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针刺调控胶质细胞改善阿尔茨海默病神经炎症反应的机制研究进展

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【摘要】 胶质细胞介导的神经炎症反应与阿尔茨海默病(AD)的发生发展密切相关。针刺能有效减轻AD症状,延缓病情进展。本文梳理了针刺调控胶质细胞改善AD神经炎症反应的相关研究,总结发现,针刺干预可通过促进MG向M2表型极化,诱导M1向M2转化;抑制AS的过度/异常活化,调节AS功能修复血脑屏障;良性调节MG→AS与AS→MG间的串扰对话等途径改善神经炎症反应,延缓AD进展。

【关键词】 阿尔茨海默病;针刺;胶质细胞;神经炎症反应;综述

Research progress on the mechanism of acupuncture regulating glial cells to alleviate neuroinflammation in Alzheimer's disease

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【ABSTRACT】 Glial cell-mediated neuroinflammation is closely related to the occurrence and development of Alzheimer's disease (AD). Acupuncture can effectively alleviate AD symptoms and slow disease progression. This article reviews reports on acupuncture regulation of glial cells to improve AD-related neuroinflammation and summarizes that acupuncture intervention can improve neuroinflammation and delay AD progression through the following mechanisms: (1) promoting microglia (MG) polarization toward the M2 phenotype and inducing the conversion of M1 to M2; (2) inhibiting excessive/abnormal activation of astrocytes (AS) and regulating AS function to repair the blood-brain barrier; (3) benign regulation of crosstalk between MG→AS and AS→MG through dialogue and other pathways improves neuroinflammation and delays AD progression.

【KEYWORDS】 Alzheimer's disease; Acupuncture; Glial cells; Neuroinflammation; Review

阿尔茨海默病(AD)是老年人群中常见的慢性神经退行性疾病,临床主要表现为渐进性认知功能减退、日常生活能力丧失,并伴有精神或行为异常^[1]。研究证实,认知类疾病是针灸的主导性疾病之一^[2],针灸干预可显著改善AD患者的认知功能、提高日常生活能力,是治疗本病的临床有效方法之一^[3-4]。AD的发病机制主要为细胞外 β -淀粉样蛋白(A β)沉积与细胞内tau蛋白过度磷酸化引起的神经元功能损害或丢失^[5-7]。研究显示,胶质细胞介导的神经炎症反应贯穿于本病发展的全过程^[8-9]。近年来,针刺通过调控胶质细胞,改善神经炎症级联反应,延缓AD进展的机制研究日益增多。本文基于

现有研究,总结小胶质细胞(MG)、星形胶质细胞(AS)功能异常及两者间串扰在AD发生发展中的作用,并梳理总结了针刺调节胶质细胞介导的神经炎症反应改善AD的相关研究,以期针刺治疗AD提供科学依据。

1 针刺调控MG改善AD神经炎症反应

MG是中枢神经系统中的固有免疫细胞。生理状态下以静息态巡视脑内微环境,履行免疫监视功能^[10];在病理改变下转为活化态,发挥吞噬作用并参与炎症反应、免疫应答等过程^[11]。活化后的MG可转化为促炎表型M1和抗炎表型M2^[12],M1型释放促炎因子诱导并加剧神经炎症反应,导致神经细胞

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变性;M2型通过释放抗炎因子抑制炎症反应,发挥神经保护作用^[13]。在AD早期,沉积的A β 寡聚体结合髓样细胞触发受体2(TREM2)与Toll样受体(TLRS),激活MG并使其向M2表型转化,发挥吞噬功能降解A β ^[14];同时M2通过释放白细胞介素-(IL)-10、IL-4、转化生长因子- β (TGF- β)等抗炎因子,抑制炎症反应并修复损伤的神经元^[15]。在AD后期,当A β 持续沉积且无法清除时,MG过度活化转为M1型,一方面释放IL-1、肿瘤坏死因子- α (TNF- α)等神经毒性趋化因子损伤神经元^[16];另一方面,分泌IL-6等促炎因子,将健康神经元卷入炎症反应,扩大损伤范围^[17]。此外,M1可激活核因子- κ B(NF- κ B)通路,而NF- κ B作为调控M1活化的关键转录因子^[18],其持续激活会促进促炎因子的大量产生,不断加剧炎症反应。这表明M1型的活化是AD神经炎症反应恶性循环的关键诱因。研究表明,针刺可通过调控MG的表型极化及改善相关通路的活性起到抑制神经炎症反应,减轻AD病情进展的效果。

1.1 调节MG表型极化

研究表明,电针治疗可促进AD模型大鼠海马区MG向M2抗炎表型极化,同时抑制其向M1表型极化,减少下游促炎因子的释放^[19]。杨佳一等^[20]研究结果显示,电针“百会”“印堂”,可改善SAMP8小鼠的空间学习记忆能力,其机制与抑制MG向M1转化并降低AD小鼠海马区内IL-1 β 、IL-6、TNF- α 等促炎因子的表达相关;同时能降低脾脏相关炎症因子的表达,提示针刺可能通过调节外周免疫状态间接影响中枢神经炎症反应。由此表明针刺可通过调控MG的表型减少促炎因子的释放,改善神经炎症反应。

1.2 调控MG相关信号通路的活性

1.2.1 JAK/STAT信号通路

酪氨酸蛋白激酶2/信号转导与转录激活因子3(JAK2/STAT3)是介导MG活化并促使其向促炎极化的关键通路之一^[14]。李真等^[21]观察了电针对AD大鼠海马CA1区MG及JAK2/STAT3信号通路相关分子的影响,结果表明电针干预后海马神经元形态得以修复,这与MG激活程度下调,JAK2、STAT3、mRNA表达量显著降低,海马CA1区 γ -干扰素(IFN- γ)含量降低密切相关。细胞信号抑制蛋白3(SOCS3)是细胞因子信号抑制蛋白SOCS家族中的一员,可抑制JAK2/STAT3的活化^[22]。刘静等^[23]研究证实,针灸干预可显著上调AD模型大鼠

负调控因子细胞SOCS3的表达水平,降低JAK2、STAT3的表达量,抑制JAK2/STAT3通路的过度激活,减轻神经炎症反应的发生,改善AD大鼠的学习记忆功能。综上表明针刺可通过抑制JAK/STAT通路的过度激活减轻AD神经炎症。

1.2.2 TLR4/NF- κ B信号通路

MG中高表达的TLR4是识别配体并启动促炎信号的关键分子^[24];NF- κ B作为其下游转录因子,在炎症应答中起核心作用^[25]。抑制TLR4的表达,可阻断MyD88/NF- κ B/NLRP3激活,促进MG表型从M1向M2转化^[26]。何川等^[27]观察了预针刺对AD大鼠空间学习记忆能力、MG及TLR4/NF- κ B信号通路相关分子表达的影响,结果显示预针刺可降低TLR4、NF- κ B p65蛋白表达,抑制该通路活性,阻断M1型MG的极化,减轻神经炎症。NLRP3是TLR4/NF- κ B的下游炎症小体,经电针治疗后,AD小鼠海马区TLR4、NF- κ Bp65、NLRP3的表达降低^[28],再次说明针灸可通过调控TLR4/NF- κ B/NLRP3炎症通路的活性,抑制MG向促炎表型转化,减轻神经炎症反应。

1.2.3 PI3K/Akt信号通路

磷脂酰肌醇3-激酶/蛋白激酶B(PI3K/Akt)信号通路参与调节神经元的增殖、分化、凋亡及调控突触可塑性等过程^[29]。研究显示,在AD中PI3K/Akt通路的信号失调,将加剧A β 沉积和促炎因子的产生,促使MG异常激活^[30]。GSK-3 β 是PI3K/Akt信号通路的下游激酶^[31],参与调控NF- κ B等转录因子,驱动MG向促炎表型转化与迁移。通过嗅三针干预可显著提高PI3K/Akt的活性,促进GSK-3 β 磷酸化失活,同时上调突触素(SYN)、突触后致密物(PSD-95)和GAP43的蛋白表达,缓解A β ₁₋₄₂诱导的神经炎症^[32]。曹育等^[33]的研究结果显示,“通督调神”针法可改善A β ₂₅₋₃₅诱导的AD大鼠认知障碍,减少A β 生成和神经元损伤,其机制与激活PI3K/Akt/GSK-3 β 通路有关。综上,针刺干预通过调控PI3K/AKT信号通路的活性可显著减轻神经炎症反应,延缓AD病情进展。

2 针刺调控AS减轻AD神经炎症

AS是中枢神经系统中占比最多的胶质细胞,主要发挥维持突触与血脑屏障(BBB)稳态,为神经元提供营养支持并调控其活动的作用^[34-35]。病理状态下AS将分化为A1(神经毒性)和A2(神经保护)表型^[36]。A1型会诱导促炎反应,通过丧失突触支持

功能、引发谷氨酸稳态失调导致兴奋性毒性进而损伤神经元^[37-39]。A2型则释放神经抗炎因子发挥神经保护作用^[37]。在AD早期,沉积的A β 与AS表面的 $\alpha 7$ 烟碱型乙酰胆碱受体结合后激活AS,并优先极化为A2表型。A2通过清道夫受体、低密度脂蛋白受体相关蛋白、胰岛素受体识别并吞噬异常的A β ,将其转运至溶酶体降解^[40],同时可分泌IL-4、IL-10、IL-13和TGF- β 等抗炎因子抑制炎症^[39]。随着AD进展至晚期,A β 大量沉积、线粒体碎片堆积、氧化应激加剧及神经炎症持续加重等多重病理因素作用下,AS由A2向A1转化。A1型分泌的促炎因子与突触变性和兴奋性毒性共同构成一个正反馈环路,使AS从初期的“清道夫”转变为神经炎症的推动者,加速AD病情恶化^[41-42],针刺可通过抑制AS的异常活化、调控AS功能修复血脑屏障以及调控相关通路的活性起到减轻神经炎症级联反应,改善认知功能的目的。

2.1 抑制AS的过度/异常活化

在AD中,针刺通过调节AS的功能状态,发挥神经保护作用。胶质纤维酸性蛋白(GFAP)的含量升高是AS活化的标志。邵淑君等^[43]证实,音乐电针与脉冲电针均可改善AD小鼠学习记忆能力并减少海马CA1区GFAP阳性细胞的表达,抑制AS的活化,但前者优于后者。此外,Wang等^[44]在APP/PS1转基因小鼠模型中发现,为期4周的重复电针治疗可改善小鼠的学习能力并下调海马区GFAP及N-myc下游调节基因2(NDRG2)的表达水平,而NDRG2仅存在于GFAP免疫阳性的AS中。提示针刺可通过下调GFAP的表达,抑制AS的异常活化。此外,针刺可抑制AS的过度活化,促使其向静息态或适度活化态转变,通过增强突触内环境稳态,发挥神经保护作用。柯超等^[45]研究表明,电针心经、心包经的“极泉”“少海”“灵道”等穴可降低A β 沉积、调控谷氨酸转运体EAAT2、VGLUT2的表达并修复突触损伤。谷氨酸受体相互作用蛋白1(GRIP1)和谷氨酸受体相互作用蛋白2(GRIP2)调节突触后膜 α -氨基-3-羟基-5-甲基-4-异唑丙酸(AMPA)受体亚基在于细胞膜与突触后膜上的分布,而AMPA受体决定突触传递功能。在AD病理中,该调控失衡会引发突触功能异常与认知损害。刘若兰等^[46]的报道进一步揭示了电针可降低GRIP1和GRIP2的表达水平,提高突触后膜AMPA受体数量,增强突触可塑性,减少神经元的丢失。

2.2 调节AS功能修复血脑屏障

BBB是维系血液与脑之间的结构性屏障,其功能受损可导致脑内环境紊乱、级联反应激活及神经元的损伤^[47-48]。AS是BBB的结构之一,与内皮细胞、周细胞共同维持脑内微环境^[49]。研究表明,AS的异常活化通过释放NO和ROS毒性物质,诱导紧密连接蛋白发生磷酸化以及降解,进一步破坏BBB的功能^[50]。冯智鹏等^[51]研究显示,电针干预可提高小鼠的学习记忆能力,并上调小鼠海马中紧密连接蛋白的含量,修复BBB的功能,进一步改善AD认知功能障碍。邓畅等^[52]研究表明,电针干预可改善痴呆大鼠BBB的通透性,其机制与抑制AS的过度活化密切相关。综上,针刺可通过调控AS的活化,修复BBB的结构与功能,发挥改善认知的作用。

2.3 调控AS相关信号通路的活性

2.3.1 MAPK信号通路

丝裂原活化蛋白激酶(MAPK)由细胞外信号调节激酶(ERK)、p38 MAPK和c-Jun氨基末端激酶(JNK)组成,参与调节细胞的增殖、运动、分化和迁移等^[53]。其中p38 MAPK的抑制可降低AS的炎症损伤,表明抑制p38MAPK信号通路可改善AD的神经炎症损伤^[54]。张敏等^[55]报道,电针“百会”“肾俞”后,AD大鼠海马区p-p38MAPK和p-tau Thr181含量降低,学习记忆能力提高。方剑乔等^[56]的研究结果与张敏一致。由此表明,针刺可通过抑制MAPK信号通路的活性减轻中枢炎症反应,改善AD认知功能。

2.3.2 Notch信号通路

Notch信号通路包括Notch受体、Notch配体和DNA结合蛋白,参与细胞增殖、分化、凋亡等^[57]。在AD中,Notch通路表现持续性过度激活,将增殖分化作用变成病理因素,驱动AS过度激活,诱发并加剧神经炎症。碱性螺旋—环—螺旋(bHLH)转录抑制因子(Hes1)是Notch通路中的负性转录控制因子,Hes1含量升高将抑制细胞增殖和分化。李龙洋等^[58]以APP/PS1小鼠为模型,电针“百会”“风府”“肾俞”,观察Notch通路的变化,结果显示,与模型组相比,电针组A β 斑块减少,海马区Notch1的mRNA含量升高,而Hes1的mRNA的表达下降,提示针刺通过调控Notch信号通路,增强细胞增殖和分化,并抑制AS的过度活化,减少促炎因子的释放,修复神经元,改善AD认知功能。

3 针刺调节胶质细胞串扰防治AD神经炎性

MG与AS存在“串扰(crosstalk)”表型,即二者利用细胞间的相互作用,发生动态功能“对话”,通过分泌生长因子、趋化因子、神经递质等多种可溶性介质,进行双向信息交流与调控^[59],这对维持神经系统的稳态至关重要。研究发现,疾病状态下MG与AS间的串扰具有抗炎和抑炎的双重性,提示其参与AD的发生发展过程。

3.1 调节MG→AS的相互作用

3.1.1 调节不同阶段介导MG→AS表型转换

AD早期,在A β 寡聚体、过度磷酸化Tau蛋白等刺激下,MG极化为M2表型,通过分泌IL-10等与AS表面的IL-10R结合,激活下游JAK/STAT3通路,促使AS向A2型极化并分泌保护性的TGF- β ,二者协同起到抗炎作用^[60]。在AD晚期,积聚的异常蛋白将作为危险信号刺激MG表面的TLR受体,驱动MG活化为M1型,释放IL-1、TNF- α 及补体因子C1q。其中前两者分别与IL-1受体、TNF- α 受体结合激活AS并与AS上的C1q共同促使AS向A1型转变^[61],诱导炎性级联反应。同时,A1型AS下调谷氨酸转运体GLT-1,降低对谷氨酸的摄取能力,导致突触间隙谷氨酸堆积引发产生兴奋毒性,加剧神经元损伤与AD的病理进展。针刺干预可显著降低脑损伤大鼠海马区IL-1、TNF- α 的表达,上调GLT-1的含量,降低MG→AS的异常串扰,抑制A1型活化,减少神经元损伤^[62]。这为针刺调控MG→AS间的相互作用,减轻AD神经炎性,发挥神经保护作用提供了实验依据。

3.1.2 调控细胞因子介导MG→AS抗炎反馈

在神经炎性中,MG极化为M1通过释放促炎因子,诱导AS活化。一方面,针刺干预可使MG向M2型极化,抑制AS的激活,并减少促炎因子的释放,增加抗炎因子的表达^[36];另一方面,静息态的AS也可通过分泌脑源性神经营养因子(BDNF),进一步维持M2型极化状态,形成抗炎正反馈循环。这一推论可在针刺治疗AD的相关研究中得到间接佐证,针刺可减少促炎因子含量,同时提升BDNF含量并且胶质细胞活化程度明显降低,提示二者的串扰模式发生有益转变。相关研究已证明^[63],电针可抑制三叉神经脊束核尾侧亚核区MG和AS活化及促炎细胞因子释放,缓解神经病理性疼痛。由此可知,针刺可通过多靶点调控MG与AS之间的复杂串扰途径,缓解神经炎性,但在AD中的机制仍有待深入研究。

3.2 调节AS→MG的相互作用

3.2.1 介导抗炎因子促进AS→MG保护性交互作用

AS活化后可向A2极化,分泌IL-3、IL-4等抗炎细胞因子,是介导AS→MG正向调控、维持神经免疫稳态的核心物质,可增强MG的A β 吞噬能力、抑制过度神经炎性。研究发现,A2型分泌的IL-3可增强MG的吞噬,减少A β 沉积,提示IL-3是介导AS→MG相互作用的关键物质^[64]。此外,A2分泌的IL-4与MG上的受体结合,可激活下游JAK/STAT6信号通路,上调TREM2表达并调控MG的自噬水平,抑制TLR4诱发的神经炎性,缓解AD病情进展^[65]。结合上述机制推测针刺可通过调节神经—免疫微环境,促进AS分泌IL-3、IL-4等抗炎因子,增强MG的A β 吞噬并调控其自噬,抑制神经炎性。

此外,二者还可通过纤溶系统调控因子纤溶酶原激活物抑制物(PAI-1)实现相互作用。AS主要分泌PAI-1,炎性条件下MG也参与PAI-1的分泌,共同维持其在脑内的有效浓度^[66]。胶质细胞(以AS为主)分泌的PAI-1通过旁分泌结合MG表面的该受体激活下游JAK/STAT1信号通路,促进MG的迁移;同时通过玻璃体链接素介导结合MG的TLR2/6调控其对病理产物的吞噬作用^[66]。吴绪平等^[67]报道,针刺“百会”“水沟”后,PAI-1的含量降低,提高了纤溶系统的活性。由此可知,PAI-1介导的胶质细胞交互及针刺调控效应,可进一步推导其在AD中的潜在作用机制。

3.2.2 抑制C3/C3aR通路阻断AS→MG有害串扰

在A β 等病理产物刺激下,AS合成并分泌补体蛋白C3a,与MG表面的C3aR发生特异性结合后可诱导MG内信号转导与转录激活因子3(STAT3)磷酸化,损害MG吞噬A β 能力并促进其向促炎极化,加重神经炎性与认知功能受损^[68-69]。陈丽敏等^[70]观察到SAMP8小鼠CA1区AS标志物GFAP与MG标志物离子钙结合衔接分子1(Iba1)增多,同时下游p-STAT3信号激活并伴随突触蛋白丢失和小鼠记忆功能障碍,电针干预可抑制C3/C3aR/STAT3信号通路的激活,改善突触功能,提高小鼠的学习记忆能力。这表明电针改善认知功能可能是通过抑制C3/C3aR介导的胶质细胞间串扰,进一步阻断STAT3信号通路的激活。陈莉等^[71]研究指出,通过七氟烷可激活NF- κ B/C3a/C3aR通路,而C3a抑制剂能靶向阻断该通路中C3a与C3aR的结合,共同

抑制该通路的过度激活,进而减轻神经炎性与海马组织损伤,最终改善大鼠的工作记忆力。基于陈丽敏研究中“电针抑制 C3/C3aR 通路”的结果,结合陈莉的研究,由此推测,针刺的作用可能是阻断 C3 与 C3aR 的结合,进而抑制 NF- κ B/C3a/C3aR 通路的过度激活,减少胶质细胞间有害串扰。

4 小结

综上所述,胶质细胞介导的神经炎性在 AD 发生发展中起关键作用,针刺调控胶质细胞活性与功能改善 AD 中枢炎性的作用机制主要包括:(1)促进 MG 向 M2 表型极化;抑制 JAK/STAT、TLR4/NF- κ B 信号通路,激活 PI3K/AKT 信号通路诱导 M1 向 M2 转化。(2)控制 AS 的过度活化;抑制 p38MAPK 通路、Notch 通路活性减少 AS 异常活化;调节 AS 功能修复血脑屏障。(3)抑制 C3/C3aR 通路、调控细胞因子表达良性调节 MG $\rightarrow$ AS 与 AS $\rightarrow$ MG 间的对话。

但目前的研究仍存在一些不足:(1)AD 中胶质细胞具有双重作用,既可清除有害物质、分泌神经营养发挥神经保护效应,又因过度活化触发神经炎性级联反应,加剧神经元与突触损伤。但当前研究尚未系统阐明针刺如何介导胶质细胞保护/损伤表型精准转换,其调控机制仍缺乏跨分子、细胞、组织及整体层面的多层次验证,也缺少多时序、多组学的实验支撑;(2)现阶段采用的 AD 动物模型多为单一基因或病理诱导模型,无法完整模拟人类 AD 病程中胶质细胞活化的异质性、神经炎性网络的复杂性与真实性。同时,多数研究偏重体外细胞培养或离体脑组织检测,无法还原脑内微环境下细胞间动态交互与神经-免疫网络的整体调控状态,易导致对胶质细胞活化特征、炎性反应强度及针刺干预效应被放大或降低,难以真实反映针刺在体内调控胶质细胞表型转换的动态规律与实际效果;(3)针刺对串扰机制的系统性研究仍较薄弱,现阶段多数集中于单一细胞类型的功能观察,缺乏对细胞-细胞、细胞-神经元等细胞间交互串扰的探究,未阐释针刺刺激参数(如穴位选择、刺激强度)与胶质细胞间串扰的对应关系。未来研究应结合多组学技术、光遗传学等现代手段,深入探讨针刺调控胶质细胞网络的分子与细胞基础,推动针刺在 AD 的防治。

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