温阳化瘀方改善大鼠脑缺血再灌注损伤的作用及机制研究Δ

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摘　要　目的　基于核转录因子红系2相关因子2（Nrf2）/谷胱甘肽过氧化物酶4（GPX4）信号通路和线粒体铁死亡途径，研究温阳化瘀方对大鼠脑缺血再灌注损伤的改善作用及机制。**方法**　将SD大鼠随机分为假手术组、模型组、尼莫地平片组（10.8 mg/kg）、温阳化瘀方组（28 g/kg），每组24只。除假手术组外，其余各组大鼠均采用Longa线栓法构建大脑中动脉闭塞模型。造模成功后，各给药组大鼠灌胃相应药液（连续给药7 d或者14 d），假手术组和模型组大鼠灌胃等体积生理盐水，每天1次。分别于给药后第7、14天时，计算大鼠神经功能缺损评分；观察大鼠缺血侧脑组织神经元线粒体超微结构；检测大鼠缺血侧脑组织中丙二醛（MDA）、谷胱甘肽（GSH）、Fe^{2+}含量以及Nrf2、溶质载体家族7成员11（SLC7A11）、GPX4蛋白和mRNA表达水平。**结果**　给药后第7、14天时，与假手术组比较，模型组大鼠缺血侧脑组织神经元线粒体呈铁死亡典型改变，且随时间推移损伤持续加重；神经功能缺损评分和MDA、Fe^{2+}含量均显著升高（$P<0.05$），GSH含量以及Nrf2、SLC7A11、GPX4蛋白和mRNA表达水平均显著降低（$P<0.05$）。与模型组比较，尼莫地平片组和温阳化瘀方组大鼠缺血侧脑组织神经元线粒体形态随时间推移逐步改善，上述定量指标均显著逆转（$P<0.05$），且温阳化瘀方组大部分指标的改善效果均显著优于尼莫地平片组（$P<0.05$）。**结论**　温阳化瘀方可改善大鼠脑缺血再灌注损伤，其作用机制可能与激活Nrf2/GPX4信号通路、抑制线粒体铁死亡有关。

关键词　温阳化瘀方；脑缺血再灌注损伤；Nrf2/GPX4信号通路；线粒体；铁死亡；神经元

Study on the effect and mechanism of Wenyang huayu formula in improving cerebral ischemia-reperfusion injury in rats

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ABSTRACT　OBJECTIVE To investigate the improving effect and mechanism of Wenyang huayu formula on cerebral ischemia-reperfusion injury in rats based on nuclear factor-erythroid 2-related factor 2 (Nrf2)/glutathione peroxidase 4 (GPX4) signaling pathway and mitochondrial ferroptosis pathway. **METHODS** SD rats were randomly divided into sham operation group, model group, Nimodipine tablet group (10.8 mg/kg), and Wenyang huayu formula group (28 g/kg), with 24 rats in each group. Except for the sham operation group, rats in other groups were all subjected to middle cerebral artery occlusion model by Longa thread occlusion method. After successful modeling, rats in each administration group were intragastrically gavaged with corresponding liquid for 7 days or 14 days, while rats in sham operation group and model group were given equal volume of normal saline once a day. At 7 and 14 days after administration, neurological deficit scores of rats were calculated; the ultrastructure of neuronal mitochondria in ischemic brain tissue of rats was observed; the contents of malondialdehyde (MDA), glutathione (GSH) and Fe^{2+}, as well as the protein and mRNA expression levels of Nrf2, solute carrier family 7 member 11 (SLC7A11) and GPX4 in ischemic brain tissue of rats were detected. **RESULTS** At 7 and 14 days after administration, compared with the sham operation group, the neuronal mitochondria in ischemic brain tissue of rats in the model group showed typical changes of ferroptosis, and the injury continued to worsen over time; the neurological deficit scores, the contents of MDA and Fe^{2+} were significantly increased ($P<0.05$), while the content of GSH and the protein and mRNA expression levels of Nrf2, SLC7A11 and GPX4 were significantly decreased ($P<0.05$). Compared with the model group, the morphology of neuronal mitochondria in ischemic brain tissue of rats in Nimodipine tablet group and Wenyang huayu formula group was gradually improved over time, and the above quantitative indicators were significantly reversed ($P<0.05$); moreover, the improvement effect of most indicators in Wenyang huayu formula group was significantly better than that in Nimodipine tablet group ($P<0.05$). **CONCLUSIONS** Wenyang huayu formula can improve cerebral ischemia-reperfusion injury in rats, and its mechanism may be related to activating Nrf2/

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