·基础研究·

瘦素对新生期大鼠惊厥性脑损伤的康复作用及对皮质 Drd2/cPLA2 表达的影响

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【摘要】 **目的** 探讨瘦素对新生期大鼠惊厥性脑损伤的神经康复作用及对脑皮质多巴胺受体 D2(Drd2)和胞浆型磷脂酶 A2(cPLA2)表达的影响。**方法** 采用随机数字表法将 5 日龄 SD 大鼠分为对照组、瘦素对照组、惊厥组及瘦素干预组。惊厥组和瘦素干预组大鼠于实验第 6 天给予氯化锂(212 mg/kg 体重)腹腔注射,24 h 后给予匹鲁卡品(320 mg/kg 体重)腹腔注射,在匹鲁卡品注射前 30 min 给予氢溴酸东莨菪碱(1 mg/kg体重)腹腔注射以拮抗其副作用。从实验第 8 天开始,瘦素对照组及瘦素干预组大鼠每日给予瘦素(4 mg/kg体重)腹腔注射,连续注射 7 d。于实验进行 23 d 时检测各组大鼠平面翻正、负向趋地反射情况,于实验进行 30 d 时采用旷场实验评定各组大鼠认知情绪改变。于实验进行 34 d 时取各组大鼠脑组织,采用实时 PCR 技术检测脑皮质中 Drd2 及 cPLA2 表达。**结果** 4 组大鼠平面翻正时间及负向趋地时间组间差异具有统计学意义($P<0.05$);与对照组及瘦素对照组比较,惊厥组和瘦素干预组平面翻正时间及负向趋地时间均明显延长($P<0.05$);与惊厥组比较,瘦素干预组平面翻正时间及负向趋地时间均明显缩短($P<0.05$)。各组大鼠旷场实验开场得分组间差异具有统计学意义($P<0.05$),与对照组和瘦素对照组比较,惊厥组和瘦素干预组开场得分明显降低($P<0.05$);与惊厥组比较,瘦素干预组开场得分明显升高($P<0.05$)。瘦素对照组、惊厥组和瘦素干预组 Drd2 表达均明显高于对照组($P<0.05$);惊厥组和瘦素干预组 Drd2 表达较瘦素对照组显著增加($P<0.05$)。瘦素对照组及惊厥组 cPLA2 表达均明显高于对照组($P<0.05$);瘦素干预组 cPLA2 表达较惊厥组和瘦素对照组明显降低($P<0.05$)。**结论** 瘦素对新生期大鼠惊厥所致神经行为损伤具有神经康复作用,其作用机制可能与调节大脑皮质 Drd2 介导的 cPLA2 表达有关。

【关键词】 惊厥; 瘦素; 神经康复; 胞浆型磷脂酶 A2; 多巴胺受体 D2

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【**Abstract**】 **Objective** To explore the effect of leptin on neurorehabilitation and on the expression of dopamine receptor D2 (Drd2) and cytosolic phospholipase A2 (cPLA2) in the cerebral cortex after convulsive brain injury. **Methods** Five-day-old Sprague-Dawley rats were randomly assigned to a control group (CONT), a leptin injection control group (Leptin), a seizure group (RS), or a seizure with leptin injection group (RS+Leptin). The rats in the RS group and the RS+Leptin group were injected intraperitoneally with lithium chloride (5 mEq/kg) and pilocarpine (320 mg/kg) on day 6, and then scopolamine methyl chloride (1 mg/kg) 30 minutes later to block the peripheral effect of pilocarpine. The animals in the Leptin and RS+Leptin groups were then given leptin (4 mg/kg, i.p.) injections daily from days 8 to 14. The animals' plane righting reflex and negative geotaxis reaction reflex were observed on day 23. The open field test was performed on D30. Real-time reverse-transcription polymerase chain reactions (RT-PCRs) were used to detect the expression of Drd2 and cPLA2 mRNA in the rats' cerebral cortexes on day 34. **Results** There were significant differences in the plane righting times and negative geotaxis reflexes among the four groups, with those in the RS and RS+Leptin groups significantly longer than among the controls. Both reflexes were significantly quicker in the RS + Leptin group than in the RS group. There were also significant differences in the locomotor scores in the open field test among the four groups, with the average scores in the RS

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and RS+Leptin groups significantly higher than in the other two groups. The RS+Leptin group′s average was significantly higher than that of the RS group. The expression of Drd2 was significantly higher in the leptin, RS and leptin +RS groups than in the control group, and that of the RS and leptin+RS groups was significantly higher than that of the Leptin control group. The expression of cPLA2 in the Leptin and RS groups was significantly higher than in the CONT group, while that of the RS + Leptin group was significantly lower than in the Leptin and RS groups. **Conclusions** Leptin has a neurorehabilitation effect on the behavioral impairment caused by seizures, at least in neonatal rats. Its neuroprotective mechanism may be related to the regulation of Drd2-mediated cPLA2 expression in the cerebral cortex.

【**Key words**】 Seizures; Leptin; Neurorehabilitation; Cytosolic phospholipase A2

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新生儿惊厥是导致小儿脑瘫等神经功能伤残的重要原因[1]。侯文敏等[2]对 226 例脑瘫患儿发病危险因素进行回顾性分析,发现新生儿期惊厥致脑瘫的危险性仅次于窒息。2015 年 Gluckman 等[3]报道,大约 75%缺氧缺血性脑病(hypoxic-ischemic encephalopathy,HIE)新生儿发生惊厥,部分患儿成年期演变为癫痫患者。目前临床采用的传统抗癫痫药物对 HIE 致惊厥患儿有白质损伤等不良副作用[4],因此针对惊厥新生儿开展早期康复干预是儿科康复领域面临的迫切任务之一。

瘦素(leptin)是一种主要由脂肪细胞合成、分泌的脂肪因子,对调节食物摄入、能量消耗及代谢具有多重效应,近年来瘦素在神经康复中的作用备受关注。急性脑卒中患者血清瘦素水平较正常人明显升高,可预测患者神经康复水平,并指导临床康复治疗[5]。最近瑞士和意大利的一项联合前瞻性队列研究显示瘦素/脂联素比率在病程第 1 天升高预示急性缺血性脑卒中患者神经学预后良好,并可能作为脑卒中预后生物标志物[6];另外瘦素还能加速创伤性脑损伤后骨折愈合[7]。但瘦素对惊厥性脑损伤的神经康复作用及相关治疗机制尚不明确。Torolira 等[8]首次构建氯化锂-匹鲁卡品致生后 7 d 大鼠癫痫动物模型,并于癫痫持续 6 h、24 h 时在大鼠脑组织中均检测到广泛神经元损伤。基于此,本研究向氯化锂-匹鲁卡品致新生期惊厥大鼠腹腔注射瘦素,通过行为学方法观察大鼠远期神经反射变化,并采用实时 PCR 技术检测大鼠脑皮质中多巴胺受体 D2(dopamine receptor D2, Drd2)及胞浆型磷脂酶 A2(cytosplic phosphlipase A2, cPLA2)表达,从而探讨瘦素的神经保护机制。

材料与方法

一、实验动物分组与制模

采用随机数字表法将 50 只 5 日龄 Sprague-Dawley(SD)大鼠分为对照组、瘦素对照组、单纯惊厥组及瘦素干预组,其中对照组及瘦素对照组各 10 只大鼠,单纯惊厥组和瘦素干预组共有备用大鼠 30 只。单纯惊厥组及瘦素干预组大鼠于实验第 6 天给予氯化锂(212 mg/kg体重)腹腔注射,24 h 后给予匹鲁卡品(320 mg/kg体重)腹腔注射,在匹鲁卡品注射前 30 min 给予氢溴酸东莨菪碱(1 mg/kg 体重)腹腔注射以拮抗其副作用。注射完成后观察大鼠惊厥发作情况,如大鼠出现肢体痉挛伴抽搐则视为造模成功[8]。采用随机数字表法将造模成功的大鼠分为单纯惊厥组及瘦素干预组,每组 10 只大鼠。从实验第 8 天开始,瘦素对照组及瘦素干预组大鼠每日按每千克体重 4 mg 腹腔注射瘦素,连续注射 7 d。对照组不给予特殊处理,4 组大鼠饲养条件均相同。

二、神经反射测评

于实验进行 23 d 时对各组大鼠进行神经反射测评,包括:①平面翻正实验,将大鼠仰面朝上放于实验台上,记录从松手到大鼠躯体完全翻正所需时间,时间越短表示大鼠反应越快[9];②负向趋地实验,用手遮挡大鼠眼睛,将其头朝下放在与地面呈 45°的自制实验板上,松开手,记录大鼠头部回转 180°所需时间,时间越短表示大鼠反应性越佳[10]。

三、认知情绪功能测评

本研究采用旷场实验观察大鼠在新环境下的自发性探索活性及紧张焦虑行为,从而分析大鼠在应激状态下认知情绪功能变化。首先准备 50 cm×50 cm×50 cm的无盖旷场实验箱,底部划分为若干个 5 cm×5 cm大小的正方形格子,将大鼠置于底部正中央一格中,记录大鼠 5 min 期间水平移动格子数(即水平得分)及肢体直立次数(即垂直得分),开场得分为二者之和,开场得分越高表示大鼠在陌生环境下的空间探索能力越强[11]。

四、脑皮质 Drd2、cPLA2 检测

于实验进行 34 d 时每组各取 5 只大鼠用 4%水合氯醛(1 ml/100 g 体重)腹腔注射麻醉致深昏迷后取脑,取大脑皮质存放于 EP 管中并迅速置入-80 ℃冰箱内保存。组织细胞总 RNA 提取采用 Trizol 一步法,以所得细胞总 RNA 作为模板。使用 Promega 公司提供

的试剂盒进行逆转录反应得到 cDNA，以 cDNA 为模板进行荧光实时（real-time）定量 PCR 反应。本研究以 β-actin 作为内参，检测目的基因 Drd2 及 cPLA2 表达量。反应体系及反应条件如下：反应体系均为 25 μl，其中 cDNA 模板 2.0 μl，Universal PCR Master Mix（ABI，USA）12.5 μl，基因上、下游引物（10 pmol/μl）各 0.5 μl，探针（10 pmol/μl）0.3 μl，dH_2O 9.2 μl。在 DNA Engine OpticonTM 2（MJ Research 公司）中进行扩增反应。具体反应条件如下：52 ℃反应 2 min，94 ℃预变性 10 min，94 ℃反应 15 s，60 ℃反应 60 s，重复 45 个循环。

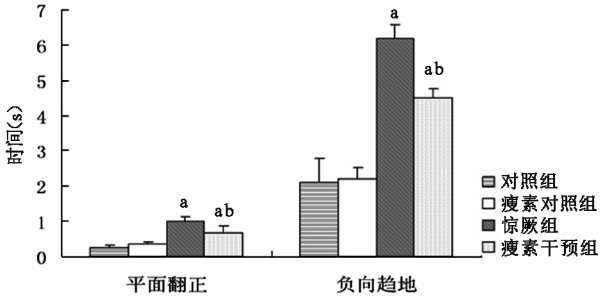
五、统计学分析

本研究所得计量数据以（$\bar{x}\pm s$）表示，各组大鼠神经行为学数据及 RT-PCR 数据（经 $2^{-\Delta CT}$ 法处理）采用单因素方差分析（one-way analysis of variance，one-way ANOVA）进行组间比较，$P<0.05$ 表示差异具有统计学意义。

结　果

一、各组大鼠神经反射测评结果比较

4 组大鼠平面翻正时间及负向趋地时间组间差异均具有统计学意义（$P<0.05$）；与对照组和瘦素对照组比较，惊厥组和瘦素干预组平面翻正时间及负向趋地时间均明显延长（$P<0.05$）；与惊厥组比较，瘦素干预组平面翻正时间及负向趋地时间均明显缩短（$P<0.05$）；对照组与瘦素对照组平面翻正时间及负向趋地时间组间差异均无统计学意义（$P>0.05$），具体情况见图 1。

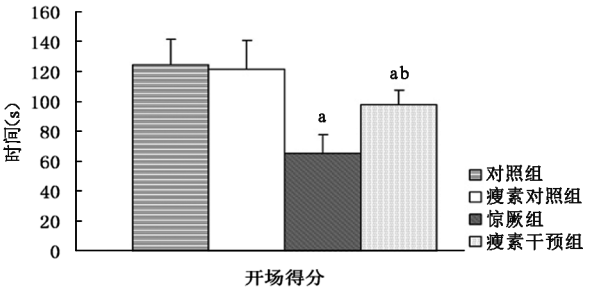


注：与对照组及瘦素对照组比较，[a]$P<0.05$；与惊厥组比较，[b]$P<0.05$

图 1　实验进行 23 d 时各组大鼠平面翻正、负向趋地时间比较

二、各组大鼠认知情绪功能比较

实验进行 30 d 时发现各组大鼠旷场实验开场得分组间差异具有统计学意义（$P<0.05$）；与对照组和瘦素对照组比较，惊厥组和瘦素干预组开场得分均明显降低（$P<0.05$）；与惊厥组比较，瘦素干预组开场得分明显升高（$P<0.05$）；对照组与瘦素对照组开场得分组间差异无统计学意义（$P>0.05$），具体情况见图 2。

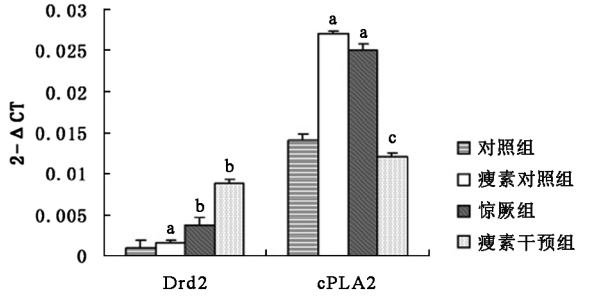


注：与对照组和瘦素对照组比较，[a]$P<0.05$；与惊厥组比较，[b]$P<0.05$

图 2　实验进行 30 d 时各组大鼠旷场实验开场得分比较

三、各组大鼠脑皮质 Drd2 及 cPLA2 mRNA 检测结果比较

实验进行 34 d 时通过实时定量 PCR 检测发现，瘦素对照组、惊厥组和瘦素干预组 Drd2 表达均明显高于对照组（$P<0.05$）；惊厥组和瘦素干预组 Drd2 表达均较瘦素对照组显著增加（$P<0.05$）；瘦素干预组 Drd2 表达较惊厥组有增加趋势，但组间差异无统计学意义（$P>0.05$），具体情况见图 3。瘦素对照组和惊厥组 cPLA2 表达均明显高于对照组（$P<0.05$）；瘦素干预组 cPLA2 表达较惊厥组及瘦素对照组明显降低（$P<0.05$），与对照组间差异无统计学意义（$P>0.05$），具体情况见图 3。



注：与对照组比较，[a]$P<0.05$；与瘦素对照组比较，[b]$P<0.05$；与瘦素对照组及惊厥组比较，[c]$P<0.05$

图 3　各组大鼠脑皮质 Drd2 及 cPLA2 检测结果比较

通过相关性分析发现，各组大鼠脑皮质 Drd2 与 cPLA2 间均无显著相关性（$P>0.05$），将 4 组大鼠数据合并后亦未发现 Drd2 与 cPLA2 有明显相关性（$P>0.05$）；而将瘦素对照组、惊厥组和瘦素干预组 3 组数据合并后发现 Drd2 与 cPLA2 具有明显相关性（$r=-0.5959$，$P<0.05$），具体情况见图 4。

讨　论

急性惊厥发作是新生儿期神经功能障碍及脑损伤的常见征兆，也是小儿脑瘫主要原因之一[12]。新生期反复长程惊厥会造成神经元兴奋性损伤，从而影响未成熟大脑发育进程及突触构建方式，造成远期神经行

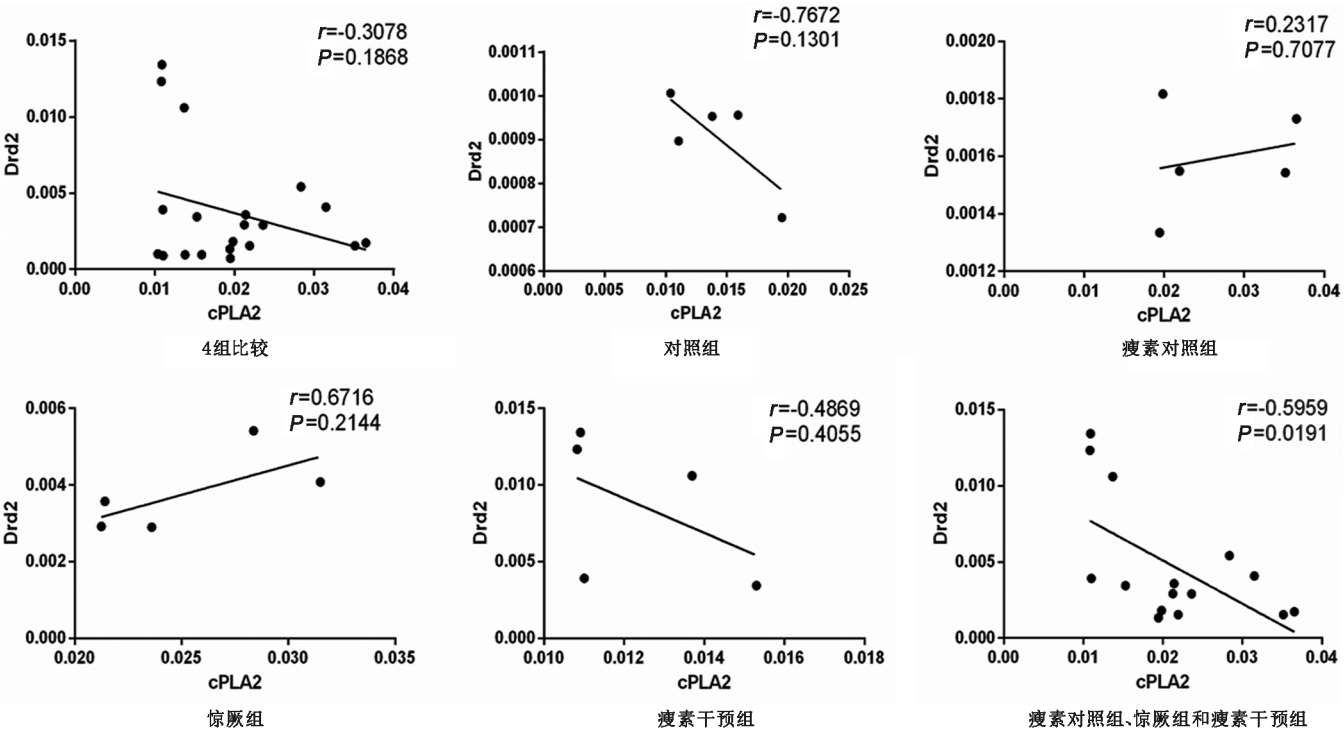


图 4　各组大鼠脑皮质 cPLA2 与 Drd2 相关性分析

为和认知功能受损[13]。目前临床针对反复长程惊厥新生儿的康复策略主要集中在抑制急性期神经兴奋毒性损伤方面。

脂肪组织分泌的脂肪因子对于调节和维持机体能量平衡至关重要。瘦素(leptin)最初于 1994 年从肥胖基因中克隆而成,在众多脂肪因子中与能量代谢关系最为密切,与许多疾病发生有关,包括动脉粥样硬化、糖尿病和某些类型癌症等[14]。近年来有研究发现,瘦素及其受体在中枢神经系统中广泛存在,并可能提供神经元存活信号,发挥神经营养及神经保护作用,缓解急性脑疾病(如脑卒中等)以及长期神经退行性变过程中的神经元损伤[15]。相关动物实验发现,瘦素对 N-甲基-d-天冬氨酸(N-methyl-D-aspartic acid, NMDA)诱导的大鼠皮质神经元死亡具有神经保护作用[16],急性期应用瘦素能保护神经元免受兴奋毒性及氧化损伤,抑制细胞死亡[17]。Lopez-Rodriguez 等[18]证实瘦素(在损伤后立即腹膜内施用 1 次)能恢复创伤性脑损伤小鼠模型神经行为参数。Malekizadeh 等[19]也发现瘦素能促进活性依赖的海马突触可塑性,防止突触破坏和神经元死亡。但目前为止瘦素对惊厥性脑损伤的保护作用鲜见报道。Mela 等[20]发现瘦素干预能部分抵消新生期母爱剥夺应激大鼠在旷场实验中的神经行为改变。本研究结果也显示惊厥组大鼠旷场实验开场得分较对照组明显降低,而瘦素干预组开场得分较惊厥组明显升高,提示瘦素可改善惊厥后大鼠在陌生环境下的空间探索及适应能力。另外本实验还发现惊厥组大鼠平面翻正反射和负向趋地反射时间均较对照组明显延长,而瘦素干预组平面翻正反射和负向趋地反射时间均较惊厥组明显缩短,提示瘦素对惊厥大鼠反应性、警觉性及协调能力等均具有明显改善作用。

目前关于瘦素改善神经行为功能的分子机制研究相对较少。多巴胺受体 D2(Drd2)参与脑内“喂养奖赏系统”功能,能抑制强迫性进食行为[21]。肥胖人群大脑特定区域存在 Drd2 表达改变,能与瘦素受体协同作用控制过度肥胖[22]。Drd2 激动剂能促进脂肪组织中瘦素表达,而 siRNA 介导的 Drd2 沉默能降低瘦素含量,提示 Drd2 刺激能促进瘦素产生[23]。本研究结果发现瘦素对照组脑皮质 Drd2 表达较对照组显著上调,表明连续 7 d 的外周瘦素注射能影响脑内 Drd2 表达,进一步提示 Drd2 与瘦素在脑功能调节方面具有密切联系。本研究惊厥组大鼠脑皮质 Drd2 表达较对照组显著上调,同时存在神经反射测试及旷场实验结果异常,提示大脑皮质 Drd2 表达上调参与新生期惊厥所致远期神经行为损伤的病理生理过程。另外本研究瘦素对照组 Drd2 表达较单纯对照组显著上调,但 2 组大鼠神经反射及旷场实验结果无明显差异,提示正常大鼠给予连续 7 d 的瘦素注射能调节脑内能量代谢相关基因表达,但对其神经行为无远期不良影响。

最新研究表明,与质膜损伤相关的脂质代谢分子是发育期脑损伤干预的新靶点[24]。cPLA2 是 PLA2

家族中的一种亚型,以细胞浆内多见,是一组作用于细胞内膜磷脂的磷脂酶,广泛存在于中枢神经系统中,也是神经质膜完整性的重要调节分子[25]。cPLA2 参与机体神经元兴奋、细胞间联系、突触分泌、行为及认知功能以及炎症反应等病理生理过程[26]。已有文献证明cPLA2表达上调是多种神经退行性疾病的关键致病因素,如帕金森病、阿尔茨海默病等[27]。Bate 等[28-29]研究发现,cPLA2 活化诱导神经突触损伤,而 cPLA2 抑制剂预处理能降低突触损伤;小鼠脊髓损伤模型可见 cPLA2 表达上调,阻断 cPLA2 能改善小鼠运动功能,减少脊髓损伤后细胞损失及组织损伤。本研究结果显示,惊厥组 cPLA2 表达明显高于对照组,提示新生期惊厥造成远期大脑皮质神经细胞损伤;而瘦素干预组 cPLA2 表达较惊厥组明显降低,与对照组间差异无统计学意义($P>0.05$),说明瘦素通过下调 cPLA2 表达能改善新生期惊厥所致远期神经行为功能损伤,这可能是瘦素发挥神经康复作用的内在分子机制之一。需要指出的是,瘦素对照组 cPLA2 表达明显高于对照组,而瘦素干预组明显低于惊厥组,显示瘦素对 cPLA2 具有双向调节作用。这种双向表达特征与 Drd2 明显不同,其原因尚不清楚。本研究将瘦素对照组、惊厥组、瘦素干预组数据合并后进行相关性分析,发现 Drd2 与 cPLA2 呈负相关,提示瘦素干预组 cPLA2 表达下调可能与 Drd2 高表达有关,即瘦素可能通过上调 Drd2 表达改善大脑皮质神经元能量代谢,从而发挥神经康复作用。

综上所述,本研究结果表明,瘦素对新生期大鼠惊厥所致神经行为损伤具有神经康复作用,其神经保护机制可能与调节大脑皮质 Drd2 介导的 cPLA2 表达有关,瘦素干预为高危新生儿神经康复治疗提供了新思路和理论支持,具有重要临床意义。

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·外刊撷英·

Cardiac output and cerebral perfusion after a stroke

BACKGROUND AND OBJECTIVE Restoring penumbral perfusion is the key therapeutic target in patients with acute ischemic stroke. In cases of insufficient or unsuccessful vessel recanalization, maintaining normal to higher mean arterial pressure (MAP) is an accepted goal. MAP is expected to improve cerebral perfusion (CP), as constant cerebral blood flow (CBF) is maintained over a wide range of MAP due to vessel autoregulation. This study assessed to relationship between CP and CO.

METHODS Subjects were ten consecutive inpatients with a large ischemic stroke in the middle cerebral artery (MCA) territory. Symptom severity was assessed using the the National Institute of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) on admission and at discharge. Following hemodynamic baseline measurements, all patients were monitored with transcranial color-coded duplex sonography (TCCD) and transcranial perfusion sonography (TPS). Cerebral perfusion was assessed by transcranial color-coded duplex and transcranial perfusion sonography. Time-to-peak (TTP) values of defined regions of interest (ROI), as well as hemodynamic parameters, were assessed, including MAP and cardiac index (CI).

RESULTS The analyses of CI and MAP levels, TTP and MCA velocity revealed highly significant inverse correlations of CI and TTP in the affected and unaffected basal ganglia ($P<0.001$) and ($P<0.0001$), respectively.

CONCLUSION This study of patients with acute ischemic stroke suggests that the cardiac output may be more relevant than mean arterial pressure as a guide while optimizing cerebral penumbral perfusion.

【摘自:Fuhrer H, Reinhard M, Niesen WD, et al. Paradigm change cardiac output better associations with cerebral perfusion than blood pressure in ischemic stroke. Front Neurol, 2017, 22; 8(706).】

Transcranial magnetic stimulation for the elderly with cognitive impairment

BACKGROUND AND OBJECTIVE Medications to improve cognitive impairment among patients with Alzheimer's Disease include acetylcholinesterase inhibitors and N-Methyl-D aspartame receptor antagonists. However, these drugs often have only limited and transient effects. As recent studies have suggested that repetitive transcranial magnetic stimulation (rTMS) may be effective for improving cognition in older adults, this systematic review and meta-analysis was designed to clarify the efficacy of this treatment modality for patients with mild cognitive impairment.

METHODS After completing an extensive medical literature search, the authors identified 13 published studies of which 9 were randomized controlled trials. From these, 7 parallel-group randomized controlled trials with complete outcome data were used for the final analysis. Most of the subjects had mild to moderate cognitive impairment at the onset of the trials.

RESULTS Subjects included elderly patients with cognitive impairment, with 107 in the active and 87 in the sham treatment. The most common target of the rTMS was the dorsolateral prefrontal cortex. With sessions ranging from 1-30 per study treatment, and most including five sessions per week, those treated with rTMS were found to have a moderate improvement in cognition ($P=0.01$). No serious side effects were reported in the studies.

CONCLUSION This study found that high frequency repetitive transcranial magnetic stimulation may improve cognition among elderly patients with mild to moderate cognitive impairment.

【摘自:Cheng CPW, Wong CSM, Lee KK, et al. Effects of repetitive transcranial magnetic stimulation on improvement of cognition in elderly patients with cognitive impairment: a systematic review and meta-analysis. Int J Geriatr Psychiatry, 2018, 33: e1-e13.】