☆ 综　　述 ☆

针刺调节γ-氨基丁酸能系统改善痛情绪的机制研究进展

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【摘　要】 痛情绪是由疼痛引发的抑郁、焦虑等负性情绪反应，严重影响患者身心健康和生活质量。γ-氨基丁酸（GABA）能系统是脑内的主要抑制性递质系统，在痛情绪的发生、发展过程中具有重要的作用。针刺能有效改善疼痛引发的抑郁、焦虑等负性情绪，其机制与针刺调节GABA能系统密切相关，针刺可通过调节GABA能神经元、上调GABA能神经元亚型小清蛋白神经元、下调GABA能神经元亚型神经肽Y的表达来发挥作用；上调杏仁核GABAA受体（GABAAR）mRNA、GABAB2蛋白的表达，下调前扣带皮层GABAAR蛋白的表达。此外，针刺可调节影响GABA系统的关键因子谷氨酸脱羧酶、γ-氨基丁酸转运体的表达从而改善痛情绪。这为针刺治疗痛情绪的机制研究和临床应用提供了参考。

【关键词】 针刺；痛情绪；γ-氨基丁酸能系统；综述

Mechanism research progress of acupuncture for ameliorating pain-related emotions through regulating GABAergic system

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【ABSTRACT】 Pain-related emotions refer to the negative emotions such as depression and anxiety triggered by pain, which seriously impact patients' physical and mental health as well as the quality of life. The gamma-aminobutyric acid (GABA) ergic system is the primary inhibitory neurotransmitter system in the brain and plays a significant role in the onset and development of pain-related emotions. Acupuncture can effectively ameliorate the negative emotions such as depression and anxiety caused by pain. Its mechanism is closely related to the regulatory effect of acupuncture on GABAergic system. Acupuncture is active in modulating GABAergic neurons, up-regulating the expression of GABAergic neuron subtype parvalbumin neurons and down-regulating the expression of GABAergic neuron subtype neuropeptide Y; up-regulating the mRNA expression of GABAA receptor (GABAAR) and the protein expression of GABAB2 in the amygdala, and down-regulating the protein expression of GABAAR in the anteiror cingulate cortex. Besides, acupuncture can regulate the expressions of the key factors such as gutamate decarboxylase and gama-amino-butyrate transporter that affect the GABAergic system, thereby relieve pain-related emotions. These findings provide the references for the mechanism research and clinical application of acupuncture in treatment of pain-related emotions.

【KEYWORDS】 Acupuncture; Pain-related emotions; GABAergic system; Review

疼痛是一种与实际或潜在的组织损伤相关的不愉快的感觉和情绪情感体验，或与此相似的经历[1]。疼痛作为一种主观体验，包括痛感觉、痛情绪、痛认知、社会交往等多个维度。疼痛可诱发短时或长时的恐惧、紧张、焦虑、抑郁、痛厌恶等负性情绪改变，痛情绪又可进一步加重患者疼痛感觉，严重影响患者治疗及预后[2-3]。慢性疼痛影响全球超过30%的人口[4]，高达54%的患者受慢性疼痛诱

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发的痛情绪困扰[5]。目前，对痛情绪的治疗通常以药物治疗及心理治疗为主，对疼痛和负性情绪有一定的效果，但存在过量用药、药物成瘾等不良反应[5-7]。

针刺对痛情绪具有多维度的调节作用，可提高痛阈、改善负性情绪并对痛诱发的情绪和认知改变有积极的干预作用[2]。针刺的镇痛作用与γ-氨基丁酸（GABA）能系统关系密切[8]，GABA能系统是脑内的主要抑制系统，GABA可激活GABA能系统且与痛情绪密切相关[9]。本文就针刺调节GABA受体、GABA能神经元、GABA能系统关键因子进行总结，以期为针刺调节痛情绪的进一步研究提供依据。

1　GABA能系统概述

GABA能系统有3个主要组成部分：GABA能神经元、GABA递质和GABA受体。GABA能神经元通常具有短轴突并靶向同一脑区内的局部神经元，而投射神经元具有跨越几个脑区的长轴突，且多数GABA能神经元是中间神经元[10]。GABA能中间神经元的亚型主要有小清蛋白（PV）、生长抑素（SST/SOM）、血管活性肠肽（VIP）、神经肽Y（NPY）、5-羟色胺3A受体（5-HT3aR）神经元[10-11]。GABA是中枢神经系统（CNS）中主要的抑制性神经递质，通过与GABA受体结合从而调节神经递质释放和神经元兴奋。GABA受体主要有GABAAR、GABABR、GABACR 3种亚型。GABAAR由5个蛋白质亚基和至少19个不同的亚基亚型（α1-6、β1-3、γ1-3、δ、ε、θ、π和ρ1-3）组成[12-13]。GABABR是由GABAB1和GABAB2亚基组成的G蛋白偶联受体，并通过激活G蛋白系统来介导GABA引起反应。

2　GABA能系统与痛情绪的关系

GABA能系统的破坏可能导致各种疾病，包括抑郁症和慢性疼痛[13]。GABA神经递质及其相关受体在痛情绪中起着至关重要的作用[14-16]。在大脑皮层中，超过20%的神经元是GABA能神经元[14]，GABA能神经元的激活与疼痛和焦虑等负性情绪相关[17-20]。前扣带回皮层（ACC）中GABA能神经元的激活可减轻慢性炎性疼痛和与疼痛相关的焦虑样行为[21]，特定中脑的GABA能亚群介导不同的疼痛调节和情绪反应[22]。

GABA能神经元分泌抑制性神经递质GABA，GABA主要通过自身的合成与释放及GABAAR、GABABR的激活对神经元活动发挥抑制作用。GABAAR、GABABR与痛情绪密切相关，GABAAR介导抑制功能障碍且与疼痛体验的情感有关[21]，并在神经病变大鼠的痛感觉和情绪处理中发挥着重要作用[23]。扣带皮层GABA水平与持续慢性疼痛的强度呈负相关[24]，GABA合成不足会诱导神经元过度激活，产生焦虑和其他负性情绪，导致患者的疼痛强度增加和疼痛症状加重。此外，靶向调节GABA能系统可以缓解痛情绪症状[25]。上述研究均表明，GABA能神经元、GABA递质和GABA受体均参与痛情绪过程，GABA系统与痛情绪密切相关。

GABA系统不仅可以调节神经元的局部活动，GABA能投射也广泛分布于整个CNS，多种GABA能中间神经元通过局部途径和区域网络作用产生GABA能抑制[26]，大脑中抑制性神经递质的减少可能会改变导致疼痛体验的功能网络[25]，GABA能投射在痛情绪中起重要作用[27-28]。探讨GABA能系统在痛情绪中的作用，对于揭示二者之间的病理联系至关重要，也为临床治疗提供新的策略和思路。

3　针刺调节GABA能神经元及其亚型改善痛情绪

3.1　GABA能神经元

GABA能神经元占大鼠脑内全部神经元的50%[29]，在大脑皮层中，PV神经元占GABA能神经元的大约40%，SST神经元占GABA能神经元的大约30%[13]。慢性痛伴发负性情绪小鼠的痛情绪与GABA能神经元变化密切相关，在慢性疼痛状态下，GABA能神经元数量存在不同程度的变化[30]。激活ACC中的GABA能神经元可减轻痛情绪，而将GABA能神经细胞移植到ACC可以减轻与神经病理性疼痛相关的厌恶情绪[31]。此外，激活GABA能神经元可抑制中央杏仁核（CeA）神经元的兴奋性，并可减轻神经病理性疼痛引起的负性情绪[32-33]。GABA能神经元还参与DNA甲基转移酶对慢性疼痛诱导的抑郁的调节[34]，中枢GABA能中间神经元也与焦虑、抑郁相关，并在痛情绪中发挥重要作用[35]。电针可通过调节GABA能神经元功能达到镇痛的效果[36]，可改善慢性疼痛相关的负性情绪，GABA能神经元在其作用机制中发挥重要作用[37]。

3.2　GABA能中间神经元亚型

3.2.1　PV神经元

PV神经元是最主要的GABA能中间神经元亚型[38]，是抑制性神经元的重要组成部分[39]，且与纤维肌痛小鼠痛觉过敏的发生有关，杏仁核和海马亚区域的PV阳性神经元参与慢性神经性疼痛引起的焦虑样行为[40]。增加PV中间神经元活性可以减轻

神经损伤后产生的机械性异常疼痛，脊髓背角的PV中间神经元在控制周围神经损伤后的机械性异常性疼痛中发挥着重要作用[41]。完全弗氏佐剂（CFA）诱导的慢性炎性痛大鼠产生的痛焦虑样行为与ACC内PV中间神经元兴奋性降低有关，通过电针干预可增加PV阳性细胞数量并上调PV中间神经元兴奋性从而发挥镇痛和抗焦虑作用，但激活ACC中的SOM中间神经元对疼痛或疼痛相关焦虑没有影响[37]，而激活CeA中的SOM神经元可以缓解慢性疼痛小鼠抑郁样行为，这表明激活或抑制特定脑区的GABA能神经元可能导致不同的结果[42]。针刺可通过上调PV神经元表达来改善痛情绪。

3.2.2　NPY神经元

NPY是一种抗伤害感受的神经肽，与慢性疼痛和抑郁症密切相关[43-44]。Okabe等[45]研究结果显示电休克改善神经病理性疼痛症状的作用机制与其增加脑内NPY的表达有关。电针可通过增加CFA诱导的慢性炎性疼痛模型大鼠脊髓背角中NPY的表达，发挥抗伤害作用并缓解慢性疼痛[46]。林俊言等[47]研究显示，慢性炎性痛大鼠海马各区域NPY表达增加，电针可显著降低NPY表达从而有效缓解大鼠疼痛和焦虑样行为，表明电针改善痛情绪的机制可能与下调大鼠海马NPY表达水平相关。

3.2.3　SST神经元

杏仁核内SST阳性中间神经元在情绪调节中可能起到重要作用[48]。抑郁症患者大脑中SST的表达减少[49]，而抗抑郁药的治疗作用涉及新皮层和海马中SST阳性中间神经元对GABA能突触抑制的增加[50]。海马CA1区SST阳性中间神经元参与疼痛的发生、转归、维持和缓解过程，SST阳性中间神经元以不同方式调控疼痛的感觉维度和情绪维度，抑制SST阳性中间神经元能够显著缓解小鼠痛敏，而激活可加重痛敏[51]。针刺可通过增加小鼠ACC内SST神经元的兴奋性从而改善慢性炎性疼痛[52]。上述研究表明，SST阳性中间神经元可能在疼痛及痛情绪的形成和缓解过程中发挥重要作用，但针刺调节SST神经元改善痛情绪的机制有待于进一步研究。

4　针刺调节GABA受体改善痛情绪

4.1　GABAAR

GABAAR是GABA实现痛情绪传导作用的重要媒介[29]。GABAAR与痛情绪密切相关，敲除GABAAR γ2亚单位会导致抑郁样行为[53]，此外，GABAα激动剂可降低与痛感觉和关联情绪相关脑区的活性水平[54]。电针双侧腰4、腰6“夹脊”可以上调慢性压迫性损伤大鼠脊髓中GABAAR表达水平，从而减轻大鼠痛觉过敏[55]。电针可提高颈部切口术后大鼠的热痛阈并发挥镇痛作用，其机制与上调GABAAα2R和GABABR1的表达有关[56]。在CFA诱导的慢性炎性痛大鼠杏仁核中GABAAR mRNA表达显著降低，电针可上调大鼠杏仁核中GABAAR mRNA的表达，从而改善痛情绪[57]。此外，重复电针“足三里”“阳陵泉”可上调负性情绪大鼠杏仁核GABAAR、GABACR基因的表达，进而影响疼痛情绪和感觉成分[58]。沈科展等[59]研究显示，条件位置回避痛厌恶大鼠ACC脑区GABAAR蛋白的高表达是痛情绪产生的原因之一，预电针镇痛和缓解痛情绪的机制与电针下调GABAAR蛋白的高表达有关。以上研究均表明针刺上调杏仁核GABAAR mRNA表达、下调ACC脑区GABAAR蛋白的表达是改善痛情绪的有效方法之一。

4.2　GABABR

GABABR参与疼痛信号的处理，是治疗慢性疼痛有价值的靶点[60]。敲除星形胶质细胞中GABABR后，小鼠可表现出抗抑郁样行为，GABABR也是治疗压力相关负性情绪的新靶点[61]。神经病理性痛大鼠脊髓水平的GABABR亚型GABAB1a、GABAB2表达减少，鞘内注射GABABR激动剂巴氯酚可减轻大鼠的痛觉过敏，表明神经病理性痛可能与GABABR有关[62]。疼痛记忆会导致负面情绪，GABABR在疼痛记忆和相关的焦虑样行为中起关键作用。下调中扣带皮层（MCC）内神经元GABABR的活动可以阻止疼痛记忆并逆转焦虑情绪，而注射巴氯芬可以显著阻断电针的镇痛作用和抗疼痛记忆作用[62]。

MCC内的GABABR参与疼痛记忆和相关的类似焦虑的行为，电针可通过阻断MCC内的GABABR功能抑制疼痛记忆和相关的焦虑样行为[63]。电针干预可减轻疼痛记忆相关的疼痛和疼痛诱导的焦虑样行为，其机制可能与电针激活头端ACC中的GABA能神经元和兴奋GABAAR和GABABR有关[64]。重复电针可明显改善神经病理性慢性痛负性情绪大鼠的痛感觉和情绪，电针可通过上调大鼠杏仁核GABAAβ2、GABAB1及GABAB2蛋白表达改善痛感觉成分，上调杏仁核中GABAB2蛋白的表达改善痛情绪成分[65]。

5　针刺调节GABA能系统关键因子改善痛情绪

多种关键因子参与GABA合成、释放、转运、代谢等过程，主要涉及谷氨酸脱羧酶(GAD)、γ-氨基丁酸转运体(GAT)、GABA转氨酶(GABA-T)等关键因子，对GABA能系统产生直接影响[66-67]。针刺可通过调节这些关键因子影响GABA系统，进而参与痛情绪的调节过程。

5.1　GABA的合成

GABA由谷氨酸经GAD脱羧而成，GAD包含两种同工酶：GAD_{65}和GAD_{67}[68]。GAD_{67}普遍存在于GABA能神经元胞质中，不仅可以调控合成GABA，其活性水平还可以决定大脑中GABA的水平，是GABA能神经元最直接的标记物、特异酶[69-70]，脑中超过90%的GABA由GAD_{67}介导生成[71]，GAD_{67}含量降低会影响GABA的生成从而使GABA能系统出现脱抑制效应[72-73]，并可导致兴奋/抑制平衡改变及情绪异常，从而出现神经障碍相关的行为，激活GAD_{67}阳性抑制性神经元可以减轻神经性疼痛大鼠的痛情绪[74-76]。通过调节GAD含量影响GABA的释放和摄取，可能是改善焦虑、抑郁情绪的有效途径[77]。针刺可缓解慢性复合应激大鼠的抑郁状态，其机制与针刺增加GAD_{65}合成、增加GABA含量有关[78]。电针可通过上调疼痛大鼠背根神经节GAD_{67}的mRNA和蛋白表达从而增加GABA含量，有效地减轻超敏反应[79]。上述研究表明，针刺改善痛情绪的机制可能与其调节GAD的表达从而增加GABA含量有关。

5.2　GABA的转运

GAT-1是GAT最主要的亚型，占GAT总数的80%，在脑组织中含量最丰富，担负近85%的GABA转运任务[80]，在GABA信号的调节中起重要作用[81]。敲除小鼠的GAT-1可降低小鼠焦虑抑郁样行为[82]，这与增强GABA能系统，以及影响小鼠的血清能系统和下丘脑-垂体-肾上腺(HPA)活动改善抑郁行为有关[83]。GAT-1还参与认知过程和疼痛行为的调控，在神经病理性疼痛发生发展中起着重要作用[84-85]。此外，GAT-1的功能与疼痛敏感性关系密切，阻断其功能可产生镇痛作用[86-87]，过量表达的GAT会导致痛觉过敏，调节GAT的表达可产生镇痛作用[62]。以上研究均表明GAT与痛情绪关系密切，GAT可能参与了针刺镇痛的机制[88]。通过针刺慢性不可预知性轻度应激抑郁模型大鼠显示，GAT-1蛋白表达较正常对照组水平显著升高，针刺可显著降低GAT-1蛋白表达水平，从而改善抑郁症状[78]。然而，目前关于GAT与痛情绪之间的作用机制尚未完全阐明，GABA的转运过程与痛情绪的关系有待于进一步研究。

6　小结与展望

疼痛可诱发短时或长时的恐惧、紧张、焦虑、抑郁、痛厌恶等痛情绪，负性情绪又可进一步加重患者疼痛感觉，负性情绪与痛感觉相互依存，严重影响患者的身心健康及生活质量。针刺对痛情绪有较好的调控作用，针刺可通过调节GABA能神经元、上调GABA能神经元亚型PV神经元、下调GABA能神经元亚型NPY的表达来发挥作用；痛情绪的改善还与针刺上调杏仁核GABAAR mRNA、GABAB2蛋白的表达，下调ACC脑区GABAAR蛋白的表达有关；此外，针刺可调节影响GABA系统关键因子GAD、GAT的表达从而改善痛情绪。

影响GABA能系统关键因子除GAD、GAT外，GABA-T和琥珀酸半醛脱氢酶(SSADH)也是脑内GABA代谢的关键因子[89]，目前对GABA-T、SSADH等关键因子影响GABA系统进而参与痛情绪的作用机制研究暂未涉及，今后关于影响GABA系统关键因子的相关研究应进一步展开；此外，GABA能系统与涉及痛情绪的其他系统(如5-羟色胺能系统、去甲肾上腺素能系统、谷氨酸能系统等)之间相互作用[14]，但其相互作用机制尚未完全阐明，未来研究应在现有的基础上，运用现代科技手段，针对GABA能系统与涉及痛情绪的其他系统进行深入研究；慢性炎性痛、神经病理痛、内脏痛、癌痛均可诱发焦虑抑郁样情绪的共病状态，针刺对内脏痛及癌痛模型的影响研究较少且慢性痛动物模型有各自的局限性，今后应扩大针灸改善痛情绪研究范围，以期为痛情绪的相关研究及其临床治疗提供参考。

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