

富马酸奥赛利定通过TLR4/NF- κ B通路改善老年大鼠术后认知功能障碍的作用及机制^A

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摘要 目的 基于Toll样受体4(TLR4)/核因子- κ B(NF- κ B)通路探究富马酸奥赛利定(TRV130)改善老年大鼠术后认知功能障碍(POCD)的作用及机制。方法 将大鼠随机分为对照组(生理盐水)、模型组(生理盐水)、TRV130组(2.8 mg/kg)、TLR4/NF- κ B通路抑制剂(TAK-242)组(3 mg/kg)、 β -抑制蛋白抑制剂(Barbadin)组(3 mg/kg)和传统阿片类药物(吗啡)组(2.8 mg/kg),每组15只。除对照组外,其余各组均构建POCD模型。从术后第1天起,尾静脉注射给药/生理盐水,每天1次,连续3 d。末次给药后,观察海马组织病理损伤情况;检测大鼠认知功能,血清中炎症因子水平,海马神经元凋亡率,海马组织中离子钙结合适配器分子1(Iba-1)、胶质纤维酸性蛋白(GFAP)和TLR4/NF- κ B通路相关mRNA及其蛋白表达。结果 模型组大鼠海马CA1区神经元排列紊乱、稀疏,数量减少,核固缩碎裂伴炎症细胞浸润。与对照组比较,模型组大鼠逃避潜伏期,肿瘤坏死因子 α 、白细胞介素6(IL-6)、IL-1 β 水平,海马神经元凋亡率,海马组织中Iba-1、GFAP平均荧光强度和TLR4、NF- κ B p65 mRNA表达水平及其蛋白表达/磷酸化水平均显著延长/升高($P < 0.05$);目标象限停留时间、穿越平台次数均显著缩短/减少($P < 0.05$)。与模型组比较,TRV130组、TAK-242组、Barbadin组大鼠认知功能、病理学、炎症及凋亡相关指标均显著改善($P < 0.05$);TRV130组、TAK-242组大鼠TLR4、NF- κ B p65 mRNA表达水平及其蛋白表达/磷酸化水平均显著降低($P < 0.05$)。结论 TRV130可能通过抑制TLR4/NF- κ B通路,减轻术后中枢神经炎症反应,进而改善老年大鼠POCD。

关键词 富马酸奥赛利定;老年大鼠;术后认知功能障碍;TLR4/NF- κ B通路;神经炎症

Effects and mechanisms of oliceridine fumarate on postoperative cognitive dysfunction in elderly rats through TLR4/NF- κ B pathway

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ABSTRACT OBJECTIVE To investigate the effects and mechanisms of oliceridine fumarate (TRV130) in improving postoperative cognitive dysfunction (POCD) in elderly rats based on the Toll-like receptor 4 (TLR4)/nuclear factor- κ B (NF- κ B) pathway. **METHODS** Rats were randomly divided into the control group (normal saline), the model group (normal saline), the TRV130 group (2.8 mg/kg), the TLR4/NF- κ B pathway inhibitor (TAK-242) group (3 mg/kg), the β -arrestin inhibitor (Barbadin) group (3 mg/kg), and the traditional opioid drug (morphine) group (2.8 mg/kg), with 15 rats in each group. Except for the control group, POCD models were established in all other groups. From the first day after surgery, drugs/normal saline were administered via caudal vein injection once daily for 3 consecutive days. After the last administration, the pathological damage of hippocampal tissue was observed; the cognitive function, serum inflammatory factor levels, hippocampal neurons apoptosis rate, and the expression of ionized calcium-binding adapter molecule 1 (Iba-1), glial fibrillary acidic protein (GFAP), and TLR4/NF- κ B pathway-related mRNA and protein in hippocampal tissue were detected. **RESULTS** In the model group, the neurons in the CA1 region of the hippocampus were disordered and sparse, with decreased number, pyknotic and fragmented nuclei accompanied by inflammatory cell infiltration. Compared with the control group, the escape latency, serum levels of tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), and IL-1 β , hippocampal neurons apoptosis rate, average fluorescence intensities of Iba-1 and GFAP, mRNA expression levels of TLR4 and NF- κ B p65, and their protein expression/phosphorylation levels in hippocampal tissue were significantly increased/elevated in the model group ($P < 0.05$); the time spent in the target quadrant and the number of platform crossings were significantly shortened/decreased ($P < 0.05$). Compared with the model group, the cognitive function, pathological, inflammatory, and apoptosis-related indicators were significantly improved in the TRV130 group, TAK-242 group, and Barbadin group ($P < 0.05$); the mRNA expression levels of TLR4 and NF- κ B p65 and their protein expression/phosphorylation levels were significantly decreased in the TRV130 group and TAK-242 group ($P < 0.05$). **CONCLUSIONS** TRV130 may improve

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