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Editorial

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An Emerging Role of MrgC in Inhibiting Neuropathic Pain

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The treatment of nonmalignant neuropathic pain continues to challenge clinicians owing to the limited efficacy of available treatments, dose-limiting adverse effects of drugs that are available, and lack of pain-specific treatment targets. G protein-coupled receptors (GPCRs) have been used frequently as drug targets for a variety of pharmacotherapies, including those for pathological pain. One novel family of GPCRs, the so-called Mas-related G protein-coupled receptors (Mrgs) may play a role in the function of nociceptive neurons as well as in sensation and modulation of pain [1-3]. The Mrg family in mice can be grouped into several subfamilies (MrgA1–22, MrgB1–13, MrgC1–14, and MrgD–G). The rat genome possesses one representative each of MrgA, C, and D and 10 MrgB genes [4], and humans possess just four MrgX genes (1–4) [1,5]. Mrgs are exclusively expressed in small-diameter afferent sensory neurons (presumably nociceptive) that can be visualized by lectin IB4 labeling or by expression of the glial cell line-derived neurotrophic factor co-receptor c-Ret [1,2]. Recent preclinical studies indicated that certain Mrgs, especially MrgC (mouse MrgC11 and the rat homolog rMrgC), may be involved in pain modulation and represent a compelling new target for pain-specific therapy.

MrgC can function as a receptor for peptides terminating in RF/Y-G or RF/Y-amide, such as the molluscan peptide FMRFamide, γ2-melanocyte-stimulating hormone (MSH), and bovine adrenal medulla peptide (BAM). Intriguingly, some MrgC ligands belong to the family of endogenous opioid peptides known to be involved in pain transmission, such as proenkephalin A gene products BAM 8-22 and BAM 22 [1-3]. However, the evidence that MrgC has a role in sensory processing of pain is mixed and controversial. For example, systemic and intrathecal injection of putative MrgC ligands, such as BAM 8-22 and γ2-MSH, produced a pro-nociceptive effect in acute pain models [6]. In contrast, intrathecal injection of BAM 8-22 inhibited persistent inflammatory pain, chemical pain, and spinal c-fos expression in an opioid-independent manner [7-10]. Intrathecal BAM 8-22 also dose-dependently diminished NMDA-evoked pain behaviors in rats, suggesting that it may induce spinal analgesia partially by suppressing NMDA receptor-mediated neuronal excitation [11]. The reasons for these contradictory findings remain unclear and need to be clarified in future studies. One limitation in previous peptide injection experiments is that the selectivity and mechanism of drug action were not directly addressed. Thus, the peptides studied may activate receptors that are distinct from Mrgs, a potential explanation for the conflicting results [3,6-10]. Other reasons for the discrepancies may relate to differences in animal conditions (physiological condition vs. tissue or nerve injury), etiologies (inflammatory vs. neuropathic pain) [12,13], behavioral measures (spontaneous vs. reflex), and drug dose.

Examining the roles of MrgC in pain is challenging, as deletion of a single Mrg gene may not produce a detectable phenotype change owing to the potential for functional redundancy in the Mrg family. As yet, no one has identified an MrgC antagonist that can be used to directly examine the receptor mechanisms of BAM 8-22's action in rodents, though 2,3-disubstituted azabicyclo-octane was suggested to be a selective antagonist for both MrgC11 and human MrgX1 [14]. Recently, a unique mouse line was generated in which all nociceptive neuron-expressing Mrgs are deleted (Mrg-cluster$\Delta^{-/-}$) [15,16]. The 12 intact Mrg coding sequences that were deleted, including MrgC11, represent ~50% of the potentially functional Mrg repertoire in mice. Importantly, the Mrg-cluster$\Delta^{-/-}$ mice are viable and fertile. Deleting Mrg clusters also did not affect dorsal root ganglion (DRG) neuronal survival, nor did it alter the fate determination or differentiation of small-diameter DRG neurons. However, Mrg-cluster$\Delta^{-/-}$ mice consistently display a higher level of spontaneous pain in the second phase of the formalin test and prolonged inflammatory pain, compared to wild-type littermates [16]. The increase in c-fos+ neurons is also more evident in Mrg-cluster$\Delta^{-/-}$ mice than in wild-type mice after an intraplantar formalin injection. These findings suggest that activation of Mrgs by intense noxious input inhibits the exaggeration and prolongation of pain. Importantly, deletion of the Mrg gene cluster eliminates the analgesic effect of intrathecally applied BAM 8-22 on neuropathic mechanical allodynia [16]. Furthermore, BAM 8-22 attenuates windup of wide dynamic range neuronal response to repetitive noxious inputs in wild-type mice, an effect also eliminated in Mrg-cluster$\Delta^{-/-}$ mice. Because MrgC11 is the only Mrg activated by BAM 8-22 that is absent from the Mrg-cluster$\Delta^{-/-}$ mouse, these findings suggest that the pain inhibitory effect of BAM 8-22 is mediated by Mrg signaling, most likely MrgC11, in mice. Although MrgC may be the major receptor for BAM 8-22 [2,15,17], and BAM 8-22 at the spinal site might inhibit neuropathic pain, it is critical to determine the specificity of these compounds for MrgC in pain inhibition. So far, information regarding the roles of MrgC in persistent pathological pain states is sparse and conflicting, and the therapeutic utility of MrgC ligands in neuropathic pain remains to be established. Effects of MrgC activation on afferent sensory neuronal responsiveness and spinal pain transmission are also largely unknown, leaving open the question of the underlying cellular and neurobiological mechanisms.

Altered Ca^{2+} activity in afferent sensory neurons is essential for peripheral neuronal sensitization [18,19]. High-voltage-activated (HVA) Ca^{2+} channels play an important role in the detection and transmission of nociceptive stimuli in DRG neurons and in neuropathic pain [19,20]. Opioids are known to inhibit HVA Ca^{2+} currents in DRG neurons; this inhibition leads to an attenuation of neuronal excitability and reduced excitatory neurotransmitter release. Intriguingly, BAM 8-22 inhibits HVA Ca^{2+} current in cells that express human MrgX1 [21]. Yet, whether BAM 8-22 inhibits HVA Ca^{2+} current specifically through activation of Mrgs has not been directly tested owing to the lack of Mrg-deficient neurons. Furthermore, whether BAM 8-22 can activate endogenously expressed MrgC on native rodent DRG neurons to inhibit HVA Ca^{2+} currents

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has not been tested. Although recent studies demonstrated that MrgC ligands may function as anti-hyperalgesic agents at the spinal level, direct physiological proof of a role for MrgC in neuropathic pain is lacking. Functional and mechanistic studies are needed to elucidate details of an MrgC-mediated pain-inhibitory mechanism. Such studies could open doors that could lead to identification of a new pain-specific treatment target for neuropathic pain and development of mechanism-based pain treatment strategies.

References

1. Dong X, Han S, Zylka MJ, Simon MI, Anderson DJ (2001) A diverse family of GPCRs expressed in specific subsets of nociceptive sensory neurons. Cell 106: 619-632.
2. Lembo PM, Grazzini E, Groblewski T, O'Donnell D, Roy MO, et al. (2002) Proenkephalin A gene products activate a new family of sensory neuron--specific GPCRs. Nat Neurosci 5: 201-209.
3. Grazzini E, Puma C, Roy MO, Yu XH, O'Donnell D, et al. (2004) Sensory neuron-specific receptor activation elicits central and peripheral nociceptive effects in rats. Proc Natl Acad Sci U S A 101: 7175-7180.
4. Zylka MJ, Dong X, Southwell AL, Anderson DJ (2003) Atypical expansion in mice of the sensory neuron-specific Mrg G protein-coupled receptor family. Proc Natl Acad Sci U S A 100: 10043-10048.
5. Zhang L, Taylor N, Xie Y, Ford R, Johnson J, et al. (2005) Cloning and expression of MRG receptors in macaque, mouse, and human. Brain Res Mol Brain Res 133: 187-197.
6. Hager UA, Hein A, Lennerz JK, Zimmermann K, Neuhuber WL (2008) Morphological characterization of rat Mas-related G-protein-coupled receptor C and functional analysis of agonists. Neuroscience 151: 242-254.
7. Cai M, Chen T, Quirion R, Hong Y (2007) The involvement of spinal bovine adrenal medulla 22-like peptide, the proenkephalin derivative, in modulation of nociceptive processing. Eur J Neurosci 26: 1128-1138.
8. Cai Q, Jiang J, Chen T, Hong Y (2007) Sensory neuron-specific receptor agonist BAM8-22 inhibits the development and expression of tolerance to morphine in rats. Behav Brain Res 178: 154-159.
9. Hong Y, Dai P, Jiang J, Zeng X (2004) Dual effects of intrathecal BAM22 on nociceptive responses in acute and persistent pain--potential function of a novel receptor. Br J Pharmacol 141: 423-430.
10. Zeng X, Huang H, Hong Y (2004) Effects of intrathecal BAM22 on noxious stimulus-evoked c-fos expression in the rat spinal dorsal horn. Brain Res 1028: 170-179.
11. Chen T, Hu Z, Quirion R, Hong Y (2008) Modulation of NMDA receptors by intrathecal administration of the sensory neuron-specific receptor agonist BAM8-22. Neuropharmacology 54: 796-803.
12. Basbaum AI (1999) Distinct neurochemical features of acute and persistent pain. Proc Natl Acad Sci U S A 96: 7739-7743.
13. Julius D, Basbaum AI (2001) Molecular mechanisms of nociception. Nature 413: 203-210.
14. Kunapuli P, Lee S, Zheng W, Alberts M, Kornienko O, et al. (2006) Identification of small molecule antagonists of the human mas-related gene-X1 receptor. Anal Biochem 351: 50-61.
15. Liu Q, Tang Z, Surdenikova L, Kim S, Patel KN, et al. (2009) Sensory neuron-specific GPCR Mrgprs are itch receptors mediating chloroquine-induced pruritus. Cell 139: 1353-1365.
16. Guan Y, Liu Q, Tang Z, Raja SN, Anderson DJ, et al. (2010) Mas-related G-protein-coupled receptors inhibit pathological pain in mice. Proc Natl Acad Sci U S A 107: 15933-15938.
17. Han SK, Dong X, Hwang JI, Zylka MJ, Anderson DJ, et al. (2002) Orphan G protein-coupled receptors MrgA1 and MrgC11 are distinctively activated by RF-amide-related peptides through the Galpha q/11 pathway. Proc Natl Acad Sci U S A 99: 14740-14745.
18. Ikeda H, Stark J, Fischer H, Wagner M, Drdla R, et al. (2006) Synaptic amplifier of inflammatory pain in the spinal dorsal horn. Science 312: 1659-1662.
19. Callaghan B, Haythornthwaite A, Berecki G, Clark RJ, Craik DJ, et al. (2008) Analgesic alpha-conotoxins Vc1.1 and Rg1A inhibit N-type calcium channels in rat sensory neurons via GABAB receptor activation. J Neurosci 28: 10943-10951.
20. Altier C, Zamponi GW (2004) Targeting Ca2+ channels to treat pain: T-type versus N-type. Trends Pharmacol Sci 25: 465-470.
21. Chen H, Ikeda SR (2004) Modulation of ion channels and synaptic transmission by a human sensory neuron-specific G-protein-coupled receptor, SNSR4/mrgX1, heterologously expressed in cultured rat neurons. J Neurosci 24: 5044-5053.

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Top

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