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针刺对缺氧缺血性脑损伤大鼠脑神经功能及 5-HTR1A/cAMP/PKA 信号通路的影响机制研究 *

张 旭 刘建梁△ 张秀红 徐建明 周 钰

（新疆医科大学第一附属医院针灸推拿科 新疆 乌鲁木齐 830054）

摘要 目的:探讨与研究针刺对缺氧缺血性脑损伤大鼠脑神经功能及 5-HTR1A/cAMP/PKA 信号通路的影响机制。**方法:**研究时间为 2022 年 6 月到 2022 年 12 月,SPF 级健康雄性 SD 大鼠 36 只平分为空白组、模型组、针刺组,每组各 12 只大鼠。空白组不进行造模,针刺组在造模完成 1 周后进行针刺治疗,空白组、模型组不进行治疗。**结果:**所有大鼠都顺利完成实验,无死亡大鼠出现。针刺组、模型组治疗后 2 周与 4 周的神经功能评分都显著高于空白组（P<0.05），针刺组的神经功能评分与模型组相比显著降低(P<0.05)。针刺组、模型组治疗后 2 周与 4 周的脑缺氧缺血组织体积都高于空白组(P<0.05),针刺组的脑缺氧缺血组织体积与模型组相比显著降低(P<0.05)。针刺组、模型组治疗后 2 周与 4 周的血清超氧化物歧化酶活力低于空白组(P<0.05),血清丙二醛含量高于空白组(P<0.05),针刺组与模型组对比也有显著差异(P<0.05)。针刺组、模型组治疗后 2 周与 4 周的大脑组织 5-HTR1A 蛋白、cAMP 蛋白、PKA 蛋白相对表达水平明显低于空白组(P<0.05),针刺与模型组相比显著提高(P<0.05)。**结论:**针刺在缺氧缺血性脑损伤大鼠的应用能激活 5-HTR1A/cAMP/PKA 信号通路,能提高超氧化物歧化酶活力,降低血清丙二醛含量,能改善大鼠的脑神经功能,降低脑缺氧缺血组织体积。

关键词:针刺;缺氧缺血性脑损伤;大鼠;5-HTR1A/cAMP/PKA 信号通路

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Effect of Acupuncture on Brain Nerve Function and 5-HTR1A/cAMP/PKA Signal Pathway in Rats with Hypoxic-ischemic Brain Injury*

ZHANG Xu, LIU Jian-liang△, ZHANG Xiu-hong, XU Jian-ming, ZHOU Yu

(Department of Acupuncture and Massage,The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, 830054, China)

ABSTRACT Objective: To explore and study the mechanism of acupuncture's influence on brain nerve function and 5-HTR1A/cAMP/PKA signal pathway in rats with hypoxic-ischemic brain injury. **Methods:** The study period were from June 2022 to December 2022. 36 cases of SPF grade healthy male SD rats were equally divided into blank group, model group and acupuncture group, with 12 rats in each groups. The blank group were not subject to model building, the acupuncture group were subject to acupuncture treatment one week after the completion of model building, and the blank group and model group were not subject to treatment. **Results:** All rats were successfully completed the experiment and no dead rats were found. The scores of nerve function in acupuncture group and model group were significantly higher than that in blank group at 2 and 4 weeks after treatment (P<0.05), and the scores of nerve function in acupuncture group were significantly lower than that in model group (P<0.05). The volume of cerebral hypoxic-ischemic tissue in the acupuncture group and the model group at 2 and 4 weeks after treatment were higher than that in the blank group (P<0.05), and the volume of cerebral hypoxic-ischemic tissue in the acupuncture group were significantly lower than that in the model group (P<0.05). The activity of serum superoxide dismutase in the acupuncture group and the model group were lower than that in the blank group (P<0.05), and the content of serum malondialdehyde were higher than that in the blank group (P<0.05). There were also significant difference compared between the acupuncture group and the model group (P<0.05). The relative expression levels of 5-HTR1A protein, cAMP protein and PKA protein in the brain tissue of the acupuncture group and the model group were significantly lower than those of the blank group (P<0.05), and the acupuncture group were significantly higher than the model group (P<0.05). **Conclusion:** Acupuncture can activate the 5-HTR1A/cAMP/PKA signal pathway in rats with hypoxic-ischemic brain injury, increase the activity of superoxide dismutase, reduce the content of malondialdehyde in serum, improve the brain nerve function of rats, and reduce the volume of hypoxic-ischemic brain tissue.

Key words: Acupuncture; Hypoxic-ischemic brain injury; Rats; 5-HTR1A/cAMP/PKA signal pathway

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作者简介:张旭(1988-),男,本科,住院医师,研究方向:中医针灸相关,E-mail:xuguk661@163.com

△ 通讯作者:刘建梁(1979-),男,硕士研究生,副主任医师,研究方向:针灸推拿相关,E-mail:xuguk661@163.com

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前言

脑血管病为临床上的常见疾病，包括多种类型，其致残率与死亡率一直比较高，已经成为了一种公共卫生疾病，在临床与社会上得到了广泛关注[1]。缺氧缺血性脑损伤为脑血管疾病的主要类型之一，占 40.0 %以上，在脑组织缺血导致局部脑缺血性损伤，伴随有机体缺血区域的再灌注损伤，从而导致相关性组织器官的继续损伤，造成患者病情恶化[2,3]。缺氧缺血性脑损伤的发生机制还不确定，但是涉及的病因比较多，除了外伤外，也包括机体大量炎症因子的释放、自由基的大量释放、神经元细胞凋亡等[4]。但是缺氧缺血性脑损伤的发生具有一定的可逆性，加强早期诊治能显著改善患者的预后[5,6]。当前建立缺氧缺血性脑损伤的模型比较多，其中线栓法切断脑中动脉（middle cerebral artery oclusion，MCAO）建立大鼠缺氧缺血性脑损伤模型比较常见[7]。有研究显示 5-HTR1A/cAMP/PKA 信号通路与神经血管再生关系密切，在调节缺血脑组织的局部炎症中也起到了重要作用[8,9]。针刺疗法是当前重要的中医疗法，特别是颅脑针刺可对大脑皮层产生良性刺激，可唤起正常的兴奋作用，从而打破大脑皮层的超限界抑制，可发挥调节脑损伤的作用[10,11]。本文具体分析与探讨了针刺对缺氧缺血性脑损伤大鼠脑神经功能及 5-HTR1A/cAMP/PKA 信号通路的影响，以促进针刺的应用。

1 材料与方法

1.1 实验材料

2022 年 6 月到 2022 年 12 月，36 只 SPF 级健康雄性 SD 大鼠（体重 220 g-250 g）购于北京维通利华实验动物有限责任公司（SCXK2022-0001）。饲养环境：6 只 / 笼，室内温度 24± 1℃，湿度 60%，12 h 光暗周期，均自由饮水饮食。

酶标仪购自深圳市三莉科技有限公司，蛋白杂交与凝胶成像系统购自美国 Bio-rad 公司，蛋白定量试剂盒购自赛默飞世尔科技（中国）有限公司，抗β-actin 抗体、抗 PKA 抗体、抗 5-HTR1A 抗体、抗 cAMP 抗体购自美国 Abcam 公司，丙二醛（MDA）、超氧化物歧化酶（SOD）检测试剂盒购自南京建成生物技术有限公司。

1.2 大鼠分组与处理

将所有大鼠平分为空白组、模型组、针刺组，每组各 12 只大鼠。所有大鼠术前 4 小时禁水，术前 10 小时严格禁食。

大鼠处于仰卧位，10.0 %水合氯醛麻醉大鼠后进行进行固定，并正中切开大鼠颈部的皮肤，钝性分离肌肉。空白组大鼠分离肌肉后直接进行缝合，模型组、针刺组大鼠进一步采用线栓法切断脑中动脉建立大鼠缺氧缺血性脑损伤模型，建模过程见参考文献[2]。

针刺组在造模完成 1 周后进行针刺治疗，针刺大鼠水沟、风池、内关、足三里等穴位，行平补平泻手后留针 20 min，每日 1 次。空白组、模型组不进行治疗。

1.3 观察指标

（1）在治疗后 2 周与 4 周空白组、模型组、针刺组各处死 6 只大鼠，在处死前对大鼠进行神经功能评分，分为 0 分 -4 分，分数越高，神经功能状况越严重。

（2）处死空白组、模型组、针刺组大鼠后快速断头取脑，去除嗅球、小脑等脑组织，剩余组织作 2 mm 的病理厚冠状切片，加入 2%氯化三苯基四氮唑（青岛捷世康生物科技有限公司）进行染色 30 分钟。选择 Image-Pro Plus 计算脑缺氧缺血组织体积比例，其中梗死灶组织染色呈白色，正常脑组织染色呈红色。

（3）取空白组、模型组、针刺组处死大鼠的尾静脉血 3-5 mL，离心分离上层血清，采用 ELISA 测超氧化物歧化酶活力与丙二醛含量。

（4）取空白组、模型组、针刺组处死大鼠的大脑组织，研磨后提取总蛋白，采用 Western Blot 检测 5-HTR1A、cAMP、PKA 蛋白表达水平。

1.4 统计方法

选择 SPSS20.00 分析，计量数据（Mean± SD）表示，采用 t 检验与方差分析，检验水准为α=0.05。

2 结果

2.1 神经功能评分对比

所有大鼠都顺利完成实验，无死亡大鼠出现。针刺组、模型组治疗后 2 周与 4 周的神经功能评分都显著高于空白组（P<0.05），针刺组的神经功能评分与模型组相比显著降低（P<0.05）。见表 1。

表 1 三组大鼠治疗不同时间点的神经功能评分对比（分，均数± 标准差）

Table 1 Comparison of neurological scores (scores, mean ± standard deviation at different time points)

Groups	n	Week 2 of treatment	Week 4 of treatment
Blank group	6	1.33± 0.11[◊]	1.34± 0.09[◊]
Acupuncture group	6	2.45± 0.13[◊◊]	2.14± 0.12[◊◊]
Model group	6	3.44± 0.21	3.48± 0.18
F		24.193	25.115
P		0.000	0.000

Note: [◊] P <0.05 versus model group; [◊] P <0.05 versus blank group, the same below.

2.2 脑缺氧缺血组织体积比例对比

针刺组、模型组治疗后 2 周与 4 周的脑缺氧缺血组织体积都高于空白组（P<0.05），针刺组的脑缺氧缺血组织体积与模型组相比显著降低（P<0.05）。见表 2。

表 2 脑缺氧缺血组织体积比例对比(分,均数± 标准差)

Table 2 Comparison of tissue volumes at different time points (score, mean ± standard deviation)

Groups	n	Week 2 of treatment	Week 4 of treatment
Blank group	6	7.09± 0.44[0]	7.11± 0.52[0]
Acupuncture group	6	25.14± 0.32[0 0]	15.12± 0.48[0 0]
Model group	6	34.59± 2.18	35.02± 1.84
F		45.692	46.117
P		0.000	0.000

2.3 血清超氧化物歧化酶活力与丙二醛含量对比

针刺组、模型组治疗后 2 周与 4 周的血清超氧化物歧化酶活力低于空白组(P<0.05),血清丙二醛含量高于空白组(P<0.05),针刺组与模型组对比也有显著差异(P<0.05)。见表 3。

表 3 三组大鼠治疗不同时间点的血清超氧化物歧化酶活力与丙二醛含量对比(均数± 标准差)

Table 3 Serum superoxide dismutase viability and malondialdehyde content in three rats (mean ± standard deviation)

Groups	n	Superoxide dismutase (U / mg)		Malondialdehyde (μmol/g)	
		Week 2 of treatment	Week 4 of treatment	Week 2 of treatment	Week 4 of treatment
Blank group	6	8.24± 0.66[0]	8.56± 0.51[0]	44.98± 3.62[0]	44.09± 4.41[0]
Acupuncture group	6	4.57± 0.24[0 0]	6.10± 0.25[0 0]	66.45± 4.33[0 0]	56.87± 4.59[0 0]
Model group	6	2.28± 0.09	2.30± 0.10	81.33± 7.13	80.98± 5.67
F		29.133	30.573	18.693	19.116
P		0.000	0.000	0.000	0.000

2.4 5-HTR1A 蛋白、cAMP 蛋白、PKA 蛋白相对表达水平对比

针刺组、模型组治疗后 2 周与 4 周的大脑组织 5-HTR1A 蛋白、cAMP 蛋白、PKA 蛋白相对表达水平明显低于空白组(P<0.05),针刺与模型组相比显著提高(P<0.05)。见表 4。

表 4 三组大鼠治疗不同时间点的大脑组织 5-HTR1A 蛋白、cAMP 蛋白、PKA 蛋白相对表达水平对比(均数± 标准差)

Table 4 Comparison of relative expression levels of 5-HTR 1 A protein, cAMP protein and PKA protein in brain tissues at different time points (mean ± standard deviation)

Groups	n	HTR1A		cAMP		PKA	
		Week 2 of treatment	Week 4 of treatment	Week 2 of treatment	Week 4 of treatment	Week 2 of treatment	Week 4 of treatment
Blank group	6	4.54± 0.33[0]	4.51± 0.25[0]	5.72± 0.44[0]	5.70± 0.32[0]	6.72± 0.55[0]	6.72± 0.24[0]
Acupuncture group	6	2.79± 0.23[0 0]	2.14± 0.06[0 0]	3.21± 0.11[0 0]	2.32± 0.09[0 0]	3.27± 0.12[0 0]	2.35± 0.28[0 0]
Model group	6	1.11± 0.17	1.18± 0.09	1.29± 0.11	1.34± 0.32	1.34± 0.16	1.37± 0.18
F		56.114	55.035	59.014	58.166	62.104	61.446
P		0.000	0.000	0.000	0.000	0.000	0.000

3 讨论

缺氧缺血性脑损伤当前在临床上比较常见,但是具有一定的可逆性,加强早期干预能显著改善机体的预后[12-14]。中医认为缺氧缺血性脑损伤的病机为神志昏蒙、经络瘀阻、血溢脉外、气滞血瘀等,针刺治疗具有多途径、多靶点的特征,起效机制多样[15,16]。有研究显示显示针刺针刺水沟、百会等穴位可使创伤大鼠脑组织的神经细胞凋亡率降低, 可改善大鼠的认知功能[17]。本研究显示针刺组、模型组治疗后 2 周与 4 周的神经功能评分都显著高于空白组,针刺组的神经功能评分与模型组相比显著降低;针刺组、模型组治疗后 2 周与 4 周的脑缺氧缺血组织体积都高于空白组,针刺组的脑缺氧缺血组织体积与模型组相比显著降低,表明针刺在缺氧缺血性脑损伤大鼠的应用能改善脑神经功能,降低脑缺氧缺血组织体积。分析可知,祖国医学认为,水沟、风池靠近病变所在,内关和足三里位于四肢,针刺上述穴位可促进气血运行、调理心气、宁心安神[18]。针刺治疗能促进受损脑组织内神经前体细胞的增殖、迁移和分化,有利于干细胞分化为神经元或胶质细胞[19,20]。

缺氧缺血性脑损伤是人体发生脑瘫的重要病理环节,大鼠缺氧缺血性脑损伤时伴随机体氧化应激状态的表现,表现为超氧化物歧化酶活力增加与丙二醛含量降低[21,22]。超氧化物歧化酶活力增加具有一定的脑保护功能,可减轻缺氧缺血性脑损伤

程度，改善个体的预后[23]。丙二醛含量的降低可缓解缺氧缺血性脑损伤状态[24,25]。本研究显示针刺组、模型组治疗后 2 周与 4 周的血清超氧化物歧化酶活力低于空白组，血清丙二醛含量高于空白组，针刺组与模型组对比也有显著差异，表明针刺在缺氧缺血性脑损伤大鼠的应用能提高超氧化物歧化酶活力，降低血清丙二醛含量。分析可知，针刺治疗可提高脑缺血后海马神经元密度，可保护尼氏体，有利于神经元内的蛋白质合成，减轻脑组织的水肿，从而改善缺血缺氧性脑瘫大鼠的氧化应激状况[26,27]。

在 5-HTR1A/cAMP/PKA 信号通路中，三者的高表达可促进神经修复与神经再生，有利于神经细胞的增殖与生长，进而有利于神经功能的改善[28]。特别是 5-HTR1A 可上调 cAMP 与 PKA 的表达，促使血管生成，可以改善脑缺血后神经血管再生微环境，有利于恢复个体的脑血管功能[29]。本研究显示针刺组、模型组治疗后 2 周与 4 周的大脑组织 5-HTR1A 蛋白、cAMP 蛋白、PKA 蛋白相对表达水平较空白组低，针刺与模型组相比显著提高，表明针刺在缺氧缺血性脑损伤大鼠的应用能激活 5-HTR1A/cAMP/PKA 信号通路。针刺治疗可以防止细胞外钙离子入胞和细胞内钙离子释放，保护神经元免受损伤，稳定细胞内环境。针刺还可以促进脑部组织正常清除代谢产物，保障机体的能量代谢，有利于机体进行未坏死神经元的恢复，改善机体的预后[30,31]。

总之，针刺在缺氧缺血性脑损伤大鼠的应用能激活 5-HTR1A/cAMP/PKA 信号通路，能提高超氧化物歧化酶活力，降低血清丙二醛含量，能改善大鼠的脑神经功能，降低脑缺氧缺血组织体积。不过本研究没有进行细胞学研究，没有明确针刺治疗的直接作用靶基因，分组也比较少，将在后续研究中探讨。

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