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 cytokines1,2; however, pathways that suppress itch remain poorly understood (Figure 1).

• Chronic pruritus, defined as itch persisting for ≥6 weeks,3 may arise from a range of dermatologic, systemic, neuropsychiatric, and psychological conditions4-8 and can be challenging to treat.

• 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 centrally9-11.

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

Iitch 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).11-12

• Both in the periphery and more centrally, itch signaling pathways support itch in a variety of chronic pruritic conditions, including urticaria and prurigo nodularis.12

• Preclinical Models Evaluate 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.14

• The endogenous KOR agonist dynorphin reduces neuronal excitability15.

• Dynorphin is produced by inhibitory interneurons that modulate the neurons that respond to itch stimuli.15

KORs and MORs as Therapeutic Targets

• Agents that actuate KORs have been shown to act within the peripheral nervous system and CNS to attenuate itch.16-18

• Attenuation of itch has been demonstrated by KOR agonists, including the endogenous ligand dynorphin and drugs like nalfurafine and difelikefalin.16

• The association of MOR activation with increased itch19 supports blockade of MORs as another rational approach to inhibit itch.20

• Likewise, the MOR antagonist naltrexone is employed as an antipruritic agent as another rational approach to inhibit itch.20

• Kappa- and mu-opioid receptors have emerged as important therapeutic targets in itch.

Conclusions

• 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

• Kappa- and mu-opioid receptors have emerged as important therapeutic targets in itch.

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