综　述

鞘内激活MrgC受体在病理性疼痛和吗啡耐受中的作用

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摘 要：啮齿类动物的MrgC受体(Mas-related G-protein-coupled receptor subtype C)与人类Mas相关基因X受体1 (human Mas-related gene X receptor 1, hMrgX1)享有65%的同源序列和相似的表达模式以及结合谱，因此学者一般通过研究MrgC受体的功能来探索hMrgX1的作用。MrgC受体属于G蛋白耦联受体家族的一员，特异性地表达在背根神经节(dorsal root ganglion, DRG)和三叉神经节(trigeminal ganglion, TG)的小直径神经元上，与痛觉的传递过程密切相关。本文综述了鞘内激活MrgC受体在病理性疼痛和吗啡耐受中的镇痛作用。

关键词：人类Mas相关基因X受体1；MrgC受体；背根神经节；脊髓背角；病理性疼痛；吗啡耐受
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Involvement of intrathecal activation of MrgC receptor in pathological pain and morphine tolerance

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Abstract: Rodent MrgC receptor (Mas-related G-protein-coupled receptor subtype C) shares 65% sequence homology and similarities in terms of expression pattern and binding profile with human Mas-related gene X receptor 1 (hMrgX1). Therefore, researchers generally explore the role of hMrgX1 by studying the function of MrgC receptor. Murine MrgC receptor is uniquely expressed in small-diameter neurons of dorsal root ganglia (DRG) and trigeminal ganglia (TG), which is closely related to the transmission process of pain. This review summarizes the analgesic effects of intrathecal activation of MrgC receptors in pathological pain and morphine tolerance.

Key words: human Mas-related gene X receptor 1; Mas-related G-protein-coupled receptor subtype C; dorsal root ganglion; spinal dorsal horn; pathological pain; morphine tolerance

1 MrgC受体

人类 Mas 相关基因 X 受体 (human Mas-related gene X receptors, hMrgXs) 具有四个亚型 (hMrgX1~4)，属于 G 蛋白耦联受体 (G-protein-coupled receptors, GPCRs) 超家族 [1]。在这四个亚型中，人们对 hMrgX1 和 hMrgX2 较为熟悉。其中 hMrgX1 特异性地表达在背根神经

节 (dorsal root ganglia, DRG) 和三叉神经节 (trigeminal ganglia, TG) 的小直径神经元 [1, 2]，这些神经元是疼痛信息传入的第一级神经元 [3]。为了阐明 hMrgX1 的功能，学者将该受体异源表达于大鼠离体培养的不同神经元中 [4]，结果显示 hMrgX1 可与 $G_{q/11}$ 或 $G_{i/o}$ 耦联，激活后显著抑制高电压激活 (high voltage-activated, HVA) 钙离子通道、M 型钾离子通道以及

突触传递[4]，提示类似过程如果存在于人体中，hMrgX1 将可能调节疼痛过程。

小鼠和大鼠的 MrgC 受体 (Mas-related G-protein-coupled receptor subtype C) 与 hMrgX1 享有 65% 的同源序列和相似的表达模式以及结合谱[1, 2, 5, 6]。同样的，MrgC 受体也是 GPCRs 的一员，该受体也特异性地分布于 DRG 和 TG 小直径神经元，因而该受体曾被称为感觉神经元特异性受体 (sensory neuron-specific receptors, SNSRs)。放射性配体结合实验和免疫组织化学研究表明，MrgC 受体在胞体合成后一部分转运到初级神经元外周端，一部分转运到脊髓背角浅层 (初级神经元中枢端)[6–9]，从而与脊髓背角浅层多个突触后神经元联系。有趣的是，初级神经元外周端和脊髓背角浅层都是接受、传递疼痛信息的重要区域，这提示了 MrgC 受体在感觉 (痛觉、痒觉) 中具有重要作用。

牛肾上腺髓质 8-22 肽 (bovine adrenal medulla peptide 8-22, BAM8-22)[2, 10]、Tyr6-2-MSH-6-12[2, 5] 和 JHU58[11] 是 MrgC 受体的特异性激动剂。研究显示，在正常生理状态下，大鼠足底注射 MrgC 受体激动剂 (外周端激活) 会降低热痛阈和机械痛阈[6]，人手臂注射 MrgC 受体激动剂 (外周端激活) 则以独立于组胺的方式诱导瘙痒[12]，但是正常生理状态下大鼠鞘内注射 MrgC 受体激动剂 (中枢端激活) 不影响动物对伤害性化学刺激或热刺激的反应[13]；其次，正常生理状态下敲除 MrgC 基因[10]、或干扰 MrgC mRNA 也不改变动物对伤害性化学刺激或热刺激的反应[14]。即，在正常生理状态下外周端激活 MrgC 受体诱导疼痛、瘙痒行为，而在正常生理状态下中枢端激活 MrgC 受体或者是敲除、干扰 MrgC 受体不影响大鼠正常痛反应。但是在病理状态下，中枢端激活 MrgC 受体参与痛觉的处理，抑制炎性介质的释放，阻断伤害性刺激信号的传递，最终发挥镇痛作用。例如鞘内注射 BAM8-22 后通过抑制 c-Fos 和一氧化氮合酶 (nitric oxide synthetase, NOS) 减轻 *N*- 甲基 -*D*- 天冬氨酸受体 (*N*-methyl-*D*-aspartic acid receptor, NMDA) 诱发的大鼠疼痛行为[15]；病理状态下敲除 MrgC 基因则阻断 BAM8-22 在炎性痛和神经病理性疼痛中的镇痛作用[10]。

2　鞘内激活MrgC受体在病理性疼痛中发挥镇痛作用

炎性痛、神经病理性疼痛和癌性痛都属于病理性疼痛。目前用于治疗病理性疼痛主要有阿片、精神类药物、电针刺激、微创介入等药物和治疗手段，但是治疗效果往往不如人意，并且会带来较严重的副作用，因此寻找组织特异性表达的镇痛药物靶点，是解决当前镇痛药物普遍存在复杂不良反应的重要途径。MrgC 受体限制性地分布于外周神经系统，不会引起类似吗啡的中枢副作用，因此可作为独特的药用靶点来治疗病理性疼痛和吗啡耐受。

2.1　鞘内激活MrgC受体在神经病理性疼痛中发挥镇痛作用

DRG 小型神经元中的 N 型 HVA 钙电流对 DRG 神经元持续性放电和伤害性介质的释放具有重要作用，是外周致敏的关键参与者，具有放大疼痛信号的作用[16–18]。N 型钙通道可以被不同的 G 蛋白依赖性通路调节[19–21]。L5 脊神经结扎 (spinal nerve ligation, SNL) 小鼠 N 型钙通道表达增加[22]。SNL 小鼠鞘内给予 JHU58 激活 MrgC 受体，活化的 MrgC 受体通过耦联 $G_{\alpha q/11}$ 蛋白激活磷脂酶 C (phospholipase C, PLC)，稳定 N 型钙通道的失活状态，从而抑制钙通道的过量表达[23, 24]。N 型钙通道的抑制减少了 DRG 神经冲动的产生、传导以及神经递质的释放，形成信号传导抑制，最终减少 DRG 神经元中枢突末梢兴奋性神经递质的释放，阻止了伤害性信息向脊髓背角的传递[24]，疼痛信号传递受阻，从而介导镇痛。除了 N 型钙通道，Li 等[24]采用全细胞膜片钳技术对鞘内注射 JHU58 的成年 SNL 小鼠离体 DRG 施用高强度 (该强度能够刺激 C 纤维) 双脉冲刺激，并记录投射到脊髓薄片胶状质层的神经元中由 C 纤维诱发的兴奋性突触后电流 (evoked excitatory postsynaptic current, eEPSC) 的变化情况，结果显示，鞘内施用 JHU58 降低了 SNL 小鼠脊髓胶状质层神经元中 C 纤维诱发的 eEPSC 幅度，阻断了对 DRG 进行双脉冲刺激而产生的兴奋向背角神经元的传递。该研究结果表明 MrgC 受体能够通过突触前机制 (即减少外周初级传入神经元向脊髓伤害性信息的输入) 发挥镇痛作用。与此相一致的是，He 等[11]研究显示，敲除 MrgC 基因、鞘内注射 MrgC siRNA (small interfering RNA) 或鞘内注射 MrgC 抗体可在小鼠上消除 JHU58 诱导的镇痛作用[11]。

MrgC 受体的镇痛作用还涉及到对小胶质细胞和星形胶质细胞的抑制。小胶质细胞主要在疼痛的早期被激活，参与疼痛的产生[25, 26]，而星形胶质细胞主要在疼痛的晚期被激活，参与疼痛的维持[27]。

活化的小胶质细胞[28]和星形胶质细胞[29]释放炎性因子，提高脊髓的兴奋性，加剧脊髓痛敏的形成。大鼠鞘内给予 BAM8-22 激活 MrgC 受体抑制小胶质细胞和星形胶质细胞的活化[30, 31]，它们释放的炎性因子随之减少，小胶质细胞和星形胶质细胞间正循环反馈减弱[32](即小胶质细胞和星形胶质细胞能够促进彼此释放炎性介质的作用减弱)，脊髓兴奋性降低，最终达到了镇痛的效果。

综上，我们可知，在神经病理性疼痛中，鞘内激活 MrgC 受体分别从外周端和中枢端起到了镇痛作用。

2.2 鞘内激活MrgC受体在炎性痛中发挥镇痛作用

完全弗氏佐剂 (complete Freunds adjuvant, CFA) 炎性痛大鼠脊髓背角 G_q 蛋白表达量上调[33]，激活其下游的蛋白激酶 Cγ (protein kinase Cγ, PKCγ)，活化的 PKCγ 从胞浆转移到胞膜[34, 35]，增强脊髓背角微小兴奋性突触后电流 (miniature excitatory postsynaptic currents, mEPSCs) 和 c-Fos 的表达[36]，促进脊髓的敏化。鞘内给予 BAM8-22 后，膜上 G_q 蛋白的表达减少[33]，该信号通路受到抑制，导致依赖 G_q 通路激活的 PKCγ 不能移位到膜上，PKCγ 下游的疼痛信号传递受到抑制，mEPSCs 的强度下降, c-Fos 的表达降低，背角神经元兴奋性降低[33]。与 G_q 蛋白不同的是，虽然足底注射 CFA 不改变脊髓背角 G_i 蛋白的表达量[33]，但是 MrgC 受体也能通过耦联 G_i 蛋白[37]进而抑制腺苷酸环化酶 (adenylate cyclase, AC) 的表达，导致胞内第二信使环磷酸腺苷 (cyclic adenosine monophosphate, cAMP) 浓度下降，胞内的炎性介质降钙素基因相关肽 (calcitonin gene related peptide, CGRP) 和 NOS 水平下调，细胞的兴奋性降低，痛敏现象显著下降[38]。CFA 注射 24 h 后脊髓背角和 DRG 的细胞外调节蛋白激酶 (extracellular regulated protein kinases, ERK) 磷酸化增加[33]，ERK 通路被激活，释放炎性因子，促进外周[39, 40]和中枢[41, 42]敏化。鞘内激活 MrgC 受体，背角神经元和 DRG ERK 磷酸化减少，ERK 调制的基因转录不能进行，使得该通路中神经激肽 -1 (neurokinin-1, NK1)、c-Fos 等炎性介质合成减少，背角神经元和 DRG 敏感性降低，从而起到镇痛的作用[33]。

在 CFA 大鼠中，MrgC 受体通过激活 G_i 蛋白通路、抑制 G_q 蛋白通路以及 ERK 信号通路的激活缓解 CFA 炎性痛；其次，在 CFA 炎性痛大鼠模型的 DRG 神经细胞中，MrgC mRNA 表达量增加，MrgC

受体的上调能够使激动剂具有更大的生物活性，从而发挥更强烈的镇痛作用[43]。

以往的研究表明，BAM8-22 和 MSH 在给药后立即发挥作用[10, 15, 44]，并在 10~30 min 内降解[6]。有趣的是，CFA 炎性大鼠鞘内给予 BAM8-22 或 MSH 后 24 和 48 h 也观察到痛觉过敏减轻的现象[43]，这种现象主要是因为激活 MrgC 受体可提高 DRG 神经元和脊髓中阿片受体 mRNA、DRG 神经元中前阿黑皮 mRNA 和脊髓中 β- 内啡肽 (β-endorphin) 的表达水平，这些抑制性分子表达上调有利于减轻疼痛，从而表现出延迟抗痛觉过敏[43]。

与其它病理性疼痛 (癌性痛、神经病理性疼痛等) 不同的是，鞘内激活 MrgC 受体不会影响 CFA 大鼠的机械痛阈，但是能够减轻热痛觉过敏，提高热痛阈[43]。这可能和 CFA 炎性痛模型机械痛敏、热痛敏发生机制不同有关[45, 46]，具体机制仍需更深入的研究和探索。

2.3 鞘内激活MrgC受体在癌性痛中发挥镇痛作用

骨癌痛 (bone cancer pain, BCP) 主要是由于肿瘤细胞侵蚀骨组织，压迫骨神经造成的慢性痛。BCP 大鼠背角神经元 MrgC 受体、G_i 和 NR2B 及 nNOS 表达上调[47, 48]。NR2B 通过调控突触可塑性导致中枢敏化[49]，加剧 BCP。NR2B 在突触后膜激活 NOS，活化的 NOS 释放一氧化氮 (NO)，增加突触兴奋性，有利于 BCP 的维持[50, 51]。鞘内给予 BAM8-22 激活 MrgC 受体，活化的 MrgC 受体耦联 G_i 蛋白，下调 NR2B、nNOS 表达量，使疼痛得到抑制[47]。与此相一致的是，Sun 等[47]的研究显示，鞘内注射 BAM8-22 2 h 后显著减少了 BCP 小鼠自发性抬脚次数，并提高了缩足阈值。由此我们可知，BCP 小鼠中 MrgC 受体通过 G_i-NR2B-nNOS 信号转导通路分别在细胞学水平和行为学水平起到了抗伤害的作用。

镜像疼痛是指未受损侧相应部位表现出机械超敏的现象[52]，BCP 也伴随镜像痛。与患侧相反的是，鞘内注射 BAM8-22 对健侧产生的镜像痛却没有显著的影响，这可能是由于 BCP 和镜像疼痛之间不同的发生机制导致的，但是具体原因仍然不清楚[53]。其次，直到目前，鞘内激活 MrgC 受体在 BCP 中的镇痛作用研究相对较少，除了与 G_i-NR2B-nNOS 信号通路有关外，不清楚是否还通过其他因子起作用。例如鞘内激活 MrgC 受体是否会通过抑制 P 物质、c-Fos 等炎性因子在 BCP 中发挥镇痛作用？这些都是将来研究的方向。

3 鞘内激活MrgC受体抑制吗啡耐受

目前临床上用于治疗疼痛的主要药物还是以吗啡为代表的阿片类药物[54]，但是长期使用会产生耐药性，而剂量的增加会引起严重的中枢副作用，例如便秘、恶心、呕吐、抑郁、呼吸困难等[55–58]，若能降低吗啡的耐药性和副作用，将大大扩展其在临床的应用范围。

吗啡主要是通过激活阿片受体中的 μ 阿片受体亚型发挥镇痛作用[59]。μ 阿片受体通过与 $G_{i/o}$ 蛋白耦联，抑制下游 AC[60] 和钙离子通道[61, 62]，从而阻止伤害信息传递。长期使用吗啡减少 μ 阿片受体与 $G_{i/o}$ 蛋白耦联，促进 μ 阿片受体与 G_S 蛋白耦联[63]，激活兴奋性信号通路，释放炎性介质，对抗吗啡的镇痛效力，产生耐受[64]，而活化 MrgC 受体能降低 μ 阿片受体的耐药性。MrgC 受体和 μ 阿片受体在 DRG 神经元中大量共表达，形成异源复合物，并通过其 C 端结构域 (C-terminal domain, CTD) 与 μ 阿片受体相互作用[65]。鞘内注射 BAM8-22 激活 MrgC 受体，诱导 MrgC 受体和 μ 阿片受体的共同内吞作用，避免神经元持续性兴奋或者过度活动，并促进 MrgC 受体和 μ 阿片受体进入循环通路，重新插到质膜上[65]，恢复 μ 阿片受体激活 G_i 蛋白的能力[64, 65]。此外，MrgC 受体与吗啡联合使用时，可以显著抑制 DRG 中辣椒素引起的胞内钙离子浓度增加，而在 MrgC 基因敲除的小鼠 DRG 中，吗啡对 DRG 神经元中钙离子浓度的降低作用显著受抑[65]。

慢性应用吗啡导致脊髓背角浅层谷氨酸转运体 [谷氨酸转运体 1 (glutamate transporter 1, GLT-1)、谷氨酸 / 天冬氨酸转运体 (glutamate/aspartate transporter, GLAST) 和兴奋性氨基酸载体 1 (excitatory amino acid carrier 1, EAAC1)] 表达减少[66]，鞘内应用 BAM8-22 或者 MSH 激活 MrgC 受体可上调脊髓背角谷氨酸转运体，降低细胞间隙谷氨酸浓度，细胞兴奋性降低，从而抑制吗啡耐受[67]。除谷氨酸外，活化的 MrgC 受体还能抑制吗啡耐受诱导的 DRG
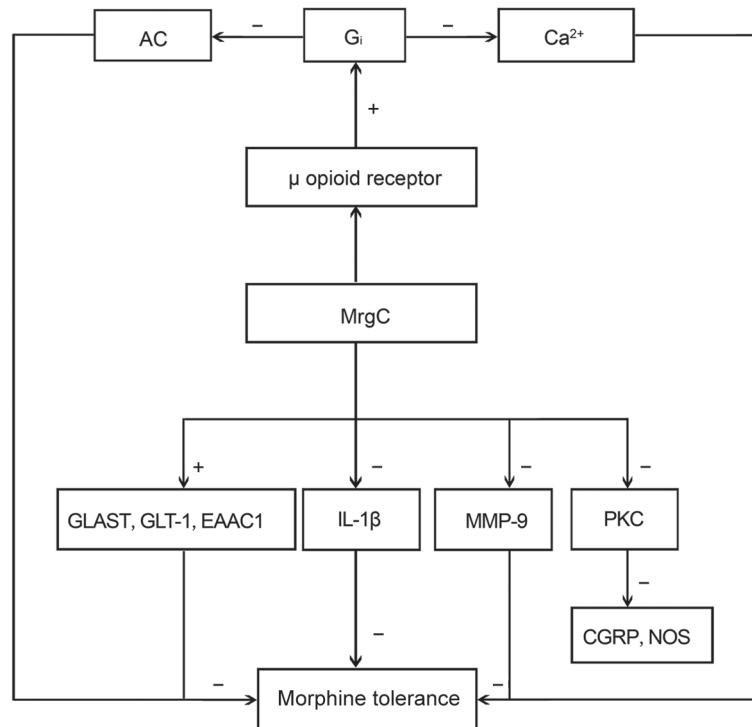

图 1. 鞘内激活MrgC受体抑制吗啡耐受的机制示意图

Fig. 1. Diagrammatic sketch showing the mechanism of inhibition of morphine tolerance by intrathecal activation of MrgC receptor. MrgC receptor interacts with the μ opioid receptor, promotes μ opioid receptor to activate G_i protein, and reduces expression of the adenylate cyclase (AC) and $[Ca^{2+}]$. At the same time, MrgC receptor up-regulates expression of glutamate transporter 1 (GLT-1), excitatory amino acid carrier 1 (EAAC1) and glutamate/aspartate transporter (GLAST), and down-regulates expression of matrix metalloproteinase 9 (MMP-9), interleukin-1β (IL-1β), calcitonin gene related peptide (CGRP) and nitric oxide synthetase (NOS). Plus and minus signs represent promotion and inhibition, respectively.

神经元中基质金属蛋白酶 9 (matrix metalloproteinase 9, MMP-9) 和白细胞介素 1β (interleukin-1β) 表达的增加 [68]；并通过 PKC 途径下调 DRG 和脊髓背角 CGRP、nNOS 表达水平 [69]。通过以上路径，MrgC 受体实现部分延缓甚至翻转吗啡耐受 (图 1)。

4 展望

　　近年来，学者们已经研发出若干种 MrgC 受体的配体，但主要是应用"反向药理学"的方法，所采用的化合物库也是已发现的一些神经肽，这样必然使其候选配体的种类限定在一定的范围之内；其次，直到目前，该受体的拮抗剂还没有研发出来。以上种种限制了我们对 MrgC 受体生理药理活性的认识。未来的研究可以采用反向药理学和生物信息学相结合等方法，进一步探索该受体三维结构、特异性结合位点、拮抗剂以及其它种类激动剂，期待未来能够全面彻底地认识 MrgC 受体的镇痛机理，以便开发出以 hMrgX1 为镇痛靶点治疗临床病理性疼痛和吗啡耐受的新药物。

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