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

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 treat⁶
- 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 centrally⁷⁻¹⁰

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)

Presence of Opioid Receptors

MOR

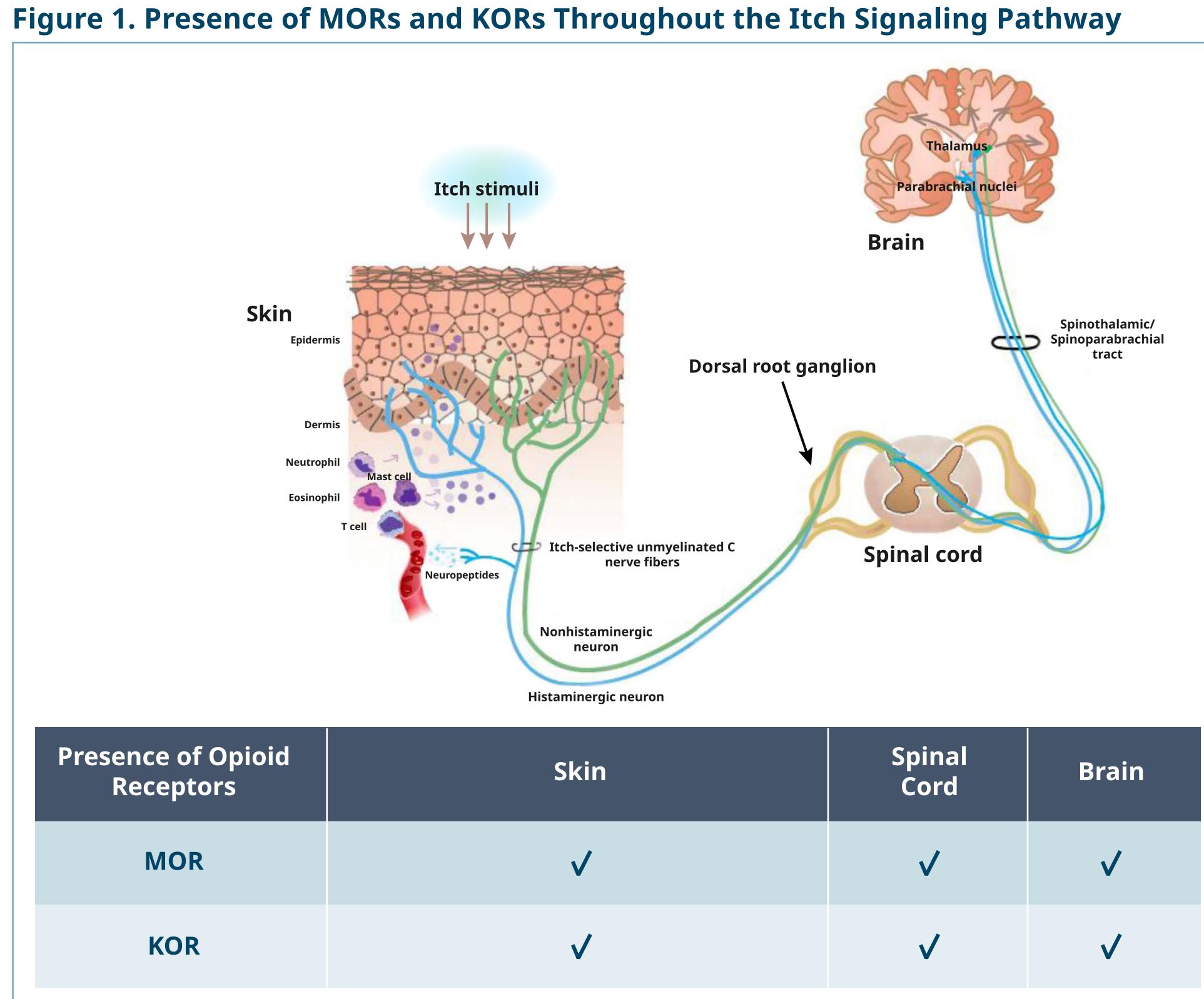
KOR

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.

- distinct (**Figures 2B and 2C**)

- novel treatments¹⁵

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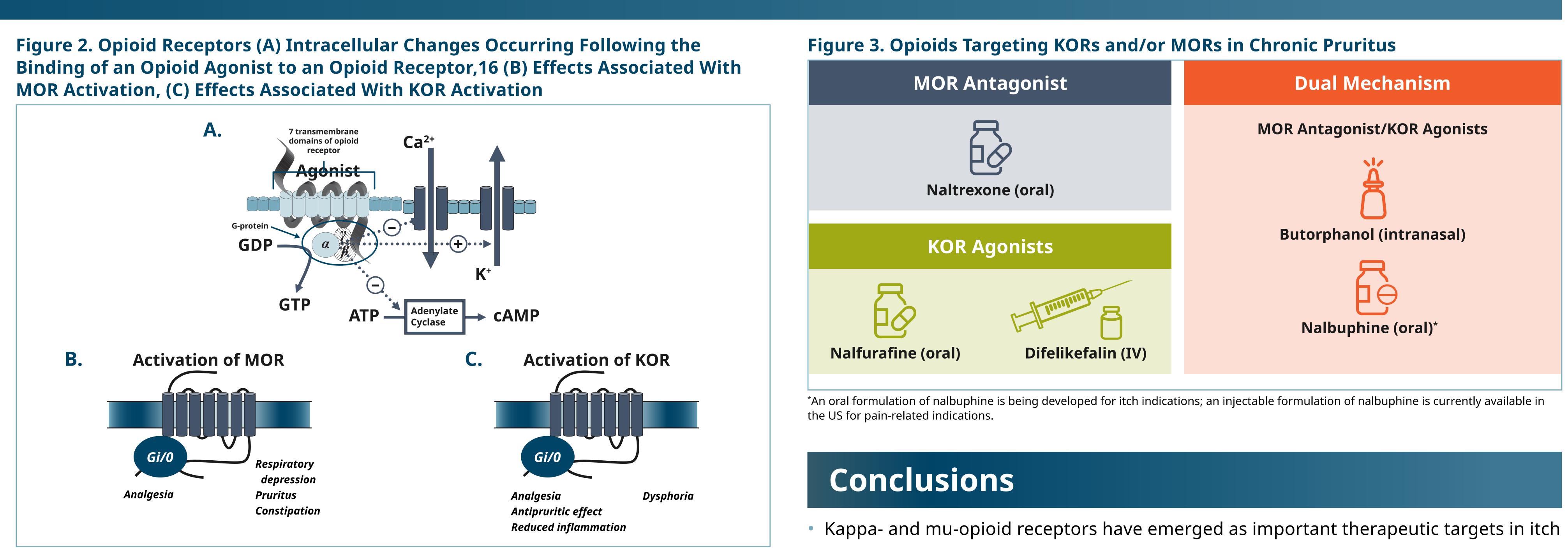
• Following binding of an opioid to an opioid receptor, a cascade of intracellular changes occurs, resulting in reduced cellular excitability (**Figure 2A**)¹⁶

Although activation of both KORs and MORs results in analgesia, other effects are

– In particular, whereas activation of KORs results in attenuation of itch⁷ in a variety of contexts, activation of MORs is associated with increased itch¹⁷ (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-10¹⁸

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



Panel A is an illustration of opioid receptors, which are large membrane-bound proteins with the opioid-binding domain on the extracellula surface and 7 transmembrane domains.^{16,19} These receptors are "coupled" to an intracellular guanine nucleotide-binding protein (G proteir 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 epidermis⁸
- The endogenous KOR agonist dynorphin reduces neuronal excitability⁸
- Dynorphin is produced by inhibitory interneurons that modulate the neurons that respond to itch stimuli²¹
- 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 itching¹⁷ supports blockade of MORs as another rational approach to inhibit itch
 - Likewise, the MOR antagonist naltrexone is employed as an antipruritic agent off-label²³
- 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 nodularis²³⁻²⁸

KORs and MORs as Therapeutic Targets

by the authors.

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1. Dong X, Dong X. Neuron. 2018;98(3):482-94. 2. Acton D, et al. Cell Reports. 2019;28(3):625-39.e6. 3. Ständer S, et al. Acta Derm Venereol. 2007;87(4):291-4. 4. Dhand A, Aminoff MJ. Brain. 2014;137(Pt 2):313-22. 5. Yosipovitch G, Bernhard JD. N Engl J Med. 2013;368(17):1625-34. 6. Fowler E, Yosipovitch G. Ann Allergy Asthma Immunol. 2019;123(2):158-65. 7. Kardon AP, et al. Neuron. 2014;82(3):573-86. 8. Snyder LM, et al. Neuron. 2018;99(6):1274-88.e6. 9. Paul B-QL, et al. J Am Acad Dermatol. 2004;50(3 suppl):P29. 10. Yosipovitch G, et al. Lancet. 2003;361(9358):690-4. **11.** Phan NQ, et al. Acta Derm Venereol. 2012;92(5):555-60. **12.** Peng J, et al. Drug Alcohol Depend. 2012;124(3): 223-8. **13.** Potenzieri C, Undem BJ. Clin Exp Allergy. 2012;42(1):8-19. **14.** Chen XJ, Sun YG. Nature Communications. 2020;11(1):3052. **15.** Fowler E, Yosipovitch G. Acta Derm Venereol. 2020;100(2):adv00027. **16.** Pathan H, Williams J. Br J Pain. 2012;6(1):11-6. **17.** Tubog TD, et al. J Perianesth Nurs. 2019;34(3):491-501.e8. 18. Inan S, et al. Eur J Pharmacol. 2019;864:172702. 19. Sehgal N, et al. Pain Physician. 2011;14(3): 249-58. **20.** Valentino RJ, Volkow ND. Neuropsychopharmacology. 2018;43(13):2514-20. **21.** Pereira PJ, Lerner EA. Neuron. 2014;82(3):503-5. **22.** Ross SE, et al. Neuron. 2010;65(6):886-98. **23.** Lee J, et al. Ann Dermatol. 2016;28(2):159-63. **24**. Kumagai H, et al. Nephrol Dial Transplant. 2010;25(4):1251-7. 25. Fishbane S, et al. Kidney Int Rep. 2020;5(5):600-10. 26. Fishbane S, et al. N Engl J Med. 2020;382(3):222-32. 27. Khanna R, et al. J Am Acad Dermatol. 2020;83(5):1529-33. 28. Mathur VS, et al. Am J Nephrol. 2017;46(6):450-8.

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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References