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在线全文

下丘脑室旁核参与针灸治疗疾病的机制*

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【摘要】 近年来，研究表明，针灸可以通过调控下丘脑室旁核（paraventricular hypothalamic nucleus, PVN）来治疗多种疾病，如功能性胃肠道疾病、心血管疾病以及焦虑和抑郁等。针灸可能通过调节PVN中的特定神经元，如促肾上腺皮质激素释放激素（corticotropin releasing hormone, CRH）神经元，或调节PVN相关的神经环路和激素〔如催产素（oxytocin, OXT）、血管升压素（vasopressin, VP）〕的释放，发挥其治疗作用。本文总结了PVN在针灸治疗中的机制，包括其在胃肠道疾病、心血管疾病、负性情绪和疼痛的调控机制。未来研究可深入探究针灸调控PVN治疗疾病的精确机制，如明确信号通路传导的详细过程，探究不同穴位配伍、刺激频率与强度对PVN的特异性影响等。

【关键词】 下丘脑室旁核 针灸 高血压 胃肠道 心脏病 综述

Mechanisms by Which Paraventricular Hypothalamic Nucleus Participates in the Acupuncture Treatment of Diseases

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[Abstract] In recent years, a growing body of research has demonstrated that acupuncture can be used to effectively treat a diverse range of diseases, including functional gastrointestinal disorders, cardiovascular diseases, as well as anxiety and depression, through the modulation of the paraventricular hypothalamic nucleus (PVN). Acupuncture may exert its therapeutic effect either by modulating specific neurons within the PVN, such as corticotropin releasing hormone (CRH) neurons, or by regulating the release of hormones, such as oxytocin (OXT) and vasopressin (VP), and the activity of neural circuits associated with the PVN. This review summarizes the mechanisms by which PVN is involved in acupuncture treatment, including its regulatory mechanisms in gastrointestinal diseases, cardiovascular diseases, and negative emotions and pain. Future research should be conducted to further explore the precise mechanisms by which acupuncture regulates PVN to treat diseases, focusing on clarifying the specific processes of signaling pathway transduction, and exploring the specific effects of acupunture of different acupoint combinations and stimulation frequencies and intensity on PVN.

[Key words] Paraventricular hypothalamic nucleus Acupuncture Hypertension Gastrointestinal tract Heart disease Review

针灸的历史可追溯到距今两千多年前的《黄帝内经》，已成为中医学的重要组成部分[1]。针灸技术主要包括传统手针和电针两种形式，也通常与其他治疗方式结合，如拔罐与中草药等[2]。在临床实践中，根据疾病特点和患者中医证型，刺激不同穴位处方，能治疗多种疾病[3]，尤其适用于疼痛类疾病[4]和缺血性脑卒中及其后遗症等[5]。如今，针灸凭借其安全性、高效性和便捷性，在全球范围内赢得了广泛的认可与应用[6]。

下丘脑室旁核（paraventricular hypothalamic nucleus, PVN）是大脑中至关重要的一个整合中心，它在协调多种生理和行为反应中发挥着不可替代的作用。该核团通过广泛连接中枢神经系统的不同区域，包括脑干核团和脊髓，来实现其复杂的调控功能，如维持代谢稳态和通过交感神经控制心血管等[7]。一旦PVN出现功能异常，将会引发一系列严重的健康问题。例如，可导致内脏高敏感性、高血压、心脏疾病和下丘脑-垂体-肾上腺轴（hypothalamic-pituitary-adrenal axis, HPA）紊乱等病症[8-11]。这些疾病不仅影响患者的生活质量，还可能带来严重的医疗负担。

近年来，针灸作为一种传统疗法，在调控PVN以治疗

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某些疾病方面展现出了良好的潜力。多项研究发现，针灸能够通过特定的穴位刺激，影响PVN的神经活动，从而实现对胃肠道、心血管、负面情绪、疼痛等疾病的调控作用[12-18]。这一发现为针灸治疗疾病提供了新的理论依据和实践指导。本综述初步介绍了PVN的基本结构与其调控相关疾病的机制，综合叙述了针灸通过调控PVN治疗疾病的机制，以期寻找针灸和PVN相关的疾病靶点，为中西医结合疗法治疗这些疾病提供新的策略和思路。

1　PVN的解剖位置与结构

PVN是第三脑室上部边界的一小块区域，其解剖位置在丘脑内侧区视上核的背侧与尾侧部位[19]。作为下丘脑中的重要神经内分泌核团，PVN由多种类型的神经元组成，它们通过不同的神经通路调节代谢稳态、心血管功能等生理活动，且与内脏器官的调控密切相关[20-22]。

同时，PVN也是一个信息汇聚的中心。它接收多种传入信息，包括反映外界化学环境变化的小分子，如一氧化氮。PVN接受的传入信息能够触发PVN对炎症因子的调控，如白细胞介素（interleukin, IL）-1β[23]、IL-6[24]和肿瘤坏死因子α[25]等。这些信息通过下丘脑和室周器官，以及部分通过迷走神经中的传入神经和孤束核进行接收和传递[26]。因此，PVN是调节自主神经活动的关键位点[27]。

2　PVN调控疾病的机制

2.1　PVN参与胃肠道疾病调控

肠易激综合征（irritable bowel syndrome, IBS）是功能性胃肠道疾病（functional gastrointestinal disorders, FGIDs）的典型疾病，其关键特征之一是内脏高敏感[11, 28]。同时，胃动力障碍也是FGIDs的典型症状之一[28]。近年来的研究表明，PVN在胃肠道疾病的调控中发挥了重要作用，尤其是在内脏高敏感性和胃动力障碍的调节中。调控PVN内的促肾上腺皮质激素释放激素（corticotropin releasing hormone, CRH）[8, 29]和催产素（oxytocin, OXT）[11]神经元可有效缓解FGIDs的症状，改善胃排空延迟和胃张力。

除了对FGIDs的调控外，还有研究表明，在葡聚糖硫酸钠诱导的结肠炎早期，PVN中G蛋白偶联雌激素受体可能激活PVN神经元，进而刺激交感神经释放激素或激活HPA轴，调节机体发挥防御性抗炎作用[30]。

2.2　PVN对心血管疾病的调控作用

PVN作为下丘脑中的一个重要神经核，与心血管系统的功能及疾病状态密切相关。PVN内某些激素及神经元，如血管升压素（vasopressin, VP）和CRH神经元，在心血管调节及疾病治疗中发挥着关键作用[31-32]。

多项研究证明，PVN在高血压的诱发和调节过程中扮演着关键角色。PVN内的胰高血糖素样肽-1（glucagon-like peptie-1, GLP-1）及其受体的激活，可以触发一系列复杂的生化反应，最终导致高血压的发生[33]。PVN还可以通过调控包括磷脂酰肌醇-3-激酶（phosphatidylinositol 3-hydroxy kinase, PI3K）-蛋白激酶B（protein kinase B, Akt）通路、沉默信息调节因子2同源蛋白-1（silencing type information regulation 2 homolog-1, SIRT1）/核因子κB（nuclear factor kappa-B, NF-κB）/丝裂原活化蛋白激酶（mitogen-activated protein kinase, MAPK）通路在内的信号通路诱导高血压[34-36]。同时，PVN中VP神经元与终板中对血管紧张素（angiotensin, Ang Ⅱ）敏感的神经元之间存在功能性兴奋性连接，激活该回路可升高血压[37]。此外，PVN中一些特殊物质，如ELA-21、趋化素-9（chemerin-9）、内源性硫化氢等，也可通过不同信号通路的激活、氧化应激以及交感神经系统激活，诱导血压升高[38-39]。

PVN在高血脂、心肌梗死、心力衰竭等常见心血管疾病中也发挥着重要作用。PVN中IL-17A可增加炎症介质表达，使交感神经活性增加。因此，抑制PVN的IL-17A/IL-17RA轴有治疗高血脂的潜力[40]。PVN-OXT网络可维持心肌内毒蕈碱性受体（muscarinic receptor, Chrm2）的表达，而Chrm2可以促进节后神经元释放乙酰胆碱（acetylcholine, ACh），ACh释放后可激活心肌细胞内抑制性通路，进而触发副交感神经系统在心肌梗死期间对心脏的保护效应[41]；患心肌梗死后，PVN-延髓头端腹外侧区（rostral ventrolateral medulla, RVLM）神经元的交感兴奋输入增强，作为中枢神经系统回路的一部分，也可能导致交感血管运动张力升高，进一步导致心力衰竭[42]。

2.3　PVN参与负性情绪及其相关疾病的调控

PVN可以通过调节HPA轴来调控负性情绪。PVN可响应压力源释放CRH，CRH使垂体释放促肾上腺皮质激素（adrenocorticotropin, ACTH）。同时，PVN中部分CRH神经元共表达的VP可以促进ACTH释放[43-44]。ACTH随后导致HPA轴释放皮质醇等应激激素，长期的高皮质醇水平会导致情绪异常，进而导致抑郁症状[45]。此外，HPA轴的过度激活导致炎性细胞因子水平增加，而血清素水平下降，使人更容易感到抑郁和焦虑[46-48]。同时。慢性应激通过加强与PVN的连接，增强腹内侧下丘脑神经元的兴奋性输入促进焦虑[49]。

与女性（尤其是青春期及孕期女性）情绪相关的疾病，也与PVN有密切的联系。慢性社会挫败应激实验中，PVN-雌性伏隔核壳部投射调节女性情绪和社交行为[50]。当孕期独特的PVN青春期编程相关激素变化时，会导致

妇女HPA轴反应异常[51],从而导致精神疾病发病率上升;而产后HPA轴功能失调会使PVN中CRH表达增加和CRH受体表达减少,这些分子变化也会导致产后HPA轴功能紊乱和行为、情绪异常[52]。

2.4 PVN参与调控多种疼痛

PVN在疼痛调控中发挥重要作用,可作为"疼痛分拣中心"分别对内脏痛和躯体痛信号进行处理。有研究发现,终纹床核前腹侧区域(anterior ventral region of the bed nucleus of the stria terminalis, avBNST)的谷氨酸能神经元和γ-氨基丁酸(γ-aminobutyric acid, GABA)能神经元可以分别投射到PVN的CRH神经元。进一步实验证明,avBNST-PVN神经元中谷氨酸能投射的激活和GABA能投射的抑制共同介导小鼠慢性内脏疼痛的发生和发展[53]。PVN不仅接收来自avBNST的投射,还投射到腹侧外侧隔核(ventral lateral septum, LSV)。由于嘌呤能P2X3受体在内脏痛相关的PVN神经元中特异性高表达,通过PVN-LSV环路调控内脏痛[54],故抑制PVN-LSV通路可以缓解慢性内脏痛[55]。

此外,实验证明,PVN中与躯体痛相关的神经元投射到未定带尾侧部分(caudal part of zona incerta, ZIC)。血管活性肠肽受体2特异性集中表达在与躯体痛相关的PVN神经元中,通过PVN-ZIC环路调节躯体痛[54]。

c-Fos阳性细胞的数量是衡量PVN中神经元活动的一个重要指标。有研究表明,在双侧注射6-羟基多巴胺制备的帕金森病(parkinson disease, PD)大鼠模型中,PVN中c-Fos阳性细胞数量减少参与PD大鼠对福尔马林诱导的三叉神经分布区域痛觉过敏的形成[56]。同时,在皮质扩散性去极化(spreading depolarization, SD)诱导的三叉神经痛小鼠模型中,SD可激活PVN的OXT神经元从而减轻三叉神经痛,此外,该作用还具有性别差异性[57]。因此,PVN通过调节其内部神经元的活性,参与对三叉神经痛的调控过程。在PD患者中,疼痛是其主要非运动型症状。PD患者的疼痛可能与PVN释放到血浆的OXT的镇痛作用受到抑制有关[58]。上述研究提示,增加PVN中分泌OXT的神经元的活性,可能会缓解PD患者的疼痛。

2.5 PVN参与体内多种代谢紊乱的调控

PVN参与体内众多物质的代谢过程,包括激素代谢、糖代谢和水盐代谢等。在激素代谢紊乱方面,PVN参与调控糖尿病的病理过程。研究表明,通过PVN输入可以激活RVLM神经元,进一步导致脊髓中间外侧柱的神经元活性增加,这一系列反应可能与糖尿病的发病机制有关[59]。

PVN也是调节糖代谢和体重的关键枢纽[60],PVN通过调节代谢相关的物质(如蛋白质)含量以及调控神经系统的功能来参与肥胖的发病机制与调节过程。肥胖可能会破坏PVN神经元的染色质结构,导致核质变化及染色质异常聚集,这可能是肥胖影响PVN功能的一个重要机制[61]。进一步的研究揭示,PVN中轴突蛋白-3(neurexin-3, Nrxn3)依赖性神经通路可能与肥胖症之间存在潜在联系。具体来说,Nrxn3可以促进产热和脂肪动员以维持能量与葡萄糖平衡,而Nxrn3的缺乏则可能导致明显的肥胖和葡萄糖不耐受[62]。此外,神经调节蛋白-4(neuregulin 4, Nrg4)也可调节葡萄糖和脂质代谢,与肥胖密切相关。Erb-B2受体酪氨酸激酶4(Erb-B2 receptor tyrosine kinase 4, ErbB4)是Nrg4的受体,在下丘脑尤其是PVN神经元中大量表达,在肥胖个体中磷酸化降低。因此,通过在PVN中过表达ErbB4受体调节能量代谢,可能为预防肥胖的发生提供了一种新的策略[63]。这一发现为我们理解肥胖的发病机制并寻找潜在的治疗靶点提供了新的视角。

值得注意的是,肥胖也会对PVN产生反馈作用。早期的肥胖会增强PVN中神经酰胺合成关键酶丝氨酸棕榈酰转移酶长链亚基1(serine palmitoyltransferase long chain base subunit 1)的表达,进而促进卵巢去甲肾上腺素能系统的成熟,这可能是导致青春期提前到来的一个重要原因[64]。

此外,PVN在水盐代谢平衡及紊乱调节中也发挥着重要作用。当PVN神经元被激活时,下丘脑神经重体分泌VP和OXT增加,调节水盐排出和电解质代谢平衡,维持体液的平衡[65]。

2.6 PVN参与调控肾脏的相关疾病

PVN也参与多囊肾病、肾纤维化等肾脏疾病的调控。多囊肾病的病理生理特征包括循环VP和交感神经血管舒缩张力升高以及高血压等,表明脑肾素-Ang Ⅱ系统激活。具体来说,这种激活体现在Ang Ⅱ在PVN中的传递作用增强,这不仅表现为VP分泌神经元对Ang Ⅱ的敏感性提高,还反映在CRH神经元中Ang-1a型受体表达上调[66];肾脏传入神经激活PVN神经元中的Ang Ⅱ信号,驱动交感神经放电,从而导致肠梗阻、肾损伤后肾脏纤维化的发生[67-68]。

2.7 PVN参与调控肺部疾病

哮喘和肺动脉高压等肺部疾病同样受到PVN的调控。PVN中OXT神经元向DVC的投射及杏仁核向PVN的投射均可参与调节哮喘的发作[69]。PVN调节肺动脉高压(pulmonary hypertension, PH)与合成CRH的神经元有关,其可被缺氧等条件激活,增加向心血管系统的交感神经输出,进而加剧PH;但细胞内血管紧张素转换酶2(angiotensin-converting enzyme 2)的过表达可减少CRH的合成,使HPA轴活性降低,从而对缺氧诱导的PH具有一定的保护作用[70]。未来,可开展针对PVN及其

相关调控通路的研究, 以为这些疾病的预防和治疗提供新的策略和思路。

2.8 PVN亦参与调控其他多种疾病

PVN还广泛参与对败血症、瘙痒等疾病的调控作用。在败血症中, 交感神经过度活跃是其发病机制之一。PVN对败血症有双重调控作用, 既可通过激活小胶质细胞, 进而激活中枢交感神经系统, 导致器官功能障碍加重[71]; 又可通过其内部α2-肾上腺素受体的激活抑制交感神经活动, 从而减少败血症的发病[72]。

在个体衰老过程中, 肠道微生物群衍生代谢物氧化三甲胺会诱导PVN小胶质细胞介导的炎症, 导致交感神经活动增加[73]; PVN中H_2S水平的降低参与了脑梗死发病后交感神经传出活动的调节[74]。在慢性前列腺炎中, 其诱导的炎症免疫反应可增加PVN中兴奋性氨基酸的NMDA受体的表达, 增强交感神经系统敏感性, 缩短射精潜伏期[75]。

在瘙痒中, 由于PVN-CRH神经元与应激相关, 故诱导该神经元激活可限制急性和慢性瘙痒刺激下形成的重复性异常搔抓行为[76]; 在帕金森病中, 除了前文所提到的疼痛这一非运动症状, 震颤也是帕金森病重要的运动症状, 而PVN可增加脑干网状结构等脑干核的下游胆碱能活动或激活小脑-丘脑-皮质网络, 从而增加震颤[77]。

3 PVN参与针灸治疗疾病的机制

针灸可以激活皮肤和肌肉中的躯体传入神经, 这些感觉神经纤维逐级投射至PVN, 从而对PVN的功能产生调节作用。鉴于PVN在众多生理和病理过程中扮演着关键角色, 针灸有望通过调节PVN治疗多种疾病。至今, 已有多项研究揭示了针灸对不同疾病的调节作用及其背后的PVN相关机制。

3.1 针灸通过PVN调节胃肠道疾病

由于FGIDs的复杂性及其多因素的病理生理机制, 目前的治疗方法效果并不理想, 近50%的FGIDs患者倾向于寻求补充和替代医学的帮助[78]。针灸作为传统中医疗法的一种, 近年来在FGIDs的治疗中展现出了显著的疗效。众多临床研究和循证医学评估都表明, 针灸治疗可以缓解FGIDs的症状, 包括改善腹痛、调节肠道功能、减轻恶心和呕吐等。这些效果可能是通过针灸对PVN的调控来实现的[15-16, 18]。

研究显示, 电针治疗可以抑制PVN中神经元支配的结肠运动和放电频率, 降低IBS大鼠的内脏敏感性, 减少其外周血清中CRH、皮质酮和促肾上腺皮质激素的水平升高, 从而达到缓解IBS的效果。此外, 电针还可下调PVN中CRH受体的表达, 从而抑制CRH的作用, 进而治疗IBS[79]。

而在胃扩张(gastric dilation, GD)引起的胃动力障碍小鼠模型中, 研究者发现电针干预抑制了GD小鼠的PVN中CRH神经元兴奋, 从而减弱CRH神经元抑制迷走神经背运动核(dorsal motor nucleus of the vagus, DMV)ACh神经元的作用(DMV是DVC的一部分), 促进ACh的释放, 缓解GD诱导的胃动力障碍[18]。

实验证明, 电针刺激胃俞募配穴可减少中央杏仁核(central amygdala, CeA)中GABA能神经元激活, 通过CeA中GABA能神经元到PVN的投射而减少PVN脑区GABA含量[80]。先前实验证明, PVN和DMV有直接纤维联系, 电针胃俞募配穴可能通过PVN-DMV-迷走神经通路调节胃运动[81], 可以得出结论: 电针刺激胃俞募配穴能够通过CeA-PVN-DMV-迷走神经通路调节胃运动。

3.2 针灸通过PVN治疗心血管疾病

目前, 电针在临床上已被用于降低血压, 其降压机制可能是诱导PVN中神经肽Y的表达来抑制交感神经活动, 从而达到降压效果。大量动物和临床研究表明, 用于降压的电针所刺激穴位可以选择足三里穴(ST36)和丰隆穴(ST40)[82], 可能的机制为ST36和ST40均位于腓深神经支配区域, 而刺激腓深神经可降低电刺激PVN引起的血压升高反应[14]。

此外, 动物实验表明, 针刺心俞穴(BL15)可调节PVN神经元的活性, 并对房颤引起的循环功能障碍提供保护作用[9]。

针灸治疗心肌损伤等疾病的机制也与PVN有关。电针可能通过PVN-间位核神经通路改善心肌损伤[83]。心肌缺血再灌注损伤(myocardial ischemia/reperfusion injury, MIRI)是加剧心肌损伤的重要因素。电针治疗对此表现出显著的疗效, 其作用机制可能涉及抑制PVN中CRH神经元, 进而降低交感神经活动的强度, 从而改善MIRI; 电针也可抑制PVN-RVLM神经通路, 调节投射到RVLM的PVN神经元活性, 缓解MIRI[84]。

3.3 针灸通过PVN治疗负性情绪

针灸能在一定程度上缓解焦虑和抑郁, 其机制也与PVN内激素及神经通路的调控有关。有研究表明, 针刺内关穴(HT7)显著降低PVN中CRH的表达, 减少因HPA轴紊乱而增加的应激激素皮质酮含量, 从而缓解焦虑等负面情绪[17, 85]。此外, Nesfatin-1在PVN中的过表达一方面引起HPA轴过度活跃, 另一方面激活了胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)/环腺苷酸反应元件结合蛋白(cAMP-response element binding protein, CREB)通路, 导致多动和焦虑。研究表明, 电针可以降低PVN中CRH和Nesfatin-1的过表达, 同

时降低ERK/CREB通路的磷酸化水平，从而减轻HPA轴激活引起的多动和焦虑样行为[86]。

3.4 针灸通过PVN治疗疼痛

针刺治疗能够通过调控PVN的功能来降低基础痛阈，并有效治疗内脏痛、牙髓痛以及子宫痛。实验证明，电针可促进PVN释放VP来提高大鼠的基础痛阈[87]。电针ST36可降低PVN中VP的浓度，升高下丘脑其他核团中VP的浓度，进而降低大鼠的基础痛阈[13]。实验证明，电针刺激大鼠上下唇中相当于人体的人中穴(GV26)和承浆穴(RN24)，可促进PVN分泌VP来缓解内脏痛[88]；在针刺调控牙髓疼痛中，牙痛引起由PVN等核团介导的心血管反射，而在ST36、合谷穴(LI4)的手针针刺则显著减少了PVN脑区分布的c-Fos阳性神经元数量，进而减弱了牙痛引起的动脉血压和心率的增加[89]；在子宫疼痛的电针调节中，PVN是体内躯体副交感神经环路(腹股沟-脊髓背角-孤束核-PVN-子宫)的重要环节，其参与的神经环路可能是躯体-内脏反射神经元基础的先决条件[90]。

4 总结与展望

如上所述，针灸通过调控PVN来治疗多种疾病的机制正在逐步被揭示和验证。通过多种神经传导通路、多位点、多途径调控，进一步证明了PVN作为大脑中至关重要的整合中心，广泛参与针灸对多种生理和病理反应的调节(图1)。PVN内神经元功能异常或相关激素及其

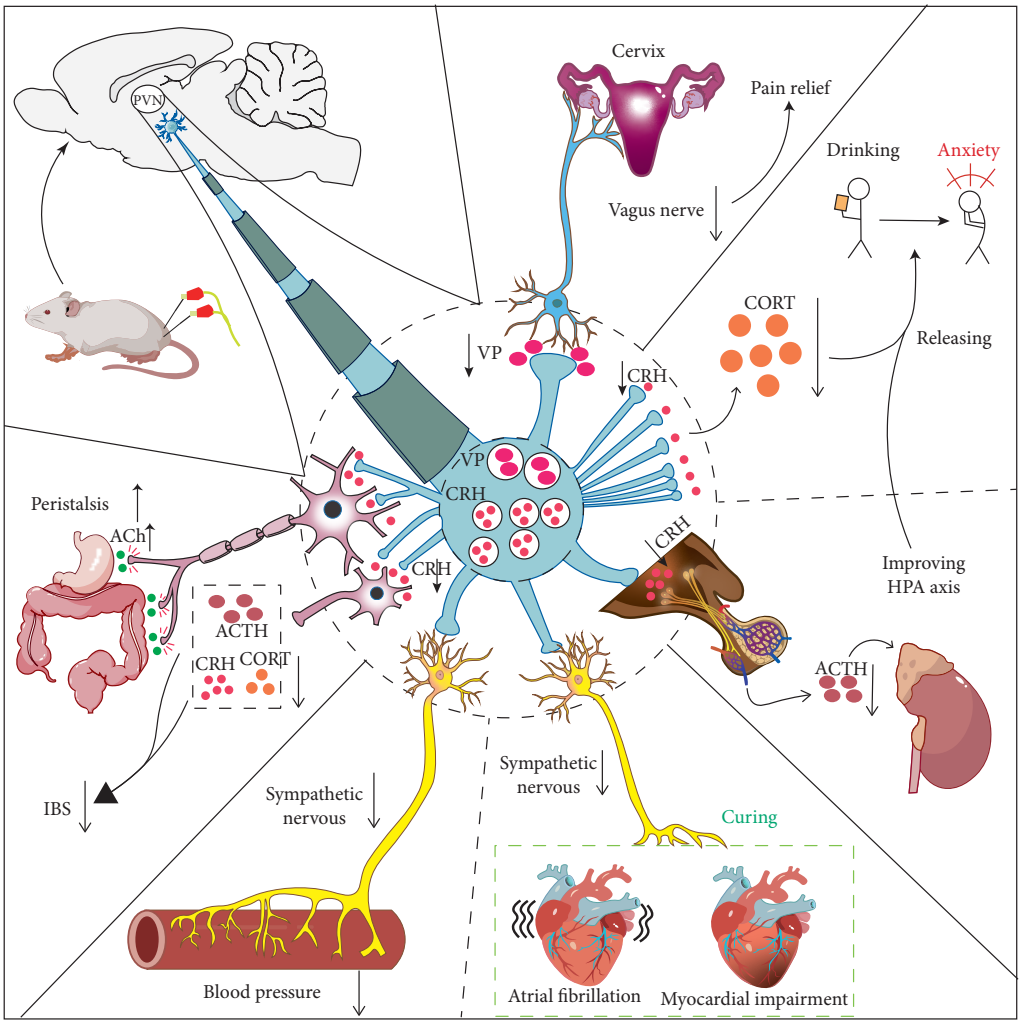

图 1 PVN参与针灸治疗疾病机制

Fig 1 The mechanisms of PVN participating in the acupuncture treatment of diseases

ACh: acetylcholine; CORT: cortisol. Acupuncture can inhibit the discharge frequency of neurons in the paraventricular hypothalamic nucleus (PVN) that innervate gastrointestinal motility, and reduce the content of corticotropin releasing hormone (CRH), adrenocorticotropin (ACTH), and CORT, thus achieving the relief of irritable bowel syndrome (IBS); Acupuncture can also reduce the excitability of the sympathetic nerves through the inhibition of the PVN, thus treating high blood pressure, and regulating cardiovascular diseases, such as atrial fibrillation and myocardial injuries; In addition, acupuncture can improve the HPA axis through the regulation of the PVN, thus alleviating anxiety and depression, especially anxiety caused by long-term alcoholism; Finally, acupuncture can also alleviate pain, such as uterine pain involved by the PVN and parasympathetic nerves, by modulating the release vasopressin (VP).

受体表达的变化与胃肠道疾病、心血管疾病、负面情绪和疼痛等众多疾病的发病机制及调控过程紧密相关。因此,针灸通过影响PVN内部结构、功能进而治疗多种疾病。未来研究可深入探究针灸调控PVN治疗疾病的精确机制,如明确信号通路传导的详细过程,探究不同穴位配伍、刺激频率与强度对PVN的特异性影响等,这些可为针灸在胃肠道疾病、心血管疾病和情绪障碍等领域的临床应用提供更坚实的理论基础,也对进一步拓展针灸治疗疾病的种类,挖掘PVN在其他未被充分研究疾病中的调控作用及针灸干预潜力有积极意义。

*　　*　　*

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