脑震宁颗粒改善多重脑震荡模型大鼠学习记忆障碍的机制研究Δ

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摘　要　目的　研究脑震宁颗粒对多重脑震荡（MCC）模型大鼠学习记忆障碍的改善机制。**方法**　采用闭合式可控皮质撞击法制备MCC大鼠模型。实验设置空白组（生理盐水）、模型组（生理盐水）、吡拉西坦组（阳性对照组，0.324 g/kg）和脑震宁颗粒高、中、低剂量组（5.4、2.7、1.35 g/kg），每组11只。每天灌胃给药/生理盐水1次，连续28 d。实验期间监测大鼠一般情况和体重变化。测定大鼠糖水偏好率和新物体识别指数；检测大鼠脑皮层中伊文思蓝渗出量；观察脑皮层神经元病理变化；检测脑皮层中B细胞淋巴瘤2（Bcl-2）、Bcl-2相关X蛋白（Bax）、白细胞介素6（IL-6）、IL-10、肿瘤坏死因子α（TNF-α）水平以及AMP活化的蛋白激酶（AMPK）、糖原合成酶激酶3β（GSK3β）、Tau蛋白磷酸化水平。**结果**　与空白组比较，模型组大鼠精神状态变差，对外界刺激反应迟缓，摄食量、饮水量减少，肢体灵活度下降，皮毛杂乱；体重、糖水偏好率、新物体识别指数均显著降低（$P<0.05$）；脑皮层中伊文思蓝渗出量显著增加（$P<0.05$）；神经元损伤严重，Bax蛋白阳性面积比以及IL-6、TNF-α水平和Tau蛋白磷酸化水平均显著升高（$P<0.05$）；Bcl-2蛋白阳性面积比、IL-10水平和AMPK、GSK3β蛋白磷酸化水平均显著降低（$P<0.05$）。与模型组比较，脑震宁颗粒各剂量组大鼠的一般情况、病理损伤均有所改善，定量指标均有所回调，其中脑震宁颗粒高剂量组定量指标差异均有统计学意义（$P<0.05$）。**结论**　脑震宁颗粒可有效改善MCC模型大鼠的学习记忆障碍；其作用机制可能与激活AMPK/GSK3β通路，抑制炎症反应、降低Tau蛋白磷酸化水平，进而修复神经元损伤有关。

关键词　脑震宁颗粒；多重脑震荡；学习记忆障碍；血脑屏障；AMPK/GSK3β通路；Tau蛋白

Study on the mechanism of Naozhenning granules in improving learning and memory impairment in multiple cerebral concussion model rats

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ABSTRACT　OBJECTIVE To investigate the mechanism by which Naozhenning granules（NZN）improve learning and memory impairment in a rat model of multiple cerebral concussion（MCC）. **METHODS** The MCC rat model was established using the closed controlled cortical impact method. The experiment was set up with a blank group（normal saline），a model group（normal saline），a piracetam group（positive control group，0.324 g/kg），and high-，medium-，and low-dose NZN groups（5.4，2.7，1.35 g/kg），with 11 rats in each group. Drugs or normal saline were administered by gavage once daily for 28 consecutive days. General condition and body weight were monitored throughout the experiment. The sucrose preference rate and novel object recognition index were measured；Evans blue（EB）extravasation in the cerebral cortex was detected；pathological changes of cortical neurons were observed；the levels of B-cell lymphoma-2（Bcl-2），Bcl-2-associated X protein（Bax），interleukin-6（IL-6），IL-10，and tumor necrosis factor-α（TNF-α）in the cerebral cortex were determined；and the phosphorylation levels of AMP-activated protein kinase（AMPK），glycogen synthase kinase 3β（GSK3β），and Tau protein were detected. **RESULTS** Compared with the blank group，the model group showed poor mental state，sluggish response to external stimuli，reduced food and water intake，decreased limb flexibility，and disheveled fur. Body weight，sucrose preference rate，and novel object recognition index were significantly decreased（$P<0.05$）；EB extravasation in the cerebral cortex was significantly increased（$P<0.05$），with severe neuronal damage. The positive area ratio of Bax protein，IL-6 and TNF-α levels，and Tau protein phosphorylation level were all significantly increased（$P<0.05$），whereas the positive area ratio of Bcl-2 protein，IL-10 level，and AMPK and GSK3β protein phosphorylation levels were significantly decreased（$P<0.05$）. Compared with the model group，all NZN dose groups showed improvements in general condition and pathological damage，with quantitative indices partially restored，and the differences in quantitative indices in high-dose NZN group were statistically significant（$P<0.05$）. **CONCLUSIONS** NZN can effectively improve learning and memory impairment in MCC model rats. The mechanism may be related to activating the AMPK/GSK3β pathway，inhibiting inflammatory response，reducing Tau protein phosphorylation level，and then repairing the neuronal injury.

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