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Pretreatment by Evodiamine is Neuroprotective in Cerebral Ischemia: Up-Regulated pAkt, pGSK3b, Down-Regulated NF-κB Expression, and Ameliorated BBB Permeability

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Background and object Inammatory response. Whether this protective effect applies to cerebral ischemic injury, we therefore investigated the potential neuroprotective role of Evo and the underlying mechanisms.

Methods Male Institute of Cancer Research (ICR) mice were subjected to permanent middle cerebral artery occlusion (pMCAO) and randomly divided into cit, brain water content and infarct size were measured at 24 h after stroke. The expression of pAkt, pGSK3b, NF-κB and claudin-5 in ischemic cerebral cortex was analyzed by western blot and qRT-PCR.

Results Compared with Vehicle group, Evo signicit, brain water content and infarct size, upregulated the expression of pAkt, pGSK3b and claudin-5, and downregulated the nuclear accumulation of NF-κB ($p < 0.05$).

Conclusion Evo protected the brain from ischemic damage caused by pMCAO; this effect may be through upregulation of pAkt, pGSK3b and claudin-5, and downregulation of NF-κB expression.

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银杏内酯和白果内酯通过下调 PAK1-PP2A 通路抑制 Cx43 去磷酸化在脑缺血中发挥保护作用

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目的 探讨银杏内酯（Ginkgolides，GK）和白果内酯（bilobalide，BB）对缺血再灌注损伤大鼠的保护作用及其可能通过 PAK1(p21-activated kinasel）和蛋白磷酸酶 2A(protein phosphatase 2A，PP2A）通路抑制缝隙连接蛋白 43（connexin 43，Cx43）去磷酸化发挥的作用机制。

方法 采用大鼠大脑中动脉阻塞（middle cerebral artery occlusion，MCAO）模型观察 GK（2.5、5、10mg/kg）组和 BB（2.5、5、10mg/kg）对大鼠神经功能缺损及脑梗死范围的影响；采用免疫荧光技术检测缺血大脑皮层 p-NF-κB，Cleaved-caspase3 的表达；应用 TUNEL 试剂盒检测缺血大脑皮层凋亡情况；行 Western blot 法检测缺血大脑皮层 MMP-9、AQP-4、p-AKT、p-NF-κB、IL-1β、HIF、VEGF，Cx43、p-Cx43、p-PAK1、p-PP2A、PP2A 蛋白水平的表达。

结果 GK 和 BB 对缺血/再灌注大鼠神经症状有明显的改善作用，能明显降低脑梗死范围，对神经细胞具有保护作用 Western blot 结果显示: 大鼠脑缺血/再灌后，MMP-9 和 AQP-4、IL-1β、p-NF-κB、Cx43 蛋白水平明显升高，HIF、VEGF、p-AKT、p-Cx43 水平下降，GK 和 BB 能明显降低 MMP-9 和 AQP-4、IL-1β、p-NF-κB、Cx43 及 p-PAK1、p-PP2A、PP2A 蛋白水平；提高 HIF、VEGF、p-AKT、p-Cx43 蛋白水平。免疫组化结果表明：大鼠脑缺血/再灌后，Cleaved-caspase3 水平升高，GK 和 BB 下调 Cleaved-caspase3 的表达；缺血后 NF-κB 从细胞浆移位至细胞核，GK 和 BB 可抑制 NF-κB 的核转位。TUNEL 染色结果提示：大鼠脑缺血/再灌见大量绿色荧光标记的凋亡神经元及胶质细胞，GK 和 BB 明显减少凋亡细胞数目。

结论 银杏内酯和白果内酯具有降低血脑屏障通透性，发挥抗炎、抗凋亡及促进血管生成对大鼠脑缺血再灌注损伤发挥保护作用，其保护作用还可能抑制 PAK1-PP2A 通路，下调去磷酸化的 Cx43 的表达而增强缝隙连接功能有关。