

电针调控HIF-1 α /PFKFB3信号通路改善阿尔茨海默病小鼠糖酵解的机制研究

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【摘要】 目的:观察电针干预对阿尔茨海默病(AD)小鼠海马组织低氧诱导因子1 α (HIF-1 α)/磷酸果糖激酶双功能酶3(PFKFB3)信号通路及糖酵解功能的调控作用,探讨其改善认知障碍的可能机制。**方法:**采用APP/PS1转基因小鼠作为AD模型,随机分为模型组、电针组和电针+二甲基草酰亚胺(DMOG)组,每组6只;另取同龄C57BL/6J小鼠6只作为对照组。电针组取“百会”针刺,同侧“肾俞”“足三里”进行电针,每次20 min,隔日1次,共4周;电针+DMOG组在电针组基础上,在第4周每次电针干预结束后30 min腹腔注射DMOG(50 mg/kg)。Morris水迷宫与新物体识别实验评估小鼠认知功能,HE染色观察小鼠海马组织结构变化,免疫组织化学法检测小鼠海马 β -淀粉样蛋白(A β 1-42)沉积情况;ELISA法检测小鼠海马组织丙酮酸激酶M2型(PKM2)、乳酸脱氢酶A(LDHA)含量;生化法检测海马组织己糖激酶(HK)活性、乳酸含量;实时荧光定量PCR法检测海马HIF-1 α 、PFKFB3、HK、PKM2、LDHA mRNA表达水平;Western blot法检测海马HIF-1 α 、PFKFB3蛋白水平;免疫荧光染色检测海马LDHA表达水平。**结果:**与对照组比较,模型组小鼠逃避潜伏期延长、穿越平台次数减少、新物体识别指数下降($P<0.01$),海马神经元形态异常,A β 1-42沉积增加($P<0.01$),海马组织HK活性及PKM2、LDHA、乳酸含量升高($P<0.01$),HIF-1 α 与PFKFB3蛋白表达水平及HIF-1 α 、PFKFB3、HK、PKM2、LDHA mRNA表达水平,LDHA荧光强度升高($P<0.01$)。与模型组比较,电针组逃避潜伏期降低、穿越平台次数增加、新物体识别指数升高($P<0.01$),海马神经元结构更完整,A β 1-42沉积减少($P<0.01$),海马组织HK活性及PKM2、LDHA、乳酸含量降低($P<0.01$),HIF-1 α 与PFKFB3蛋白表达水平及HIF-1 α 、PFKFB3、HK、PKM2、LDHA mRNA表达水平,LDHA荧光强度降低($P<0.01$)。与电针组比较,电针+DMOG组上述指标逆转($P<0.01$, $P<0.05$)。**结论:**电针可显著改善AD模型小鼠认知功能,其作用机制可能与抑制海马HIF-1 α /PFKFB3通路,降低糖酵解关键酶活性及乳酸异常积累有关。

【关键词】 阿尔茨海默病;电针;糖酵解;认知功能;低氧诱导因子1 α ;磷酸果糖激酶双功能酶3

Electroacupuncture improves glycolysis in Alzheimer's disease model mice via regulating HIF-1 α /PFKFB3 signaling pathway

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【ABSTRACT】 Objective To observe the effect of electroacupuncture (EA) on the cognitive ability, hypoxia-inducible factor-1 alpha (HIF-1 α)/6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase 3 (PFKFB3) signaling pathway and glycolytic function in the hippocampus of Alzheimer's disease (AD) model mice, so as to elucidate its potential mechanism underlying improvement of cognitive function. **Methods** Male APP/PS1 transgenic mice were used as the AD model and randomly divided into model, EA and EA plus dimethylxaloylglycine (DMOG, antagonist of α -ketoglutarate cofactor and inhibitor of HIF prolylhydroxylase) groups ($n=6$ each). Age-matched C57BL/6J mice served as the control group ($n=6$). EA stimulation (2 Hz, 1 mA) was applied to bilateral "Shenshu" (BL23) and "Zusanli" (ST36), acupuncture was applied to "Baihui" (GV20) for 20 min, once every other day for 4 weeks. The mice in the EA+DMOG group was received intraperitoneal injection of DMOG (50 mg/kg) solution on the basis of EA starting from the 4th week. The mouse's cognitive function was evaluated by using Morris water maze and novel object recognition tests. Hematoxylin-eosin (H. E.) staining and immunohistochemistry were used to observe hippocampal neuronal morphology and β -amyloid (A β) 1-42 deposition. The contents of pyruvate kinase M2 (PKM2) and lactate dehydrogenase A (LDHA) in the hippocampal tissue were assayed using ELISA, and the activity of hippocampal hexokinase (HK) and content of lactic acid were detected using biochemical methods. Western blot was employed to detect the expression levels of hippocampal HIF-1 α and PFKFB3 protein, and real-time quantitative PCR was employed to detect the expression levels of hippocampal HIF-1 α , PFKFB3, HK, PKM2, and LDHA mRNAs. The immunofluorescence histochemistry technique was used to measure the fluorescence intensity of hippocampal LDHA.

Results Compared with the control group, the model group showed significantly longer escape latency, fewer platform crossings and lower novel object recognition index ($P<0.01$). After EA intervention, the escape latency was evidently shorter, the platform crossings and the novel object recognition index were apparently increased in the EA group ($P<0.01$), suggesting an improvement of the recognition ability and learning-memory ability. Following administration of DMOG, the effects of EA in shortening the escape latency, and increasing the number of platform crossings and novel object recognition index were eliminated ($P<0.01$, $P<0.05$, compared with the EA group). In contrast to the control group, the model group had a considerable increase in the optical density of A β 1-42, contents of PKM2, LDHA, lactate, and HK activity, expression levels of HIF-1 α and PFKFB3 proteins and mRNAs, and HK, PKM2, LDHA mRNAs, and LDHA fluorescence density ($P<0.01$). Compared with the model group, the increased levels of A β 1-42 optical density, contents of PKM2, LDHA, lactate and HK activity, expression levels of HIF-1 α and PFKFB3 proteins and mRNAs, and HK, PKM2, LDHA mRNAs, and LDHA fluorescence density were all reversed in the EA group ($P<0.01$). In comparison with the EA group, the decreased levels of A β 1-42 optical density, contents of PKM2, LDHA, lactate, and HK activity, expression levels of HIF-1 α and PFKFB3 proteins and mRNAs, and HK, PKM2, LDHA mRNAs, and LDHA fluorescence intensity were reversed by EA+DMOG ($P<0.01$, $P<0.05$). HE staining showed swollen or disintegrated neuronal cell bodies in the hippocampal CA1 region, deepened nuclear staining and expanded intercellular space in the model group. In comparison with the model group, the EA group (not the EA+DMOG group) displayed relatively intact nuclei of neurons, mitigated swelling of cell body and reduction in the infiltration of inflammatory cells and uniform distribution of cells in the CA1 region. **Conclusion** EA can significantly improve the cognitive function in AD model mice, which may be related to its function in inhibiting the hippocampal HIF-1 α /PFKFB3 signaling pathway to reduce glycolytic enzyme activity and abnormal lactate accumulation.

【KEYWORDS】 Alzheimer's disease; Electroacupuncture; Glycolysis; Cognitive ability; Hypoxia-inducible factor-1 α ; 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3

阿尔茨海默病(AD)是一种常见神经退行性疾病,以进行性认知障碍、记忆衰退、行为异常和日常生活能力丧失为主要特征^[1-2],导致患者生活质量严重下降,并给家庭和社会造成沉重负担^[3]。AD病理特征包括脑内 β 淀粉样蛋白(A β)沉积、tau蛋白过度

磷酸化形成的神经纤维缠结及神经元丢失^[4-5],海马区作为记忆与学习的核心区域,是最早且受累最严重的脑区^[6-7]。流行病学数据显示,全球AD患者已超5 000万,预计2050年将达1.5亿^[8];我国AD发病率约5%~7%,以65岁以上老人为主,且发病率呈

上升趋势^[9]。

AD的病因病机复杂,多因素作用导致的脑内稳态失衡被认为是其病理学基础^[10]。越来越多的证据表明,糖代谢异常对神经元能量供应的干扰在AD的发生与进展中具有重要作用^[11]。研究证实,AD小鼠脑组织中糖酵解关键酶如己糖激酶(HK)、磷酸果糖激酶双功能酶3(PFKFB3)、丙酮酸激酶M2型(PKM2)和乳酸脱氢酶A(LDHA)活性升高,导致L-乳酸积累和能量失衡,增强炎症信号,进一步加剧A β 沉积及神经元损伤^[12]。此外,低氧诱导因子-1 α (HIF-1 α)作为糖酵解核心调控因子,在AD中表达上调^[13],促进PFKFB3等靶基因转录,增强有氧糖酵解^[14],虽可维持细胞存活但却有加重代谢紊乱的风险^[15]。因此,抑制异常糖酵解、恢复能量与免疫稳态,已成为AD干预的重要研究方向之一^[14]。针灸疗法在治疗神经退行性疾病方面具有独特优势^[16],相关机制研究已从调节神经炎症反应^[17]、改善突触可塑性与线粒体功能^[18]等多层面展开。本团队前期研究表明,电针可有效改善AD模型动物的突触功能损伤与认知障碍^[19-20],提示其多靶点调节潜力。电针是否通过HIF-1 α /PFKFB3通路发挥作用,尚缺乏直接而系统的证据。已有资料显示,在AD相关炎症反应状态下,多种细胞因子可影响HIF-1 α 的稳定与活性^[21-22];HIF-1 α 进一步上调HK、PFKFB3、PKM2、LDHA等基因,推动乳酸生成与糖酵解偏移^[14,23]。基于此,本研究以APP/PS1小鼠为研究对象,探究电针对AD小鼠海马HIF-1 α /PFKFB3信号通路及糖酵解的影响,为电针的临床应用提供科学依据。

1 材料与方法

1.1 实验动物及分组

雄性SPF级5月龄APP/PS1双转基因小鼠18只,同窝野生雄性5月龄C57BL/6J小鼠6只,购自江苏华创信诺医药科技有限公司,生产许可证号:SCXK(苏)2020-0009。小鼠饲养温度(20 $\pm$ 2)℃、湿度(50 $\pm$ 5)%、明暗周期12 h/12 h。适应性饲养7 d后,采用随机数字表法将APP/PS1小鼠分为模型组、电针组、电针+二甲基草酰亚胺(DMOG)组,每组6只;剩余6只C57BL/6J小鼠为对照组。实验过程中对动物的处置遵照《关于善待实验动物的指导性意见》及相关实验动物伦理要求^[24],并经湖北中医药大学动物实验伦理委员会批准(批准号为HUCMS-02161236)。

1.2 试剂与仪器

戊巴比妥钠(美国Sigma),苏木精染液(美国Sigma),伊红染液(国药集团),DAB显色试剂盒(武汉赛维尔),A β 1-42抗体(英国Abcam),HRP标记的二抗(厦门通灵生物),Trizol试剂、ChamQ SYBR qPCR Master Mix试剂盒、HiScript II Q RT SuperMix试剂盒(南京Vazyme),GAPDH、HIF-1 α 、PFKFB3、LDHA抗体(武汉三鹰),HRP标记羊抗兔、鼠二抗、正常山羊血清(武汉博士德),ECL化学发光液(美国Affinity),Cy3羊抗兔IgG(美国赛默飞),DAPI(上海碧云天),鼠PKM2、LDHA的酶联免疫吸附测定(ELISA)试剂盒(江苏酶免),HK比色法试剂盒(武汉伊莱瑞特),乳酸试剂盒(南京建成),DMOG(美国MCE)。

一次性无菌针灸针(0.25 mm $\times$ 13 mm,苏州医疗用品厂),HANS-100A型电针仪(南京济生),Multiskan FC型酶标仪(美国赛默飞),Morris水迷宫(成都泰盟),新物体识别实验装置(上海欣软),台式高速冷冻离心机(湖南可成),病理切片机(上海徠卡),LF-600S型电泳仪电源(北京龙方科技),DYCZ-24DN型垂直电泳槽(北京六一),L00686C型eBlot™ L1快速湿转仪(南京金斯瑞),化学发光成像系统(杭州申花),QuantStudio 6型实时荧光定量PCR仪(美国ABI),低温高速组织研磨仪(武汉赛维尔),生物显微镜、荧光显微镜(日本尼康),Image J软件(美国NIH)。

1.3 干预措施

电针组、电针+DMOG组小鼠予以针刺“百会”“肾俞”“足三里”,参照《实验针灸学》^[25]进行取穴定位,穴位局部皮肤碘伏消毒。采用0.25 mm $\times$ 13 mm不锈钢针灸针刺入“百会”,并直刺双侧“足三里”“肾俞”,针刺深度为3~5 mm,同侧“肾俞”“足三里”的针柄分别接电针仪导线正、负极,连续波,频率2 Hz,电流强度1 mA,双侧穴位隔次轮流针刺,留针20 min,隔日1次,总疗程为4周。电针+DMOG组小鼠在第4周每次电针干预结束后30 min,予以DMOG(50 mg/kg)腹腔注射。对照组和模型组小鼠接受与电针组相同的抓握固定,但不进行电针干预。

1.4 观察指标及检测方法

采用Morris水迷宫实验评估小鼠的学习记忆功能:干预结束后第1天开始进行Morris水迷宫实验,采用圆形四象限水池,于第2象限水下1 cm处安置隐藏平台,并使用二氧化钛混悬液消除视觉线索。

每次测试时,将小鼠背对平台放入水池,记录其 60 s 内的逃避潜伏期时长;若 60 s 内小鼠未找到平台,则手动引导其至平台停留 10 s。每日训练 1 次,连续进行 5 d。训练结束后,开展空间探索实验,撤除水下平台,将小鼠从原平台对侧象限入水,记录其穿越原平台次数,以此判断空间记忆保持能力。

采用新物体识别实验评估小鼠的识别能力: Morris 水迷宫实验结束后次日进行新物体识别实验,连续进行 3 d。第 1 天为适应阶段,实验动物在敞箱(40 cm×40 cm×40 cm)内自由活动 5 min。第 2 天为习得阶段,箱内对称放置两个完全相同的圆柱形物体(直径 5 cm,高 10 cm),小鼠从相对位置放入后,给予 5 min 自由探索时间。第 3 天为测试阶段,将其中一个旧的圆柱形物体替换为新的立方体(5 cm×5 cm×5 cm),使用视频追踪系统记录 5 min 内实验小鼠鼻尖与各物体距离≤2 cm 的探索时间。每次测试间隔均采用 75% 乙醇溶液清洁装置及测试物体,以消除残留气味干扰。新物体识别指数=新物体探索时长÷(新物体探索时长+旧物体探索时长)。

取材方法:各组小鼠行为学检测结束后,采用 2% 戊巴比妥钠(50 mg/kg)腹腔注射麻醉,每组随机取 3 只小鼠全脑行 4% 多聚甲醛固定,其余小鼠取新鲜海马组织于-80℃冰箱冻存备用。

HE 染色观察海马 CA1 区组织形态变化:取 4% 多聚甲醛固定的脑组织样本,依次进行梯度乙醇脱水、二甲苯透明、浸蜡、包埋并切成约 4 μm 厚的石蜡切片,在 60℃恒温烘箱中烘烤 3 h。切片脱蜡复水后,苏木精染色 5 min,伊红染色 2 min,随后再经梯度乙醇脱水及二甲苯透明处理,树胶封片,在光学显微镜下观察海马组织形态。

免疫组织化学法检测海马 CA1 区 Aβ1-42 阳性表达:海马组织石蜡切片依次经二甲苯脱蜡、梯度乙醇复水处理后,进行抗原热修复。以 3% H₂O₂ 阻断内源性过氧化物酶活性,用正常山羊血清封闭非特异性结合位点;将 1:100 稀释的 Aβ1-42 一抗于 4℃孵育过夜,HRP 标记的二抗 37℃孵育 30 min;经 DAB 显色后,苏木精复染 2 min,依次行梯度乙醇脱水、二甲苯透明处理,最后以中性树胶封片。经显微镜拍摄脑组织海马 CA1 区,对各组小鼠 CA1 区 Aβ1-42 的平均吸光度值进行统计分析。

生化法检测小鼠海马组织 HK 活性、乳酸含量:每组取 3 只小鼠冰冻海马组织 15 mg,充分冰浴研磨后离心 10 min 取上清。根据试剂盒说明书步骤完

成检测流程,酶标仪测定在 568 nm 波长下的每孔吸光度值,绘制标准品标准曲线后得到回归方程,并根据回归方程计算 HK 活性、乳酸含量。

ELISA 法检测小鼠海马组织 PKM2、LDHA 含量:每组取 3 只小鼠冰冻海马组织 15 mg,按照试剂盒操作步骤进行检测,酶标仪在 450 nm 波长下读取各孔吸光度值,绘制标准品曲线后得到回归方程,并根据回归方程计算 PKM2、LDHA 含量。

实时荧光定量 PCR 法检测海马组织 HIF-1α、PFKFB3、HK、PKM2、LDHA mRNA 表达水平:每组取 3 只小鼠冰冻海马组织 15 mg,Trizol 法提取总 RNA,使用超微量紫外分光光度计检测其纯度与浓度。取 1 μg RNA,先经 gDNA 去除处理,随后采用 HiScript II Q RT SuperMix 试剂反转录合成 cDNA。以 cDNA 为模板,配制荧光定量 PCR 反应体系(含 2 μL cDNA、0.2 μL 上/下游引物、5 μL SYBR Green Master Mix、0.2 μL ROX 参比染料及 ddH₂O 补足至 10 μL),置于 ABI QuantStudio 6 实时荧光定量 PCR 仪进行扩增。反应程序为:95℃预变性 10 min;95℃变性 15 s,60℃退火/延伸 60 s,共 40 个循环;随后进行熔解曲线分析。所有样本均设 3 个复孔。以内参 GAPDH 为校正,采用 2^{-ΔΔC_t} 法计算 HIF-1α、PFKFB3、HK、PKM2 及 LDHA 基因的相对表达量。所用引物由擎科公司合成,引物序列见表 1。

Western blot 法检测海马 HIF-1α、PFKFB3 蛋

表 1 引物序列
Table 1 Primer sequences

基因	序列(5'→3')	产物长度/bp
HIF-1α	上游 GCTCATCAGTTGCCACTTCC	145
	下游 CCATCTGTGCCTTCATCTCATC	
PFKFB3	上游 CTGCCTACTAGCCTACTTCCTC	143
	下游 TGCTCACCGATTCTACATTCAAG	
HK	上游 TCAGAGCGCCTCAAGACAAG	243
	下游 GTTGTCCAGTCCACGGTTCT	
PKM2	上游 GTGGGGCCATTATCGTGCT	165
	下游 TCAGCACGGCATCCTTACAC	
LDHA	上游 GCACTGACGCAGACAAGGA	260
	下游 CTTCAACATCCGAGATTCCAT	
GAPDH	上游 ATGGCCTTCCGTGTTCTTAC	167
	下游 AAGTCGCAGGAGACAACCTG	

注:HIF-1α 为低氧诱导因子 1α,PFKFB3 为磷酸果糖激酶双功能酶 3,HK 为己糖激酶,PKM2 为丙酮酸激酶 M2 型,LDHA 为乳酸脱氢酶 A。

白表达水平:每组取3只小鼠冰冻海马组织15 mg,经RIPA裂解液匀浆处理后,进行离心并收集上清液。采用BCA法进行蛋白浓度定量,取40 μ g样品在沸水浴中变性处理。通过10% SDS-PAGE凝胶电泳分离蛋白,随后转印至PVDF膜。使用5%脱脂奶粉的TBST溶液在室温下封闭2 h。依次进行抗体孵育:HIF-1 α (1:1 000)、PFKFB3 (1:4 000)、GAPDH(1:30 000)抗体于4 $^{\circ}$ C孵育过夜;HRP标记二抗(1:10 000)于37 $^{\circ}$ C孵育2 h。经ECL化学发光液显影后,利用Image J软件分析目标蛋白与GAPDH的灰度值的比值。

免疫荧光染色法检测海马组织LDHA表达水平:取石蜡包埋脑组织切片,经二甲苯脱蜡及梯度乙醇复水后,采用0.01 mol/L EDTA缓冲液(pH9.0)实施抗原热修复。山羊血清封闭30 min,滴加LDHA一抗(1:100),于4 $^{\circ}$ C湿盒中孵育过夜。次日PBS清洗后,滴加Cy3标记的羊抗兔二抗(1:400),37 $^{\circ}$ C避光孵育1 h,DAPI染核封片,PBS冲洗,滴加

含DAPI的抗荧光淬灭封片剂封片,在荧光显微镜下观察LDHA阳性表达。使用Image J图像分析软件计算LDHA的平均荧光强度。

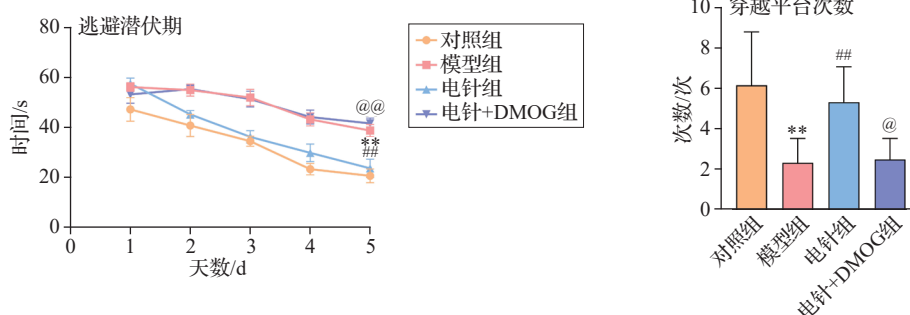
1.5 统计学分析

使用SPSS25.0软件进行统计学处理。若数据满足正态性分布,则以均数 $\pm$ 标准差($\bar{x}\pm s$)表示,多组数据比较采用单因素方差分析,进一步两两比较采用LSD法;若不满足正态性分布,采用非参数检验处理。以 $P\leq 0.05$ 为差异具有统计学意义的标准。

2 结果

2.1 各组小鼠Morris水迷宫结果比较

与对照组比较,模型组小鼠逃避潜伏期延长($P<0.01$),穿越平台次数减少($P<0.01$);与模型组比较,电针组小鼠逃避潜伏期缩短($P<0.01$),穿越平台次数增加($P<0.01$);与电针组比较,电针+DMOG组小鼠逃避潜伏期延长($P<0.01$),穿越平台次数减少($P<0.05$)。见图1。



注:DMOG为二甲基草酰亚胺。与对照组比较,** $P<0.01$;与模型组比较,## $P<0.01$;与电针组比较,@ $P<0.05$,@@ $P<0.01$ 。

图1 各组小鼠Morris水迷宫实验逃避潜伏期及穿越平台次数比较($\bar{x}\pm s$,6只鼠/组)

Fig. 1 Comparison of escaping latency and number of platform crossings in the Morris water maze test in mice of the 4 groups ($\bar{x}\pm s$, 6 mice/group)

2.2 各组小鼠新物体识别指数比较

与对照组比较,模型组新物体识别指数降低($P<0.01$);与模型组比较,电针组新物体识别指数升高($P<0.01$);与电针组比较,电针+DMOG组新物体识别指数降低($P<0.01$)。见图2。

2.3 各组小鼠海马CA1区HE染色结果比较

与对照组比较,模型组小鼠海马CA1区神经元细胞体肿胀或解体,细胞核染色加深,细胞间隙扩展;与模型组比较,电针组小鼠CA1区神经元细胞核较为完整,细胞体肿胀现象减轻,细胞周围炎性细胞浸润现象减少,细胞结构较完整,细胞分布更均匀;与电针组比较,电针+DMOG组小鼠CA1区

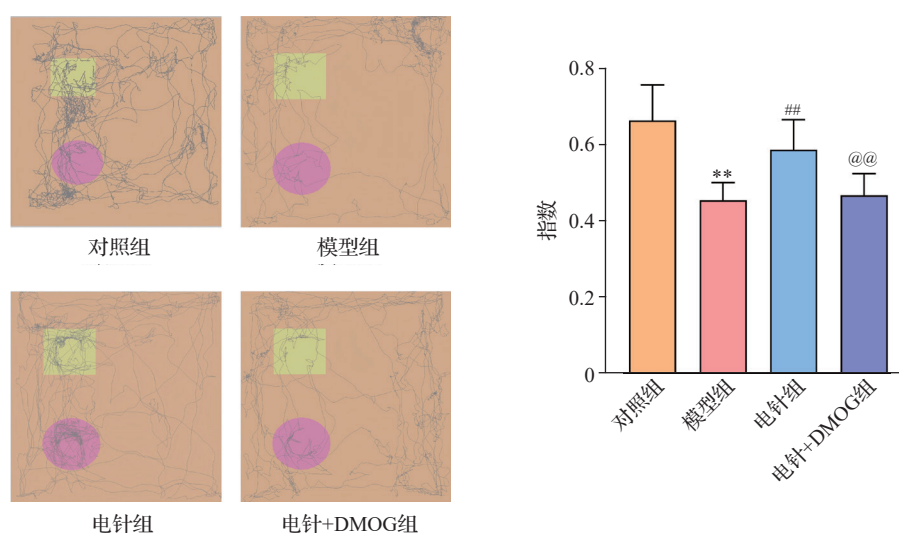
病理改善不明显,神经元细胞体肿胀,细胞核染色加深,细胞间隙扩展现象依然明显。见图3。

2.4 各组小鼠海马CA1区A β 1-42表达水平比较

与对照组比较,模型组小鼠海马CA1区A β 1-42吸光度值增加($P<0.01$);与模型组比较,电针组小鼠海马CA1区A β 1-42吸光度值减少($P<0.01$);与电针组比较,电针+DMOG组小鼠海马CA1区A β 1-42吸光度值增加($P<0.01$)。见图4。

2.5 各组小鼠海马组织PKM2、LDHA、乳酸含量及HK活性比较

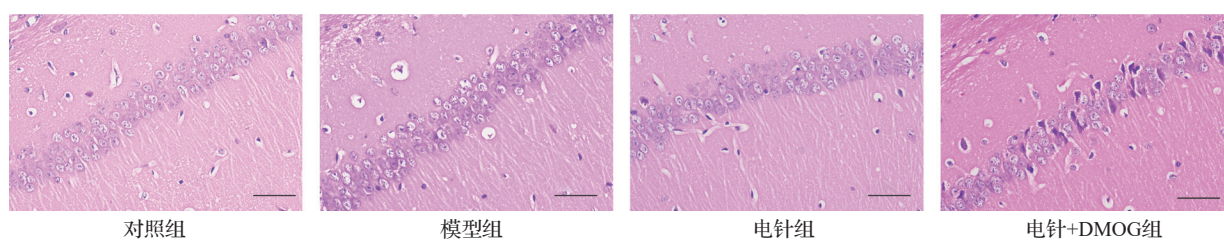
与对照组比较,模型组小鼠海马组织中PKM2、LDHA、乳酸含量及HK活性升高($P<0.01$);与模型



注:DMOG为二甲基草酰亚胺。与对照组比较,** $P<0.01$;与模型组比较,## $P<0.01$;与电针组比较,@@ $P<0.01$ 。

图2 各组小鼠新物体识别指数比较($\bar{x}\pm s$,6只鼠/组)

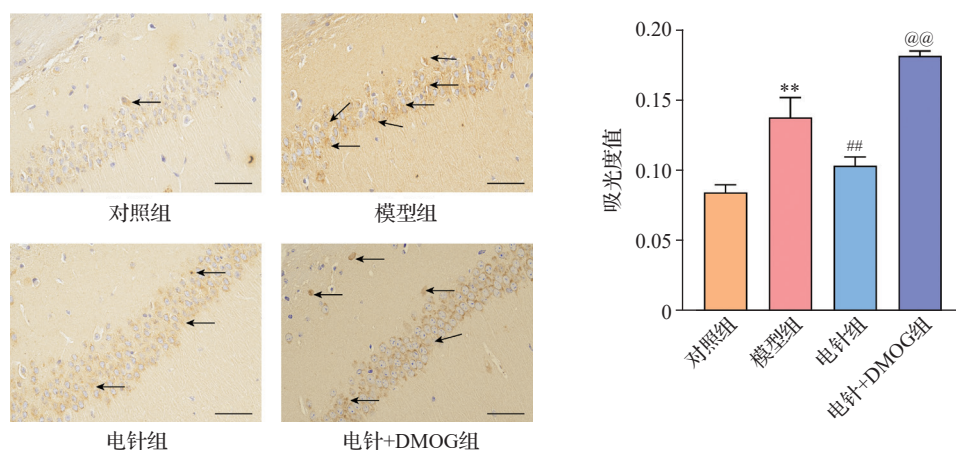
Fig. 2 Comparison of new object recognition index of mice in the 4 groups($\bar{x}\pm s$,6 mice/group)



注:DMOG为二甲基草酰亚胺。标尺=50 μm 。

图3 各组小鼠海马CA1区神经元组织形态比较(HE染色)

Fig. 3 Comparison of neuronal morphology in the hippocampal CA1 region of mice in the 4 groups(HE staining)



注:DMOG为二甲基草酰亚胺,A β 为 β 淀粉样蛋白。黑色箭头示A β 阳性细胞,标尺=50 μm 。与对照组比较,** $P<0.01$;与模型组比较,## $P<0.01$;与电针组比较,@@ $P<0.01$ 。

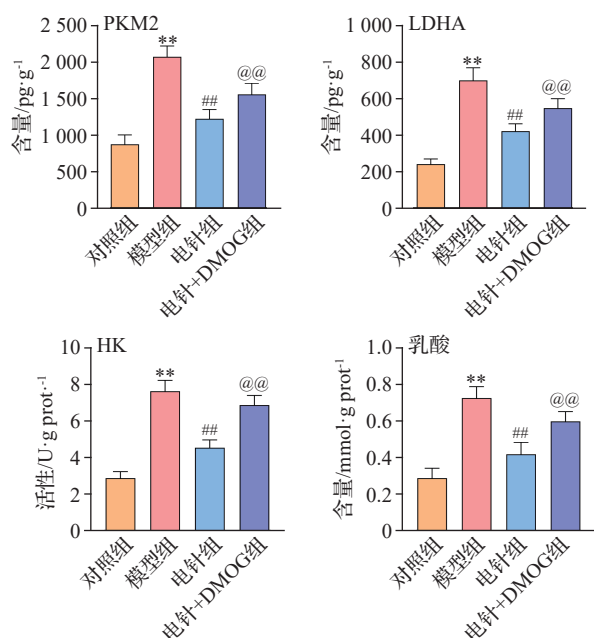
图4 各组小鼠海马CA1区A β 1-42表达比较(免疫组织化学染色, $\bar{x}\pm s$,3只鼠/组)

Fig. 4 Comparison of hippocampal CA1 A β 1-42 deposition of mice in the 4 groups (immunohistochemistry staining, $\bar{x}\pm s$,3 mice/group)

组比较,电针组小鼠海马组织中PKM2、LDHA、乳酸含量及HK活性降低($P<0.01$);与电针组比较,电针+DMOG组小鼠海马组织中PKM2、LDHA、乳酸含量及HK活性升高($P<0.01$)。见图5。

2.6 各组小鼠海马组织HIF-1 α 、PFKFB3蛋白表达比较

与对照组比较,模型组小鼠海马组织HIF-1 α 、PFKFB3蛋白表达升高($P<0.01$);与模型组比较,



注:DMOG为二甲基草酰亚胺,PKM2为丙酮酸激酶M2型,LDHA为乳酸脱氢酶A,HK为己糖激酶。与对照组比较,** $P<0.01$;与模型组比较,## $P<0.01$;与电针组比较,@@ $P<0.01$ 。

图5 各组小鼠海马PKM2、LDHA、乳酸含量和HK活性比较($\bar{x}\pm s$,3只鼠/组)

Fig. 5 Comparison of hippocampal PKM2, LDHA, and lactate contents and HK activity of mice in the 4 groups ($\bar{x}\pm s$,3 mice/group)

电针组小鼠海马组织HIF-1 α 、PFKFB3蛋白表达下降($P<0.01$);与电针组比较,电针+DMOG组小鼠海马组织HIF-1 α 、PFKFB3蛋白表达升高($P<0.05$)。见图6。

2.7 各组小鼠海马组织HIF-1 α 、PFKFB3、HK、PKM2、LDHA mRNA表达比较

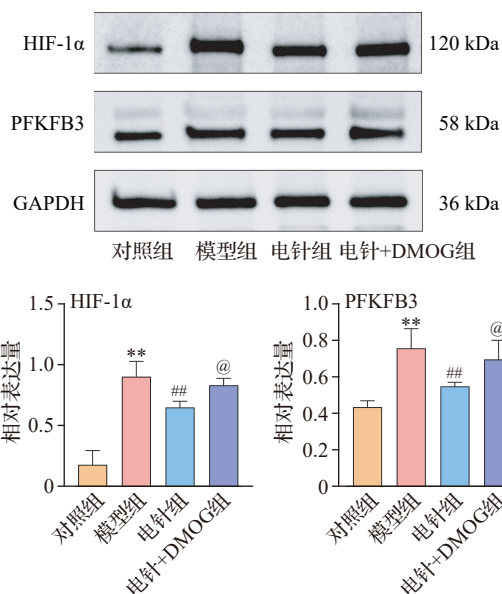
与对照组比较,模型组小鼠海马组织HIF-1 α 、PFKFB3、HK、PKM2、LDHA mRNA表达上升($P<0.01$);与模型组比较,电针组小鼠海马组织HIF-1 α 、PFKFB3、HK、PKM2、LDHA mRNA表达下降($P<0.01$);与电针组比较,电针+DMOG组小鼠海马组织HIF-1 α 、PFKFB3、HK、PKM2、LDHA mRNA表达上升($P<0.01$)。见图7。

2.8 各组小鼠海马组织LDHA荧光强度比较

与对照组比较,模型组小鼠海马组织LDHA荧光强度增加($P<0.01$);与模型组比较,电针组小鼠海马组织LDHA荧光强度降低($P<0.01$);与电针组比较,电针+DMOG组小鼠海马组织LDHA荧光强度增加($P<0.01$)。见图8。

3 讨论

AD属中医学“痴呆”“神呆”范畴,其病机以肾



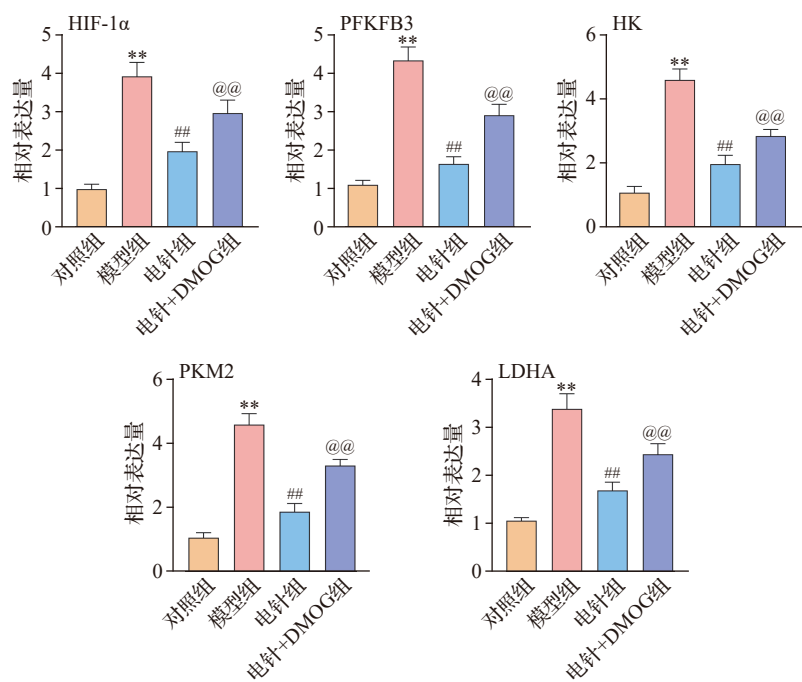
注:DMOG为二甲基草酰亚胺,HIF-1 α 为低氧诱导因子1 α ,PFKFB3为磷酸果糖激酶双功能酶3。与对照组比较,** $P<0.01$;与模型组比较,## $P<0.01$;与电针组比较,@ $P<0.05$ 。

图6 各组小鼠海马HIF-1 α 及PFKFB3蛋白表达比较($\bar{x}\pm s$,3只鼠/组)

Fig. 6 Comparison of hippocampal HIF-1 α and PFKFB3 protein expression levels of mice in the 4 groups ($\bar{x}\pm s$,3 mice/group)

精亏虚、髓海不足为本,常兼中焦失运,气血生化乏源,以致清阳不升、脑窍失养^[26]。目前现代医学多以胆碱酯酶抑制剂及N-甲基-D-天冬氨酸受体拮抗剂为主进行治疗,虽有一定疗效,但存在个体差异及胃肠道不适等不良反应,制约其长期应用^[27-28]。针灸疗法在AD防治中展现出独特优势,日益受到重视^[29-31]。在选穴方面,百会、肾俞与足三里为临床常用组合^[32-33]。脑乃精髓和神明聚藏和发出之处,百会属督脉,位于巅顶,其下为脑之所在,故刺之能通调督脉、升运精气、濡养清窍,使脑神得充、灵机复健^[34];肾俞为肾气所注之背俞穴,针刺可益肾填精、补髓充脑,以固先天之本^[35]。据《脾胃论》“脾胃虚则九窍不利”之论,中焦虚弱、气血不荣亦为AD关键病机。足三里作为足阳明胃经合穴,功擅健运脾胃、促进气血精微的化生以补益后天^[36]。本研究据此取百会以升举清阳,选肾俞以培补先天之精,择足三里以健运中州,三穴相配,共奏补肾益髓、健脾升清、通络醒脑之效。

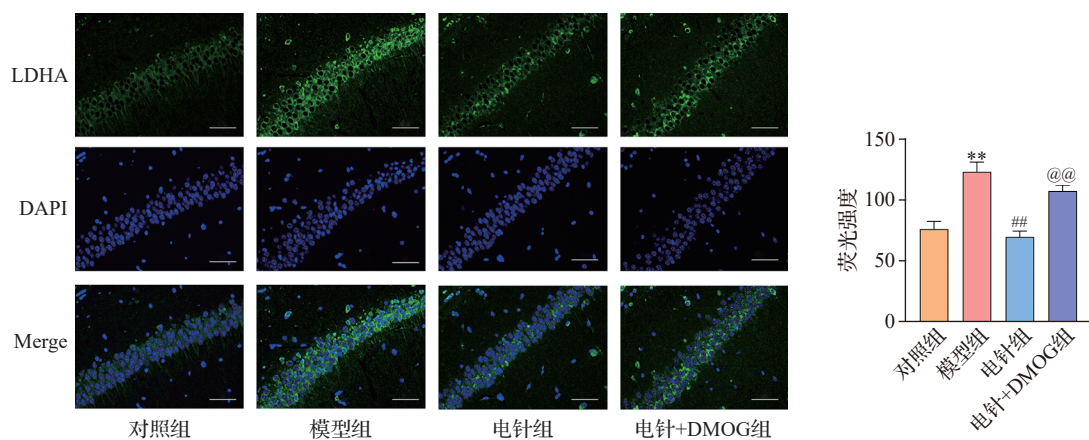
认知功能障碍是AD的核心临床表现,其病理基础与可溶性寡聚体及斑块形式的A β ,尤其是更具神经毒性的A β 1-42密切相关^[37]。A β 1-42可通过干扰海马环路内的谷氨酸受体信号与钙稳态,抑制长



注:DMOG为二甲基草酰亚胺,HIF-1 α 为低氧诱导因子1 α ,PFKFB3为磷酸果糖激酶双功能酶3,HK为己糖激酶,PKM2为丙酮酸激酶M2型,LDHA为乳酸脱氢酶A。与对照组比较,** $P<0.01$;与模型组比较,## $P<0.01$;与电针组比较,@@ $P<0.01$ 。

图7 各组小鼠海马HIF-1 α 、PFKFB3、HK、PKM2、LDHA mRNA表达比较($\bar{x}\pm s$,3只鼠/组)

Fig. 7 Comparison of hippocampal HIF-1 α , PFKFB3, HK, PKM2, and LDHA mRNA expression of mice in the 4 groups ($\bar{x}\pm s$,3 mice/group)



注:DMOG为二甲基草酰亚胺,LDHA为乳酸脱氢酶A。标尺=50 μm 。与对照组比较,** $P<0.01$;与模型组比较,## $P<0.01$;与电针组比较,@@ $P<0.01$ 。

图8 各组小鼠海马组织LDHA荧光强度比较(免疫荧光染色, $\bar{x}\pm s$,3只鼠/组)

Fig. 8 Comparison of hippocampal LDHA fluorescence intensity of mice in the 4 groups (immunofluorescence staining, $\bar{x}\pm s$,3 mice/group)

时程增强、诱导突触后致密物蛋白降解并触发树突棘退缩,从而直接导致学习记忆受损^[38]。其斑块邻域还可放大炎症反应与氧化应激,进一步破坏突触可塑性与网络整合^[39]。本研究结果显示,电针“百会”“肾俞”“足三里”可显著减少AD模型小鼠海马内A β 1-42沉积,并改善神经元形态学异常,提示其具有改善认知功能的潜力。

在常规生理状态下,糖酵解作为葡萄糖分解代谢的核心途径,与线粒体氧化磷酸化协同维持细胞的能量稳态与代谢可塑性^[40]。然而,在AD病理背景下,糖酵解过程出现异常增强,并伴随整体代谢通路的重新编程^[41],包括HK、PKM2及LDHA在内的关键酶表达上调^[41-43],导致乳酸的异常积累和能量失衡,增强炎症信号,进一步加剧A β 沉积及神经

元损伤^[12]。进一步的研究显示,在AD相关微环境中,小胶质细胞出现组蛋白H4第12位赖氨酸乙酰化显著升高,且富集于A β 斑块邻域;该修饰富集到PKM/PKM2与LDHA等糖酵解基因启动子并增强其转录,从而推动代谢向乳酸生成倾斜^[41]。AD早期患者脑脊液中亦可观察到乳酸水平升高,与认知损害及炎症反应过程密切相关^[44]。这种乳酸累积及相关代谢紊乱不仅加剧线粒体功能失调与氧化应激^[45],还可通过激活下游炎症反应信号通路(如核因子 κ B/NOD样受体蛋白3轴)的应激反应,进一步放大神经毒性效应^[46-48],从而与A β 沉积、突触损伤及认知功能衰退形成“代谢-炎症反应-病理”之间的恶性循环^[42]。

已有研究^[41]提示,靶向抑制糖酵解的过度活化能够减轻A β 负荷、改善突触形态并逆转认知行为障碍,这为以糖酵解为靶点的干预策略提供了理论依据。本研究结果与上述机制相一致:电针干预可显著降低AD模型小鼠海马组织HK活性及PKM2、LDHA、乳酸含量,免疫荧光结果进一步显示LDHA表达减弱。这些结果表明,电针可能通过抑制糖酵解的异常活化、重建脑内能量代谢平衡,进而发挥对A β 病理进展和神经元功能的保护作用。结合既往报道显示针刺在脑缺血模型中可调节糖酵解关键酶活性并减轻氧化损伤^[49],值得强调的是,糖酵解调控具有细胞类型特异性与病程阶段依赖性,适度的代谢调节可能具有神经保护意义,而过度抑制则可能影响神经胶质能量耦联。

HIF-1 α 是一种关键的转录因子,在低氧条件下调控糖酵解代谢的多个环节^[50],而在AD中,其异常激活往往促进糖酵解通路的亢进,导致能量代谢紊乱、氧化应激增强及A β 沉积加剧,进一步加重神经元损伤和认知功能障碍^[51-52]。PFKFB3作为HIF-1 α 的下游靶基因,编码磷酸果糖激酶-2/果糖-2,6-二磷酸酶-3,可催化果糖-6-磷酸转化为果糖-2,6-二磷酸,从而激活磷酸果糖激酶-1,增强糖酵解通量^[53],并间接上调下游酶如HK、PKM2和LDHA的表达,促进L-乳酸积累和酸性微环境形成^[45,54-55]。既往研究证实,HIF-1 α /PFKFB3轴在AD脑组织中过度激活,可放大神经炎症反应和A β 毒性,提示靶向该通路可能缓解AD病理进程^[56]。本研究结果显示,与AD模型组相比,电针组小鼠海马区HIF-1 α 和PFKFB3蛋白表达水平显著降低,同时HIF-1 α 、PFKFB3、HK、PKM2和LDHA的mRNA水平降低,表明电针可抑制HIF-1 α /PFKFB3通路的激活,

从而下调糖酵解关键酶的转录,恢复能量代谢平衡,进而发挥神经保护作用。为进一步验证机制,本研究引入HIF-1 α 激动剂DMOG,结果显示电针+DMOG组小鼠上述指标均较电针组逆转,提示DMOG可逆转电针对糖酵解的抑制效应。这进一步证实,电针的抗AD效应与调控HIF-1 α /PFKFB3轴相关,该通路可能通过转录调控糖酵解酶基因表达维持细胞稳态。

综上,电针可改善AD模型小鼠认知功能,减少A β 沉积,并保护海马神经元,其机制与抑制HIF-1 α /PFKFB3介导的糖酵解亢进密切相关。目前,关于电针调控AD糖酵解机制的研究尚少,本研究为其提供了新视角,但也存在局限性。糖酵解过程受多个信号通路影响,本研究仅聚焦HIF-1 α /PFKFB3轴,其在AD中的完整调控网络仍有待进一步探讨。此外,未来研究需进一步明确电针干预的时空窗口与剂量效应,并将其与线粒体功能、乳酸穿梭及神经炎症反应等指标进行整合分析,从而系统阐释电针调控糖酵解在AD治疗中的具体机制与转化潜力。

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