肥大细胞在针灸镇痛中的作用机制研究进展

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摘要：针灸是一种传统中医治疗方法，目前关于针灸镇痛的研究发现，肥大细胞参与了针灸镇痛的触发机制。皮肤肥大细胞在针灸干预期间（包括插入和操作细针）的穴位中以高密度存在。针灸操作产生力和扭矩，通过胶原网络间接激活肥大细胞。随后，各种介质如组胺、血清素、三磷酸腺苷和腺苷等，从活化的肥大细胞释放到间质空间，它们或其下游产物激活位于外周神经节感觉神经元局部神经末梢的相应受体。因此，目前研究认为针灸镇痛作用可能是通过初级感觉神经元的电活动减少而产生的。或者，这些神经元将这些信号投射到脊髓和/或大脑更高中心的疼痛相关区域。

关键词：肥大细胞；针刺镇痛；机制研究

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Research Progress on the Mechanism of Mast Cells in Acupuncture Points Analgesia

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ABSTRACT: Acupuncture and moxibustion is a traditional Chinese medicine treatment method, which has gradually been recognized and accepted by the world. At present, many studies on acupuncture analgesia have found that subcutaneous mast cells participate in the trigger mechanism of acupuncture analgesia. Skin mast cells exist in high density in acupuncture points during acupuncture intervention (including insertion and manipulation of fine needles). Acupuncture and moxibustion operation generates force and torque, and indirectly activates mast cells through collagen network. Subsequently, various mediators such as histamine, serotonin, adenosine triphosphate and adenosine are released from the activated mast cells into the interstitial space, and they or their downstream products activate the corresponding receptors located at the local nerve endings of sensory neurons in the peripheral ganglia. Therefore, current research suggests that the analgesic effect of acupuncture and moxibustion may be caused by the reduction of electrical activity of primary sensory neurons. Alternatively, these neurons project these signals to pain related areas in the spinal cord and/or higher brain centers.

KEY WORDS: mast cells; acupuncture analgesia; mechanism research

0 引言

Von Recklinghausen在1863年发现了肥大细胞（Mast cells，MCs）[1]。此后，关于肥大细胞的起源、分布和功能的研究取得了巨大进展。目前研究发现MCs起源于骨髓中的造血细胞，MCs主要分布于人体皮肤[2]、消化道[3]、气道[4]等内外环境的交界处。以前认为MCs通过活化后释放细胞因子、趋化因子、蛋白酶和生物胺来引起过敏反应。目前，MCs也被认为与保护性宿主免疫有关，是先天免疫的哨兵和适应性免疫的调节剂[5-6]。诸多研究

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相继报道了经针刺作用刺激下MCs的迁移、聚集活化[7-8]。1977年，Song[9]等研究发现针灸可刺激穴位组织中的MCs，使细胞脱颗粒，释放出组胺、血清素、三磷酸腺苷（Adenosine triphosphate，ATP）及其代谢产物等生物活性物质。随后，辽宁中医学院研究人员[10]也观察到人体截肢标本中穴位区和非穴位区的MCs总数存在显著差异。

1 肥大细胞与穴位致敏

穴位的概念被引入中医作为针灸治疗的有效靶点。在各种病理的机械或热刺激下使穴位变得敏感[11]。Fei等人发现MCs、血管、神经束和淋巴管，以结缔组织为基础，形成了一个非常复杂的结构系统[12]。袁等人发现穴位主要是胶原纤维丰富的区域，如神经血管周围结缔组织、肌间结缔组织及神经周围结缔组织等[13]。在一项开创性的截肢组织形态学观察中，Song等研究者发现穴位区域的MCs数量明显多于非穴位区域，另外，还发现MCs位于神经末梢和血管附近[9]。Zhang等人在阳明经中发现MCs和神经末梢之间存在“突触样”连接[22]。

许多化学物质参与穴位敏化，形成所谓的“穴位敏化池”[14-15]。He等学者认为降钙素基因相关肽 (Calcitonin gene related peptide，CGRP)、组胺、P物质（Substance P，SP）、血清素和类胰蛋白酶参与了穴位致敏[16]。Ding N等人报道了MCs脱颗粒过程中血清素、组胺和类胰蛋白酶的释放调节了穴位致敏[17]。Wang 等人发现建模和针灸前后腺苷(Adenosine，Ado)浓度具有显著不同[18]。这些发现暗示了穴位化学物质的动态变化，由内部环境或外部刺激操纵。

2 针灸镇痛中的肥大细胞

得气是达到针灸效果的临床标准，这种感觉包括针刺引起的刺痛、麻木及沉重感等[19]。在得气状态下，针的机械刺激（提、插、捻转）有效地引起组织变形，信号容易传递到MCs，诱导其脱颗粒。这个假设得到了动物实验的支持。对大鼠的测试表明，从提升到插入操作产生的力范围为240~280 mN，捻转操作产生的扭矩范围为10~15 mN/mm[20]，通过缠绕在针头周围的皮下胶原纤维传递到更宽更深的空间[21-22]。人体穴位激活过程中可以将机械刺激转化为可识别的生物信号，经周围神经传递和中枢处理后到达靶器官，从而产生广谱或特异的镇痛作用[23]。MCs的激活是指成熟MCs储存的颗粒释放，从而触发生物学效应到相邻的细胞或组织，这个过程被称为MCs的脱颗粒。MCs的激活主要有三种方式：免疫原性、神经源性和物理激活[24]。许多研究已经证实，MCs在针刺过程中脱颗粒过程起核心作用[25]。张等人发现在佐剂性关节炎大鼠模型中针刺足三里穴后疼痛阈值的增加取决于邻近组织中的MCs脱颗粒。用色甘酸二钠（肥大细胞膜稳定剂）减少MCs脱粒后，针刺的镇痛作用得到抑制[26-27]。因此，他们得出结论，MCs在针刺镇痛中是必不可少的。

3 针灸信号传导的中介

3.1 腺苷和ATP

胞外ATP (Extracellular ATP，eATP)和其他嘌呤和嘧啶化合物，如Ado、ADP、UTP、UDP 和 UDP-葡萄糖是嘌呤能的重要介质发信号。它们从组织细胞中释放出来，以响应各种物理刺激，尤其是机械应力，例如拉伸、变形和剪切应力[28-29]。一旦释放，细胞外核苷酸会激活靶细胞上的嘌呤能受体，包括离子型 (P2X) 和G蛋白偶联 (P2Y和P1) 受体，从而调节许多生理/病理过程。

在踝关节佐剂关节炎（Adjuvant arthritis，AA）小鼠实验中，针刺足三里30min后，发现

Ado与AMP、ADP 和ATP 在足三里穴中聚集[30]。在针灸期间，非溶解释放和细胞溶解都会导致这种间质ATP聚集。其中ATP的非溶解释放可由如电压通道[31-32]、TRPA1通道[33]、TRPV4通道[33]等机械敏感通道介导。进一步研究表明，针刺足三里穴中Ado的积累可以通过使用色甘酸防止MCs脱颗粒来消除，同时针刺镇痛作用可被明显抑制。另外，除了手工针灸，电针也可调节Ado的聚集。此外，ATP已在体外被证实可通过各种物理刺激从MCs中释放出来，包括针刺和艾灸[34]。

据报道，在正常大鼠足三里穴针刺2min，检测到损伤相关分子高迁移率组框1蛋白和toll样受体4（Toll-like receptor 4，TLR4）的表达明显增加[35]，由此，考虑到针刺时由于细胞裂解引起的ATP释放也参与了这一过程。通常认为eATP是一种促炎介质，可以通过激活嘌呤能受体（P2受体）增强疼痛感知[36]。游离ATP离子电渗入皮肤会在人体中产生中度灼痛[37]。然而，胞外核苷酸酶的存在可能通过促进Ado的产生来逆转eATP在疼痛机制中的作用。对踝关节AA大鼠的进一步研究表明，在治疗的足三里穴位中上调和下调eATP水平可以分别抑制和复制针刺镇痛作用，这进一步暗示了ATP动员（包括释放和水解）对针刺镇痛的贡献。除了作为Ado的前体，从MC释放的ATP 还可以放大针刺信号。

3.2 组胺

组胺由MCs产生并储存在MCs中。Schneide等研究人员发现大鼠体内结缔组织中MCs含有大约10~20pg 组胺[38]。一旦离开细胞，组胺就会被组胺N-甲基转移酶HMT或脱氨二胺氧化酶迅速降解。在正常大鼠的合谷穴，经免疫组化分析发现，组胺在MCs上表达较弱。但在合谷穴针刺3min后，在MCs及其分离颗粒上呈强表达[39]。

组胺H_1受体是组胺在外周组织中进行多重反应相互作用的靶点[40]。在踝关节AA大鼠中，针刺镇痛作用可以通过用2-吡啶乙胺二盐酸盐局部激活H_1受体来复制，并且可以通过用马来酸氯苯吡啶局部抑制H_1受体减弱镇痛作用。这些发现表明，MCs相关组胺通过激活局部组胺H_1受体在针刺镇痛的触发机制中起关键作用。穴位中的组胺除了在针刺的启动机制中发挥作用外，可能还参与了其他相关事件。

3.3 MCs 和神经末梢参与针刺镇痛

皮肤上的针灸治疗被转化为神经信号，并由传入神经元传导至脊髓和中枢神经系统[41]。MCs和神经之间空间接触的特异性已在体内、外[42-43]得到证实。大鼠穴位中也存在MCs和神经纤维以及微血管的共定位[44]。在正常大鼠中，针刺足三里可增加坐骨神经和腰椎4~5背根的神经放电。但是通过使用色甘酸防止MCs脱颗粒可显著减弱这一作用[45-46]。在踝关节AA大鼠中，在针刺足三里治疗中用利多卡因阻断周围神经会减弱针刺镇痛作用，但不会抑制MCs的脱颗粒[47]。这些发现表明，经针刺激活的MCs最终通过将生物信号传递到附近的神经末梢，然后上行到中枢神经系统来参与镇痛作用。

考虑到目前研究发现神经源性炎症与MCs的激活之间存在因果关系。即MCs激活诱导从周围神经末梢释放肽，包括缓激肽、SP和血管活性肠肽 (Vasoactive intestinal peptide，VIP)、CGRP和胺，如组胺和血清素，这有助于炎症介导的过敏反应恶化[48-49]。同时，由于MCs介质介导的神经激活，还通过脱颗粒导致大量炎症介质从MCs中释放，进而增强神经源性炎症和疼痛感知[50-51]。

4 肥大细胞参与针灸镇痛的数学模型

穴位对机械刺激的反应包括局部MCs脱颗粒和生物递质的级联反应。Yannick等人通过数值模拟分析了MCs密度对针灸的影响[52]。石等人建立了一个数学模型来模拟MCs内钙

信号和脱颗粒[53]。姚等人提出了一系列数学模型，展示了针灸过程中的生物物理和生化过程。使用基于离子通道行为的微分方程描述MCs中的钙升高[54]，并研究了MCs网络中的钙信号传播[55]。数值模拟结果表明，针刺效果不仅取决于穴位的MCs，还受到局部MCs密度的影响。在MCs密度低的情况下，不会引发MCs脱颗粒和神经受体激活的连锁反应。人体绝大多数穴位都富含MCs，因此在这些穴位上针灸更容易产生针灸效果。

目前研究发现械刺激会激活MCs膜上的机械敏感离子通道并允许钙进入；细胞内钙的增加会激活蛋白激酶C并增加分泌颗粒对钙的敏感性，从而驱动胞吐作用和介质释放。释放的介质通过G蛋白连接受体触发细胞反应。同时，介质在细胞外空间中扩散或流动并激活其他MCs。

5 讨论

在本文中，我们回顾了MCs和针刺镇痛的文献，揭示针刺镇痛作用是通过在穴位处阻断周围神经，或阻断神经通路，或损伤部分中枢神经系统而发挥作用。过去几十年的这些研究成果，从穴位和针灸的物质基础（解剖、细胞和分子水平），到针灸信号的启动、转化和传播，从各个方面对针灸效果做出了科学解释。

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