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电针早期干预对创伤后应激模型大鼠的行为及前额叶皮质 BDNF、IL-1β 和 IL-6 水平的影响 *

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摘要 目的：观察电针（Electroacupuncture，EA）早期干预对创伤后应激（Posttraumatic stress disorder，PTSD）模型大鼠的焦虑样行为及前额叶皮质（Prefrontal cortex，PFC）中脑源性神经营养因子（Brain-derived neurotrophic factor，BDNF）、白介素 1β（Interleukin-1beta，IL-1β）和白介素 6（Interleukin-6，IL-6）水平的影响。**方法：**将 32 只雄性 SD 大鼠经环境适应后，随机分为 Sham 组、Sham + EA 组、ESPS 组和 ESPS + EA 组，每组 8 只。对 ESPS 组和 ESPS + EA 组大鼠进行增强型单次延长应激（Enhanced single prolonged stress，ESPS）造模处理，其他两组不接受 ESPS，但是置于同一实验室环境。造模结束后 24 h，各组大鼠进行 EA 干预：Sham + EA 组和 ESPS + EA 组的大鼠每天接受 EA 刺激（百会穴，1 mA，2/15 Hz）30 min，连续 1 周；另外两组给予假刺激（无电流）每天 30 min，连续 1 周。静置一周后，采用旷场和高架十字实验观察各组大鼠的行为，之后处死大鼠，分别用蛋白质印迹法和酶联免疫法（Enzyme-linked immunosorbent assay，ELISA）检测各组大鼠 PFC 中 BDNF 的表达水平以及 IL-1β 和 IL-6 的水平。**结果：**（1）ESPS 处理导致大鼠焦虑样行为，在旷场中心区运动距离和探索时间百分比减少，在高架十字开臂运动距离及停留时间百分比减少。ESPS 组大鼠 PFC 中 BDNF 表达下降，IL-1β 和 IL-6 的水平升高；（2）EA 早期干预可以改善大鼠的焦虑样行为，提高 ESPS 模型大鼠 PFC 中 BDNF 的表达，降低 IL-6 的水平，对 IL-1β 的影响无统计学差异。**结论：**EA 早期干预改善了 ESPS 诱导的大鼠焦虑样的行为，这可能与其增加了 PFC 中 BDNF 表达，降低了炎性因子 IL-6 的表达有关。

关键词：电针；脑源性神经营养因子；白细胞介素 -6；创伤后应激障碍

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Effect of Early Intervention with Electroacupuncture on Anxiety-like Behavior and Expression of BDNF, IL-1β and IL-6 in the Prefrontal Cortex of PTSD Rats Model*

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ABSTRACT Objective: To investigate the effect of early intervention with Electroacupuncture (EA) on the anxiety-like behavior of ESPS-treated rat and the regulation of BDNF, IL-1β and IL-6 in the prefrontal cortex (PFC). **Methods:** Thirty - two male Sprague - Dawley rats were randomly divided into Sham, Sham + EA, ESPS and ESPS + EA group after adjusting the environment for 1 week. Rats in ESPS group and ESPS + EA group were exposed to ESPS, and rats in Sham and Sham + EA groups were placed in the same experimental environment but did not receive ESPS at the same time. 24 h later, rats in Sham + EA group and ESPS + EA group received EA treatment (Baihui, 1 mA, 2/15 Hz) and the other two groups received sham stimulation (acupuncture treatment without electricity) for 30 min every day for 1 week. The open field test and elevated-plus maze test were performed 1 week later. Then all rats were sacrificed and the level of BDNF and the level of IL-1β and IL-6 in PFC were measured by Western blot and ELISA, respectively. **Results:** (1) The traveled distance and the percentage of exploration time in central region of open field test and the percentage of exploration time in open arms of elevated-plus maze test were significantly decreased in ESPS group than that of other groups. The expression of BDNF in PFC was decreased, while the levels of IL-1β and IL-6 were increased in the ESPS group than that of other groups. (2) Early intervention of EA ameliorated the anxiety-like behavior of rats, elevated the expression of BDNF and reduced the level of IL-6 in PFC of ESPS-treated rats. However, there was no significant different between ESPS group and ESPS + EA group on the level of IL-1β. **Conclusions:** Early intervention with EA improved ESPS-induced anxiety-like behavior in rats, which might be related to the increase of BDNF expression and decrease of the level of IL-6 in PFC.

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前言

创伤后应激障碍(Posttraumatic stress disorder,PTSD)患病率高[1],严重损害心理健康,还会增加心血管疾病,自身免疫疾病以及过早死亡的风险[2,3]。近年来的研究发现,脑源性神经营养因子(Brain-derived neurotrophic factor,BDNF)在 PTSD 的发生发展中发挥重要作用[4],PTSD 患者的神经认知功能与血清中 BDNF 水平呈正相关[5]。此外,PTSD 的认知缺陷也与大脑中的慢性炎症反应有关[6,7]。有研究发现 PTSD 患者血清中白细胞介素 -6(Interleukin-6,IL-6)、白细胞介素 -1β(Interleukin-1beta,IL-1β)、TNF-α 水平增加[8]。

电针(Electroacupuncture,EA)作为传统针灸的改良方式,被证明可发挥神经保护的作用[9,10]。我们前期的研究发现 EA 对 PTSD 也有一定的改善作用[11]。但是 EA 早期干预对焦虑样行为的作用以及其中枢机制还有待阐明。前额叶皮质(Prefrorntal cortex,PFC)是调节焦虑恐惧情绪和认知损害的脑区之一[12]。研究发现 PTSD 患者额叶皮质体积减少[13],而一些物理治疗如重复经颅磁刺激可通过直接刺激 PFC 脑区来改善 PTSD 症状[14]。因此本研究以增强型单次延长应激(Enhanced single prolonged stress,ESPS)为模型,观察 EA 早期干预对该模型大鼠焦虑样行为和 PFC 中 BDNF、IL-1β 和 IL-6 水平的影响,为 EA 早期干预应用于 PTSD 的防治提供理论依据。

1 材料和方法

1.1 动物

实验动物 32 只 8 周龄左右的清洁级雄性 Sprague-Dawley(SD)大鼠,体质量 220 ± 20 g,由中国人民解放军空军军医大学实验动物中心提供。大鼠每笼 4 只进行饲养,温度 18 - 23℃,相对湿度 55% - 65%。大鼠自由获取食物和水。实验获得中国人民解放军空军军医大学动物使用和保护委员会的批准。

1.2 方法

大鼠适应性饲养 1 周后进行 ESPS 造模,随后连续 1 周各组大鼠每天被电针干预 30 min,再静养 1 周后,采用旷场及高架十字实验观察各组大鼠的行为,随后处死大鼠,用蛋白质印迹法检测各组大鼠前额叶皮层 BDNF 的表达,用 ELISA 检测各组大鼠前额叶皮层 IL-1β 和 IL-6 的水平。进行行为测试的研究者对动物的分组情况并不知情。

1.3 ESPS 模型构建

采用国际公认的 PTSD 动物模型 ESPS 制备方法[15]。大鼠禁锢 2 h 后,立即进行强迫游泳 20 min(水深 40 cm,水温 22-25℃)。经过 15 min 的休息(期间擦干毛发),随后用乙醚麻醉使大鼠的意识丧失,麻醉苏醒后(约 30 min),实施足底电击 2 次(1 mA,4 s,中间间隔 10 s),然后将大鼠放回鼠笼静养。

1.4 实验分组

将 32 只大鼠随机分为 4 组(每组 8 只):Sham 组,Sham + EA 组,ESPS 组,ESPS + EA 组。ESPS 组和 ESPS + EA 组的大鼠进行 ESPS 造模。造模结束后,Sham 组和 ESPS 组的大鼠(俯卧位固定)被给予假刺激(无电流)作用于百会穴(位于矢状中线与连接鼠耳的线的交叉处)。Sham + EA 组和 ESPS + EA 组的大鼠(俯卧位固定)用 EA 以 1 mA 强度、2/15 Hz 疏密波刺激百会穴。

1.5 旷场实验(Open field test,OFT)

将大鼠放入旷场实验箱(直径 47 cm × 47 cm),1 min 适应期后,通过上方的摄像机记录大鼠在旷场内的活动情况[16]。采用 clever sys 分析系统分析大鼠在 10 min 内在旷场中心区运动距离和探索时间百分比。

1.6 高架十字实验(Elevated-plus maze test,EPMT)

EPMT 被验证可很好地检测大鼠的焦虑样行为[17]。经过 1 h 的环境适应后,将大鼠置于高架十字的中央平台上,使鼠头朝向固定开臂,10 s 适应期后,记录大鼠的行为 5 min。通过自动分析系统(Top Scan,Clever Sys Inc.,USA)记录并测量大鼠在开臂运动距离及停留时间百分比。

1.7 蛋白质印迹法(Western blot)检测

行为学测试结束后,大鼠断头,在冰上迅速剥离大脑,取出前额叶皮质,其中部分组织用来制备蛋白样品。分别配制 5 %的积层胶和 10 %的分离胶,据 BCA 蛋白质测定试剂盒(Invitrogen;Thermo Fisher Scientifc,Inc)定量蛋白质结果,每个泳道上样 40 μg 蛋白。电泳 90 V / 15 min,160 V / 90 min 后,将凝胶蛋白转移到聚偏二氟乙烯膜上(100 V / 90 min)。用封闭液(25 mmol/L TBS 溶液,5 %脱脂奶粉,1 mL/L 吐温 -20)室温封闭 1 h。经 TBS 漂洗 3 次,每次 5 min。然后孵育一抗(rabbit anti - BDNF,1∶5000,TBST 稀释,Epitomics),置于 4 ℃中 16 h。随后复温 30 min,洗涤膜并入二抗(驴抗兔 IgG,1∶10000,Abcam),在室温下孵育 1 h。经 TBS 漂洗膜 3× 5 min 后,滴加化学荧光试剂,暗室中运用 X 光胶片压片成像。扫描成像后对条带进行分析,采用 Image J 软件测出条带的灰度,计算出 BDNF 与其对应的 β-actin 条带的灰度比值。

1.8 ELISA 检测

处死大鼠后,取出的另一部分前额叶皮质制备 Elisa 样品。将 IL-6、IL-1β 的 Elisa 试剂盒复温 30 min 后,按说明书加好各标准孔的液体,并将各 40 μL 的样本加入待测样品孔,再在样品孔中加入 IL-6 或 IL-1β 的抗体 10 μL 及 Str - HRP 50 μL。轻摇后置于恒温箱中(37 ℃)1h。然后用洗涤液洗板 4-5 次,每孔加入 A 液及 B 液(各 50 μL),置暗处 37 ℃反应 10 min。每孔加入 50 μL 终止液。随后在 450 nm 测吸光度值,根据制备的标准曲线计算各组 IL-6 或 IL-1β 的含量。

1.9 统计学处理

采用 SPSS 19.0 对数据进行统计分析,4 组间比较使用单因素方差分析,两两数据在比较前进行方差齐性检验,满足方差齐性则采用 LSD-t 检验,方差不齐则采用 Dunnett-t 检验。$P < 0.05$ 为差异有统计学意义。

2 结果

2.1 各组大鼠的一般情况

经过造模及干预后，各组未出现大鼠死亡的情况。各组大鼠均能自由摄取水食，体质量无明显差异。

2.2 各组大鼠旷场实验结果比较

在旷场实验中，ESPS 组大鼠在旷场中心区运动距离及探索时间百分比均低于 Sham 组（$P<0.001$，$P=0.006$），Sham + EA 组（$P<0.001$，$P=0.002$）及 ESPS + EA 组（$P=0.001$，$P=0.030$）。与 Sham 组相比，Sham + EA 组大鼠上述指标差异无统计学意义，而 ESPS + EA 组大鼠在旷场中心区的运动距离（$P=0.034$）减少。见表 1。

表 1 各组大鼠旷场中心区运动距离和探索时间百分比的比较（$\bar{x}\pm s$）

Table 1 Comparison of the distance of central movement and the time of central movement relative to overall levels values of the rats in each group（$\bar{x}\pm s$）

Groups	The distance of central movement(mm)	The time of central movement relative to overall levels values(%)
Sham	1895.43 ± 411.41 [d]	17.71 ± 4.22 [d]
Sham + EA	1691.97 ± 475.67 [d]	18.49 ± 3.23 [d]
ESPS	762.24 ± 229.64 [b]	12.51 ± 3.21 [b]
ESPS + EA	1465.20 ± 385.23 [ad]	16.53 ± 3.28 [c]
F value	13.05	4.59
P value	< 0.001	0.01

Note: Compared with Sham [a] $P<0.05$, [b] $P<0.01$; Compared with ESPS [c] $P<0.05$, [d] $P<0.01$.

2.3 各组大鼠高架十字实验结果比较

在高架十字实验中，ESPS 组大鼠在开臂运动距离及停留时间百分比少于 Sham 组（$P=0.006$，$P=0.001$），Sham + EA 组（$P=0.020$，$P=0.001$）及 ESPS+EA 组（$P=0.012$，$P=0.003$）。与 Sham 组相比，Sham + EA 组（$P=0.612$，$P=0.720$）及 ESPS+EA 组（$P=0.755$，$P=0.557$）大鼠在开臂运动距离及停留时间百分比差异无统计学意义。见表 2。

表 2 各组大鼠开臂运动距离及停留时间百分比的比较（$\bar{x}\pm s$）

Table 2 Comparison of the distance traveled and the percentage of time spent in the open arms of the rats in each group（$\bar{x}\pm s$）

Groups	The distance traveled in the open arms(mm)	The percentage of time spent in the open arms(%)
Sham	2399.15±786.23 [d]	19.36±6.69 [d]
Sham + EA	2175.19±1115.33 [c]	18.35±7.22 [d]
ESPS	1095.37± 594.96 [b]	8.57± 2.53 [b]
ESPS + EA	2261.63±913.86 [c]	17.71±4.32 [d]
F value	3.760	6.556
P value	0.022	0.002

Note: Compared with Sham [a] $P<0.05$, [b] $P<0.01$; Compared with ESPS [c] $P<0.05$, [d] $P<0.01$.

2.4 各组大鼠前额叶皮质 BDNF 表达的差异

采用 Western blot 检测各组大鼠前额叶皮质 BDNF 蛋白的表达水平。以 β-actin 吸光度值作为内参，对各组 BDNF（$F=7.521$，$P=0.001$）蛋白条带的吸光度值进行半定量分析。发现 ESPS 组 BDNF 的表达低于 Sham 组（$P<0.001$），Sham + EA 组（$P=0.001$）及 ESPS + EA 组（$P=0.003$）。见图 1。

2.5 各组大鼠前额叶皮质 IL-6 和 IL-1β 水平的比较

应用 Elisa 检测各组大鼠前额叶皮质中 IL-6 和 IL-1β 的水平，发现各组大鼠 IL-6（$F=5.430$，$P=0.005$）差异有统计学意义，而 IL-1β（$F=2.101$，$P=0.123$）差异无统计学意义。与 ESPS 组相比，Sham 组（$P=0.001$），Sham + EA 组（$P=0.003$）及 ESPS + EA 组（$P=0.009$）大鼠 PFC 中 IL-6 的水平差异有统计学意义。ESPS 组大鼠前额叶皮质中 IL-1β 的水平高于 Sham 组（$P=0.033$），Sham + EA 组（$P=0.045$）及 ESPS + EA 组（$P=0.182$）。

3 讨论

神经影像学研究表明，患有 PTSD 的个体 PFC 的结构和功能存在异常[12]。有研究发现压力导致的适应不良的行为反应与大脑内侧 PFC 功能障碍有关[18]。另有研究发现调节腹内侧PFC，海马和杏仁核中失调的恐惧和焦虑回路，也可以改善 PTSD 的相关症状[19]。此外，研究报道电针干预提高了缺血再灌注模型大鼠 PFC 中的胆碱和 N- 乙酰天冬氨酸的水平，从而改善学习记忆能力[20]。另有研究发现电针刺激百会和印堂能调节 PFC 多个基因的表达来改善幼年母子分离的大鼠的抑郁样行为[21]。因此，PFC 可能是 PTSD 相关的重要脑区之一，对 PFC 功能的调节可能在 EA 发挥防治 PTSD 中具有重要作用。

BDNF 参与神经元的活动（包括神经元的存活，分化和生长以及突触的可塑性），并调节认知功能及焦虑情绪。PTSD 模型大鼠 PFC 中 BDNF 水平下降[22,23]。尸检的结果也显示，患有

压力相关情绪障碍的患者 PFC 中 BDNF 水平显著降低[24]。我们前期的研究发现 EA 早期干预(2/15Hz,百会穴)改善了 ESPS 模型大鼠 PTSD 样行为,上调了大鼠海马 BDNF 表达[11]。与上述研究结果相似，本研究发现 EA 早期干预增加了 ESPS 模型大鼠 PFC 中 BDNF 的表达水平,改善了大鼠焦虑样行为。提示电针早期干预对 PTSD 相关症状具有缓解作用,而且这一作用可能与其上调了大鼠 PFC 中 BDNF 的表达水平有关。

许多研究和荟萃分析表明 PTSD 与炎症反应有关,PTSD 的认知功能减退也与大脑中的慢性炎症反应有关[7,8]。IL-6 在中枢神经系统功能(包括认知能力)中的作用已被证明[25]。中国人群的研究表明 PTSD 患者血清细胞因子 IL-2、IL-6 和 IL-8 的水平升高 [26]。来自日本和西方国家的研究也发现 PTSD 的患者 IL-6 水平显著增加[27]。另外,PTSD 患者在所有检查的认知领域中表现出低于平均水平的表现，并且其较高的 IL-6 水平与其更低的认知功能相关[28]。动物研究表明 PTSD 啮齿动物模型海马 IL-1β 增加。一些免疫调节药物被证明可以降低 PTSD 模型动物体内升高的 IL-1β 水平,改善动物焦虑样行为。人体研究却显示出相互矛盾的结果:PTSD 患者的血清和血浆中 IL-1β 的水平升高或与对照组无明显差异[29]。本研究发现 PTSD 模型大鼠脑中 PFC 的 IL-6、IL-1β 的表达增高，电针早期干预降低了 PFC 中 IL-6 的表达,对 IL-1β 的表达影响不大。

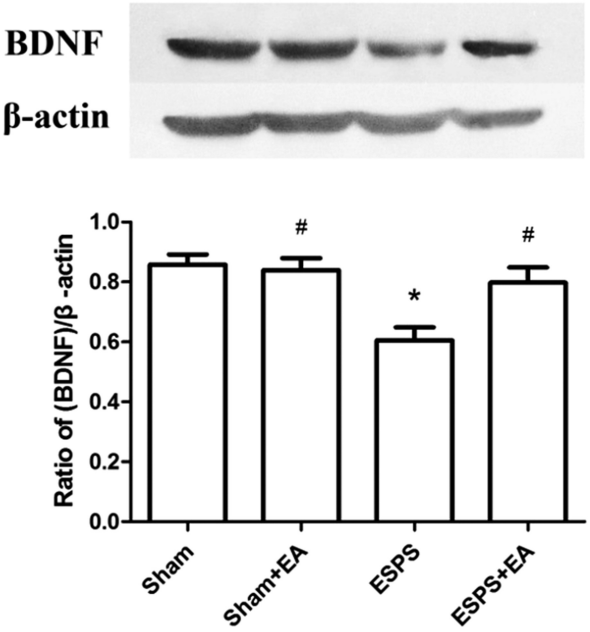

图 1 各组大鼠前额叶皮质 BDNF 的表达

Fig. 1 The expression of BDNF in prefrontal cortex of rats in each group

注:与 Sham 组比 *$P<0.05$;与 ESPS 组比 #$P<0.05$。

Note: *$P<0.05$ vs Sham; #$P<0.05$ vs ESPS.

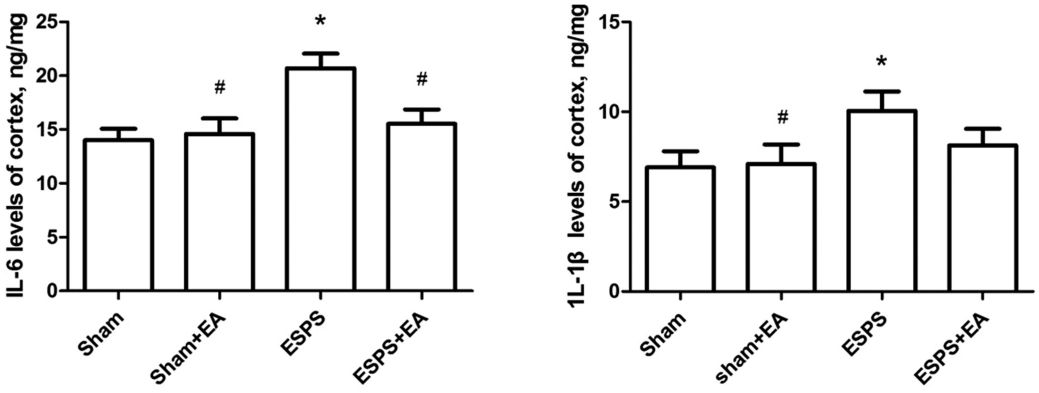

图 2 各组大鼠前额叶皮质 IL-6 和 IL-1β 水平的比较($\bar{x}\pm s$)

Fig. 2 Comparison of IL-6 and IL-1β levels in prefrontal cortex of each group

注:与 Sham 组比 *$P<0.05$;与 ESPS 组比 #$P<0.05$。

Note: *$P<0.05$ vs Sham; #$P<0.05$ vs ESPS.

重要的是,BDNF 和促炎性细胞因子之间的调节关系也被证实。已有研究提出炎症对脑功能的有害影响可能与过量水平的炎症介质的神经毒性作用以及其对神经可塑性的影响有关。高水平的促炎性因子会减少包括 BDNF 在内的神经可塑性标志物的水平[30]。值得注意的是,近期国外的一项研究也发现 PTSD 模型大鼠较正常对照大鼠相比,大脑皮质 BDNF 的水平降低,且 IL-6 的水平升高,与本研究结果一致[31]。大量的研究中,同时观察了 BDNF 与 IL-6 的水平,发现在抑郁症,焦虑症,精神分裂症等精神障碍的患者或动物模型中,脑组织或血液中 BDNF 和 IL-6 的水平存在相应的变化[32]。值得注意的是,有研究发现儿童期创伤史和近期高水平应激源刺激可通过炎症介导的途径(增加 IL-6 的水平)降低首发精神病患者 BDNF 表达[33]。另有研究发现过氧化物酶体增殖物激活的受体 γ 激动剂吡格列酮通过抑制脂多糖诱导的 NF-κB/ IL-6 / STAT3 途径的激活,改善脂多糖诱导的 BDNF 水平下调,从而改善小鼠的抑郁样行为[34]。以上研究提示 BDNF 与 IL-6 之间存在相互调节关系,但他们的相互作用机制还不完全清楚,有待进一步研究。

综上所述,本研究结果表明 EA 早期干预改善了大鼠焦虑样行为，这一作用可能与其抑制了 PFC 中 IL-6 水平，提高了 BDNF 的表达来发挥神经保护作用。未来需用其他检测手段(如免疫组化、实时定量 PCR)来进一步验证本研究的结果。同时,大脑PFC 中 BDNF 和 IL-6 相互作用机制还有待进一步研究。

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