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·综述·

AMPARs参与调控口颌面部疼痛的研究进展

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【摘要】 口颌面部疼痛的发病率高且病理机制复杂。目前临床缺乏持久有效的治疗药物，给患者及社会带来巨大的经济负担。因此，研发更加持久有效的治疗药物具有重要意义。近年来，大量证据表明α-氨基-3-羟基-5-甲基-4-异恶唑丙酸受体(α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors，AMPARs)的激活在促进躯体和口颌面部疼痛中起着至关重要的作用。其中，蛋白激酶调节亚基磷酸化及辅助蛋白相互作用等促进AMPARs的激活与转运和信号转导，从而调控AMPARs的表达。含GluA1的AMPARs的增加可促进钙离子内流，进一步激活蛋白激酶及辅助蛋白，形成自反馈环，这是促进慢性疼痛的重要机制。其次，AMPARs在三叉神经系统与脊髓神经系统中表达类似，上述调控也可参与调控口颌面部炎性疼痛。然而，在口颌面部神经病理性疼痛、癌性疼痛中AMPARs的调控研究相对不足，未来需要更深入的研究。此外，AMPARs拮抗剂治疗疼痛尚缺乏临床证据。了解AMPARs的激活与转运的调控机制，精准干预AMPARs的激活与转运，可为研发新型镇痛药提供有效策略，从而为临床上治疗口颌面部疼痛提供新思路。

【关键词】 口颌面部疼痛；　α-氨基-3-羟基-5-甲基-4-异恶唑丙酸受体；　结构特征；　激活与转运；　蛋白激酶；　磷酸化；　蛋白互作；　拮抗剂
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Research progress on AMPARs involved in regulating orofacial pain

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【Abstract】 The incidence of orofacial pain is high, and its pathological mechanism is complex. Currently, there is a lack of long-lasting and effective clinical treatment drugs, resulting in a major economic burden to patients and society. Therefore, it is important to develop more durable and effective drugs for treatment. In recent years, substantial evidence has shown that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) play a vital role in somatic and orofacial pain. Among them, subunit phosphorylation regulated by protein kinases and interactions with partner proteins promote the activation and trafficking of AMPARs and signal transduction to regulate the expression of AMPARs. The increase of GluA1-containing AMPARs promotes calcium ion influx, further activating protein kinases and auxiliary proteins, which forms a self-feedback loop. This is an important mechanism that promotes chronic pain. The expression of AMPARs in the trigeminal nervous system and the spinal cord nervous system overlaps, and the above mechanism may also participate in regulating orofacial pain. However, research on AMPARs in orofacial neuropathic pain or cancer-related pain is relatively insufficient, and more in-depth research is needed in the future. Furthermore, there is a lack of clinical evidence for AMPAR antagonists to treat pain. Understanding the regulatory mechanisms of the activation and trafficking of AMPARs and precisely intervening in the activation and trafficking of AMPARs may provide effective strategies for the development of new analgesics and offer new insights for treating orofacial pain.

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【Key words】 orofacial pain; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; structure; activation and trafficking; protein kinase; phosphorylation; protein interaction; antagonist
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口颌面部疼痛主要包括牙槽骨和解剖学相关组织的疼痛、肌肉疼痛、颞下颌关节疼痛、影响脑神经的神经病理性疼痛、类似原发性头痛的疼痛以及口颌面部区域的特发性疼痛[1]。口颌面部疼痛发病机制复杂，目前缺乏持久有效的临床治疗药物，患者生活质量较差，给社会和患者带来巨大经济负担[2]。α-氨基-3-羟基-5-甲基-4-异恶唑丙酸受体（α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors，AMPARs）是一种离子型谷氨酸受体，其经典的生物学功能是在神经系统中调控快速兴奋性突触传递，其表达和功能失调可导致多种疾病的发生[3]。近年来，众多研究报道了AMPARs在躯体和口颌面部疼痛的外周和中枢敏化机制中的重要作用[4-5]。在成人大脑及脊髓中，AMPARs主要由GluA1和GluA2亚基组成[5]。因此，本文对在疼痛相关调控区域内，含GluA1和GluA2的AMPARs的激活与转运、相关调节机制，以及其在口颌面部疼痛中的作用和拮抗剂的最新研究进展作综述。

1　AMPARs的结构特征

AMPARs是由GluA1-4亚基组装而成的同质或异质四聚体。每个亚基包括四个结构域：细胞外N端结构域（N-terminal domain，NTD，也称为氨基末端结构域）、配体结合结构域（ligand binding domain，LBD）、跨膜结构域（transmembrane domain，TMD）和细胞内侧的C端结构域（C-terminal domain，CTD）[6]。NTD驱动受体组装和锚定，是谷氨酸神经递质的结合位点[7]。LBD主序列是由“S1”（部分N端）和“S2”（C端回路）组成，其包含双叶结构并在叶间隙与配体结合，影响通道的开闭[8]。TMD包含三个跨膜螺旋（M1，M3和M4）和一个膜再入环（M2）。GluA2亚基在M2结构的顶点可发生mRNA的Q/R编辑，导致带正电的精氨酸（R）取代谷氨酰胺（Q），赋予GluA2亚基对钙离子的不可透性。因此，含有未编辑的GluA2或缺乏GluA2的AMPARs具有Ca^{2+}通透性，而含已编辑的GluA2（R）的AMPARs则对Ca^{2+}不可透性。由于99%以上的GluA2经过编辑，在缺乏GluA2的情况下，将GluA1组成的AMPARs称为钙可透性AMPARs（Ca^{2+}-permeable AMPARs，CP-AMPARs）。将含有GluA2的AMPARs称为钙不可透性AMPARs（Ca^{2+}-impermeable AMPARs，CI-AMPARs），其对多胺类通道阻滞剂不敏感[6]。C端结构域包含多个磷酸化位点和蛋白结合基序，可与亚基特异性蛋白相互作用，参与调节AMPARs的转运[9]。综上，AMPARs的结构影响了受体的亲和力、离子渗透性、受体激活与转运，使不同亚基组成的受体具有独特的功能特性。

2　AMPARs的激活与转运促进慢性疼痛

外周和中枢神经系统内AMPARs的激活与转运可以促进慢性疼痛的发生和发展。AMPARs的转运包括细胞内运输、胞吞或胞吐、横向扩散、回收和降解等，在生理条件下，突触后AMPARs的数量和组成处于动态平衡，这种平衡可以因神经元或突触活动而改变[10]。组织炎症或神经损伤等刺激可以引起轴突末端谷氨酸过度释放或N-甲基-D-天冬氨酸受体（N-methyl-D-aspartate receptors，NMDARs）过度激活，促进Ca^{2+}内流，导致疼痛调控区域内AMPARs的激活并发生转运，破坏其动态平衡并改变离子通透性，从而促进中枢和周围神经系统中细胞的兴奋性毒性[11-13]。进一步研究发现，神经或炎性损伤引起脊髓背角（dorsalhorn，DH）AMPARs亚基GluA1和GluA2的亚细胞分布有所改变。如大鼠脊神经结扎（spinal nerve ligation，SNL）和瑞芬太尼注射都可以增加大鼠DH神经元胞膜GluA1表达，从而促进脊髓痛觉敏化，这可以被NASPM（CP-AMPARs的拮抗剂）抑制[14-15]，这提示含GluA1的AMPARs膜插入参与疼痛的病理过程。此外，糖尿病神经病理性病变引起DH神经元胞膜的GluA2蛋白水平下降，而胞质内GluA2蛋白水平上升[16]，并且阻断CP-AMPARs或抑制GluA2内吞作用可以缓解神经损伤引发的疼痛过敏[16-17]。

上述研究表明，神经或炎性损伤促进脊髓神经元胞膜表面AMPARs的转运，即含GluA1的AMPARs的膜插入和含GluA2的AMPARs的膜内化，使细胞膜AMPARs从CI-AMPARs向CP-AMPARs转换。通过记录AMPARs介导的电流，进一步证实这种改变有助于慢性疼痛发展[18]。肿瘤细胞植入诱导P-Rex2（Rac特异性鸟嘌呤核苷酸交换因子）介导的AMPARs的磷酸化增加，使背角神经元中AMPARs介导的电流增加，从而促进骨癌痛觉过敏，表明AMPARs的激活与转运也参与癌性疼痛[19]。上述研究表明AMPARs的激活与转运引起其组成变化，可以调控神经系统兴奋性和可塑性，从而促进疼痛信号的传递。

3　AMPARs激活与转运的调控机制

3.1　亚基的磷酸化修饰

AMPARs亚基的C端包含多种蛋白激酶的磷酸化位点和支架蛋白的结合基序，这些磷酸化位点影响AMPARs的电生理特性、亚单位组成、突触表达，是神经系统突触可塑性和疼痛调节的重要机制[20]。伤害性感受信号可激活多种蛋白激酶，如钙离子/钙调素依赖的蛋白激酶Ⅱ（Ca^{2+}/calmodulin-dependent protein kinases Ⅱ，CaMKⅡ）、蛋白激酶A（protein kinase A，PKA）、蛋白激酶C（protein kinase C，PKC）等，从而引发细胞内级联反应。CaMKII和PKC可以使GluA1的Ser831位点磷酸化[20]，并且在跨膜AMPAR调节蛋白（transmembrane AMPAR regulatory proteins，TARPs）存在下，可增加同聚体GluA1和GluA1/GluA2异聚体的电导，并调节受体转运[21-22]。PKA引起GluA1亚基Ser845位点磷酸化，增加AMPARs通道的打开概率及其电流峰值，并且稳定质膜中的GluA1，从而增强含有GluA1的AMPARs与突触膜的结合[23]。除了Ser831和Ser845外，PKC对Ser818位点的磷酸化既可增加AMPARs的单通道电导，又促进GluA1转运和突触结合[20]，这些亚基的磷酸化可以调控受体转运和功能，进而参与调节神经系统突触可塑性和慢性疼痛的持续。

含有GluA2的AMPARs的内化是疼痛过敏的机制基础。PKC可以调控GluA2在Ser880位点的磷酸化并引发细胞内级联反应，导致GluA2从突触内化，从而促进疼痛的持续[24]。其中，GluA2亚基Ser880的磷酸化可以破坏受体与AMPAR结合蛋白（AMPAR-binding protein，ABP）/谷氨酸受体相互作用蛋白（glutamate receptor-interacting protein，GRIP）的结合，导致CI-AMPARs向CP-AMPARs转换。CP-AMPARs具有Ca^{2+}可透性，可促进细胞内钙离子累积，进一步促进胞内级联反应，形成正反馈，从而促进慢性疼痛。

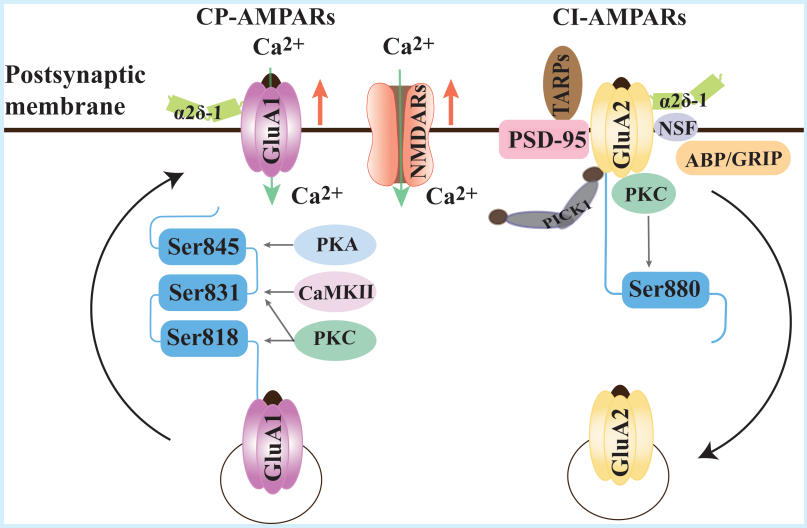
除了CaMKII、PKA及PKC，其他胞内信号通路也可以调节AMPARs转运。例如，瑞芬太尼注射激活P2X4嘌呤能受体通过脑源性神经营养因子（brain-derived neurotrophic factor，BDNF）/酪氨酸受体激酶B（Tyrosine kinase receptor B，TrkB）通路[12]、角叉菜胶注射激活磷脂酰肌醇3-激酶（phosphatidylinositol 3-kinase，PI3K）和PKA依赖性肿瘤坏死因子受体1（tumor necrosis factor receptor 1，TNFR1）通路等[25]，都可促进DH神经元上含GluA1的AMPARs表达增加。以上结果为开发AMPARs特异性磷酸化位点或胞内级联反应信号分子的选择性阻滞剂提供潜在干预靶点。

3.2　蛋白相互作用

许多辅助蛋白通过影响AMPARs突触表达来调控疼痛。最显著的是TARPs，典型的有Stargazin和γ-8。其包含在复合物中影响AMPARs的药理学和动力学，并调节亚基的转运[26]；谷氨酸受体相互作用蛋白（Glutamate receptor interacting protein，GRIP）参与AMPARs的插入和稳定；与C激酶1相互作用的蛋白（protein interacting with C kinase 1，PICK1）参与AMPARs内化和锚定[26]；突触后密度蛋白-95与Stargazin相互作用，从而参与突触AMPARs的稳定；N-乙基马来酰亚胺敏感性融合蛋白（N-ethylmaleimide-sensitive fusion protein，NSF）从PICK1-GluA2复合物中取代PICK1，从而促进GluA2在质膜上的传递或稳定[27]，上述辅助蛋白均参与慢性疼痛[27-28]。如前所述，GluA2的磷酸化会进一步减少GluA2对GRIP的结合力，从GRIP-GluA2复合物中释放GluA2，最终导致GluA2亚基的内化的正反馈，促进疼痛的持续。除了上述辅助蛋白，电压门控钙通道α2δ-1也可以通过与AMPARs的C末端与GluA1和GluA2相互作用，增加GluA2在内质网中的保留，以增强DH突触后CP-AMPARs，从而促进神经病理性疼痛[30]。总之，AMPARs与辅助蛋白的相互作用参与转运、内化和表面表达等，均与突触传递和疼痛持续有关（图1）。

4　口颌面部疼痛中AMPARs的作用

与脊髓神经系统信息传递不全相同，口颌面



Under stimulating conditions such as tissue damage and inflammation, NMDARs on the postsynaptic membrane are activated to promote Ca^{2+} influx, which activates protein kinases such as PKC, CaMKII, PKA, etc., and induces the phosphorylation of GluA1 and GluA2 subunits. This process is also regulated by auxiliary proteins such as TARPs, PSD-95, PICK1, ABP/GRIP, NSF, α2δ-1, etc. The above mechanisms increase the trafficking of receptors and signal transduction, which results in a conversion of predominantly CI-AMPARs (calcium-impermeable) to CP-AMPARs (calcium-permeable) on the postsynaptic membrane. The increase of CP-AMPARs further promotes Ca^{2+} influx, thereby promoting the activation of protein kinases and auxiliary proteins. This forms a self-feedback loop and further promotes the increase of CP-AMPARs on the postsynaptic membrane, which is an important mechanism for chronic pain. CP-AMPARs: Ca^{2+}-permeable AMPARs; CI-AMPARs: Ca^{2+}-impermeable AMPARs; NMDARs: N-methyl-D-aspartate receptors; PKA: protein kinase A; CaMKII: Ca^{2+}/calmodulin-dependent protein kinases Ⅱ; PKC: protein kinase C; TARPs: transmembrane AMPAR regulatory proteins; PSD-95: postsynaptic density protein-95; PICK1: protein interacting with C kinase 1; NSF: N-ethylmaleimide-sensitive fusion protein; ABP: AMPAR-binding protein; GRIP: Glutamate receptor interacting protein

Figure 1　Molecular biological mechanisms of AMPARs mediating chronic pain

图1　AMPARs参与介导慢性疼痛的分子生物学机制

部的伤害性感觉信号由三叉神经节(trigeminal ganglion,TG)的神经元传入至位于延髓背角内的三叉神经脊束核尾侧亚核(spinal trigeminal nucleus caudalis,SpVc)后,与次级神经元形成突触后交叉至对侧上行至丘脑,进一步通过丘脑的三级神经元,向上投射至杏仁核、前扣带皮层、岛叶皮层等[31]。正常条件下,AMPARs表达在外周背根神经节、TG等神经元胞体及其轴突末梢;在中枢神经系统,如脊髓、延髓、大脑皮层、丘脑、小脑内的神经元和胶质细胞中也有表达。突触前和突触后质膜上均有AMPARs表达,突触前AMPARs可以调节各种神经递质的释放,突触后AMPARs的功能特性或丰度的变化可导致突触后神经元兴奋性变化[32]。

目前,许多研究证明AMPARs的激活与转运在口颌面部疼痛中起重要作用。在TG中,创伤性咬合可增加神经递质P物质、谷氨酸的释放及AMPARs的表达[33],提示AMPARs的激活参与口颌面部外周敏化。AMPARs的激活还参与口颌面部疼痛的中枢敏化。Currò等[34]证明在SpVc中三磷酸腺苷通过促进突触前AMPARs的激活,直接或间接介导谷氨酸的释放,进而参与慢性疼痛的中枢敏化。此外,SpVc中AMPARs的GluA1亚基磷酸化的上调可促进硝酸甘油(nitroglycerin,NTG)引起的偏头痛样疼痛,NASPM剂量依赖性地阻断NTG引起的培养神经元中Ca^{2+}内流的增加从而抑制NTG诱导的偏头痛样疼痛[35]。进一步研究AMPARs的亚细胞分布,发现SpVc中多巴胺D2受体通过PI3K信号通路,可以促进含GluA1的AMPARs膜蛋白表达增加,这有助于大鼠慢性偏头痛[36],证明含GluA1的AMPARs膜插入增加也有助于口颌面部疼痛。除了TG和SpVc,口颌面部的伤害性感觉信号传递至大脑皮层的相关区域,AMPARs的表达也发生变化[37]。

5　AMPARs拮抗剂和相关药物研发进展

AMPARs的激活与转运在口颌面部疼痛的发生和发展中起着重要作用,因此研发针对性调控AMPARs表达和功能的拮抗剂对研发治疗口颌面部疼痛的新型药物具有广阔前景。动物实验中最常使用的是竞争性拮抗剂CNQX(喹喔啉二酮衍生物),除AMPARs外还可以阻断NMDARs、红藻氨酸受体等。同一家族的还有NBQX,其水溶性欠佳,PNQX和YM872(zonampanel)更新的衍生物可作为备选。非竞争性拮抗剂GYKI-52466已被证明有镇

痛效果，同时也拮抗上述3个谷氨酸受体[38]。此外，吡仑帕奈已被证明对疼痛治疗有效，并且可以调节炎症[39]，此广谱、非竞争性拮抗剂已被FDA批准用于治疗癫痫，但临床用于治疗疼痛功效仍需验证。上述谷氨酸受体的通用阻断剂会抑制生理性功能，导致外周和中枢神经系统的副作用。因此，IEM-1460，NASPM，AgTx-636等特异性阻断CP-AMPARs的试剂似乎更为理想[40]，但仍需进一步的研究来评估其副作用。最近关于AMPARs缓解疼痛的药物研究侧重于以下几方面：通过干扰细胞内信号级联来破坏的AMPARs的转运，如抑制PKC来抑制AMPARs的磷酸化[41]；抑制AMPARs的转运，如抑制含有GluA2的AMPARs内吞作用的肽[17]；或干预辅助蛋白与AMPARs的相互作用，如γ8[28]、支架蛋白PICK1[42]等，这些靶向调节亚基磷酸化或辅助蛋白，从而精准干预AMPARs转运的药物似乎易于减少副作用和提高镇痛功效。

6 总结与展望

AMPARs的激活和转运与躯体和口颌面部疼痛的发生发展密切相关。目前，AMPARs调控疼痛的病理机制研究主要集中于脊髓神经系统，其在三叉神经系统中的作用机制研究相对不足，需要更深入的研究。关于口颌面部疼痛的研究侧重于炎性损伤模型中GluA1的作用，未来可以研究神经损伤模型下AMPARs如何促进口颌面部神经病理性疼痛。此外，目前仍缺乏治疗口颌面部疼痛的药物的研发和临床研究。因此，基于亚基转运、磷酸化修饰或细胞级联信号传递及其相互作用的蛋白质等，研发特异性调控AMPARs表达及功能的药物对提高口颌面部疼痛的治疗效果，减少副作用具有重要意义。

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