A multitude of itch-inducing stimuli or pruritogens can trigger itch, including neurotransmitters, neuropeptides, proteases, and cytokines[1,2]; however, pathways that suppress itch remain poorly understood
- Chronic pruritus, defined as itch persisting for ≥6 weeks,[3] may arise from a range of dermatologic, systemic, neuropathic, and psychological conditions[1,4,5] and can be challenging to treat[6]
- Although opioid receptors are typically associated with their role in pain signaling, recent studies have shed light on the emerging role of opioid receptors, particularly kappa-opioid receptors (KORs) and mu-opioid receptors (MORs), respectively, in suppressing and eliciting itch both in the periphery and more centrally[7-10]

Objective

- To summarize recent work supporting the role of KORs and MORs as potential therapeutic targets in the treatment of itch

Methods

- A literature search of the PubMed database was conducted to identify English-language publications examining the role of opioid receptors in pruritus in the past decade (select references cited within identified publications were also incorporated)
  - Search terms included "opioid receptor", "kappa", "mu", "pruritus", and "itch"
- Findings from relevant publications were summarized as a narrative review

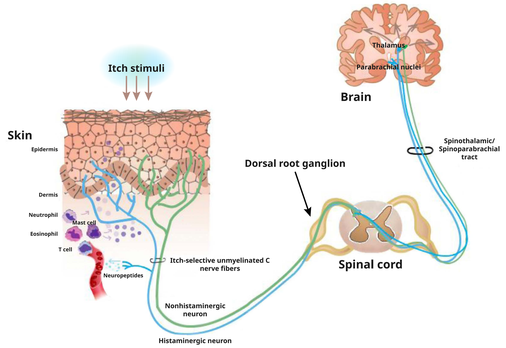
Results

Itch Signaling Pathway and the Role of Opioid Receptors

- Kappa- and mu-opioid receptors have been identified throughout the itch signaling pathway, from skin, to spinal cord, to central nervous system (CNS; **Figure 1**)[8,11,12]

Results (continued)

Figure 1. Presence of MORs and KORs Throughout the Itch Signaling Pathway

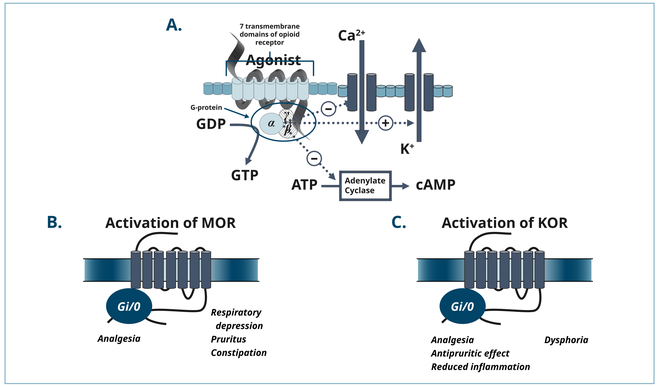


Presence of Opioid Receptors	Skin	Spinal Cord	Brain
MOR	✓	✓	✓
KOR	✓	✓	✓

The illustration depicts that itch perception involves somatosensory DRG neurons with axons extending to epidermal sensory terminals[1,13]; the DRG contains the cell bodies of neurons that carry information from the periphery to the spinal cord. Itch signals are ultimately carried to the thalamus, parabrachial nucleus, and possibly other brain centers by spinal projection neurons that cross the midline and join spinothalamic tracts.[1,14] KORs and MORs have been identified in the skin, spinal cord neurons, and brain.[8,11,12,15] DRG, dorsal root ganglion; KOR, kappa-opioid receptor; MOR, mu-opioid receptor. Reprinted from *Annals of Allergy, Asthma & Immunology*, Vol 123, Fowler E, Yosipovitch G, Chronic itch management: therapies beyond those targeting the immune system, pages 158-165, 2019, with permission from the American College of Allergy, Asthma & Immunology.

- Following binding of an opioid to an opioid receptor, a cascade of intracellular changes occurs, resulting in reduced cellular excitability (**Figure 2A**)[16]
- Although activation of both KORs and MORs results in analgesia, other effects are distinct (**Figures 2B and 2C**)
  - In particular, whereas activation of KORs results in attenuation of itch[7] in a variety of contexts, activation of MORs is associated with increased itch[17] (**Figures 2B and 2C**)
  - In addition, there are reports of KOR agonism resulting in suppression of inflammation[8,11]
    - Although the exact mechanisms are not established, in a preclinical model of atopic dermatitis, the dual KOR agonist/MOR antagonist nalbuphine decreased expression of the pruritogenic cytokine interleukin (IL)-31, and increased expression of the anti-inflammatory cytokine IL-10[18]
  - In contrast to MOR activation, neither MOR blockade nor KOR activation are associated with addiction,[11] which has important therapeutic implications given concerns about opioid use
- Imbalances of activity across the KOR and MOR systems in the skin or CNS are associated with severe chronic pruritus and are an active area of research for novel treatments[15]

Figure 2. Opioid Receptors (A) Intracellular Changes Occurring Following the Binding of an Opioid Agonist to an Opioid Receptor,16 (B) Effects Associated With MOR Activation, (C) Effects Associated With KOR Activation



Panel A is an illustration of opioid receptors, which are large membrane-bound proteins with the opioid-binding domain on the extracellular surface and 7 transmembrane domains.[16,19] These receptors are "coupled" to an intracellular guanine nucleotide-binding protein (G protein) and thus are characterized as G-protein–coupled receptors.[19] Binding of an opioid agonist to a G-protein–coupled opioid receptor triggers a cascade of intracellular events. Panels B and C illustrate the effects associated with activation of MORs and KORs, respectively.[20] ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; GDP, guanosine diphosphate; GTP, guanosine triphosphate; KOR, kappa-opioid receptor; MOR, mu-opioid receptor. Panel A: Adapted from Pathan H, Williams J, *British Journal of Pain* (Volume 6, Issue 1), pp. 11-16, copyright © 2012 by The British Pain Society. Reprinted by Permission of SAGE Publications, Ltd.

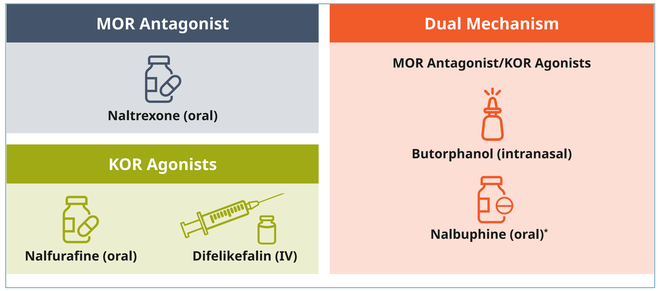
Preclinical Models Elucidate the Effects of KOR Activation

- Kappa-opioid receptors are expressed on 2 different populations of dorsal root ganglion neurons associated with hair follicles in the epidermis[8]
  - The endogenous KOR agonist dynorphin reduces neuronal excitability[8]
  - Dynorphin is produced by inhibitory interneurons that modulate the neurons that respond to itch stimuli[21]

KORs and MORs as Therapeutic Targets

- Agents that activate KORs have been shown to act within the peripheral nervous system and CNS to attenuate itch[7,8,18,22]
  - Attenuation of itch has been demonstrated by KOR agonists, including the endogenous ligand dynorphin and drugs like nalfurafine and difelikefalin
- The association of MOR activation with increased itching[17] supports blockade of MORs as another rational approach to inhibit itch
  - Likewise, the MOR antagonist naltrexone is employed as an antipruritic agent off-label[23]
- Both KOR and MOR pathways are targeted with use of dual KOR agonist/MOR antagonists such as butorphanol and nalbuphine
- Opioid agents targeting KORs and MORs (**Figure 3**) have demonstrated efficacy in a variety of chronic pruritic conditions, including uremic pruritus and prurigo nodularis[23-28]

Figure 3. Opioids Targeting KORs and/or MORs in Chronic Pruritus



*An oral formulation of nalbuphine is being developed for itch indications; an injectable formulation of nalbuphine is currently available in the US for pain-related indications.

Conclusions

- Kappa- and mu-opioid receptors have emerged as important therapeutic targets in itch
- Notwithstanding these advances, the precise mechanisms by which KOR agonists and/or MOR antagonists can be employed therapeutically remains an exciting area worthy of further investigation

Disclosures

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