中国药理学与毒理学杂志 2010 24 (3): 174-179 ISSN: 1000-3002 CN: 11-1115/R

论著

吡格列酮对淀粉样β蛋白片段1-42引起的大鼠海马c-Jun氨基端激酶信号传导通路改变的作用

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收稿日期 2009-8-31 修回日期 网络版发布日期 2010-5-25 接受日期 2010-2-1

摘要 目的 探讨吡格列酮（Pio）对淀粉样β蛋白片段1-42（$A\beta_{1-42}$）所致大鼠海马神经细胞损伤保护作用的信号传导机制。方法 SD大鼠左侧脑单次icv给予5 μl $A\beta_{1-42}$ 2.0 mmol·L^{-1}制备大鼠痴呆模型。65只大鼠随机分为正常对照组、$A\beta_{1-42}$模型组及Pio 20，40和80 mg·kg^{-1}组；Pio组大鼠在icv单次给予$A\beta_{1-42}$前24 h先ig给予Pio 20，40及80 mg·kg^{-1}，每天一次，连续给药7 d。Western印迹法检测海马CA1区磷酸化丝裂原激活蛋白激酶激酶4（MKK4）、磷酸化c-Jun氨基端激酶1(JNK1)和磷酸化c-Jun的蛋白表达水平；应用激光共聚焦显微镜观察磷酸化JNK在小胶质细胞表达部位。结果 与正常对照组比较，$A\beta_{1-42}$模型组大鼠icv给予$A\beta_{1-42}$后，可引起海马CA1区磷酸化的MKK4，JNK1和c-Jun的表达明显增加(P<0.01)；与$A\beta_{1-42}$模型组比较，Pio 20，40和80 mg·kg^{-1}可剂量依赖性地对抗$A\beta_{1-42}$引起的磷酸化MKK4，JNK1和c-Jun表达的增加(P<0.01)，Pio 40 mg·kg^{-1}使磷酸化MKK4蛋白与总量MKK4蛋白之比从$A\beta_{1-42}$模型组的1.02±0.35降低到0.44±0.06，磷酸化JNK1从0.94±0.17降低到0.55±0.05，磷酸化c-Jun从4.64±0.41降低到2.48±0.12(P<0.01)。荧光免疫组织化学双染，激光共聚焦显微镜观察结果显示，磷酸化的JNK主要在小胶质细胞表达。结论 Pio通过抑制小胶质细胞内JNK激酶信号传导通路的活化，对抗$A\beta_{1-42}$引起的海马神经细胞损伤。

关键词 吡格列酮 阿尔茨海默病 淀粉样β蛋白 促分裂原活化的蛋白激酶激酶 c-Jun氨基端激酶

分类号 R977.15，R963

Effects of pioglitazone on amyloid beta-protein fragment 1-42-induced c-Jun N-terminal kinase signal pathway in hippocampus of rats

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Abstract

OBJECTIVE To observe neuroprotective effects and protective mechanisms of pioglitazone (Pio) on amyloid beta-protein fragment 1-42 ($A\beta_{1-42}$)-induced neurotoxicity in rat hippocampus. **METHODS** Sixty-five SD rats were randomly divided into 5 groups: normal control group, $A\beta_{1-42}$ model group and Pio 20, 40 and 80 mg • kg^{-1} groups. Before rats in Pio groups were icv given 5 μl $A\beta_{1-42}$ 2.0 mmol • L^{-1} 24 h, they were ig given Pio 20, 40 and 80 mg • kg^{-1}, once a day, for 7 d. Rats in normal control group were maintained with DMSO for 6 d. After 7 d, Western blotting was used to determine the expression of phospho-mitogen-activated protein kinase kinase 4 (p-MKK4), p-c-Jun and phospho-c-Jun N-terminal kinase 1 (p-JNK1). Immunohistochemistry and double labeling immunofluorescence combined with laser scanning confocal microscope were used to investigate the expression of p-JNK and OX-42 protein in hippocampal CA1 areas. **RESULTS** Compared with normal control group, p-MKK4, p-JNK1 and p-c-Jun in $A\beta_{1-42}$ model group were significantly increased(P<0.01). Compared with $A\beta_{1-42}$ model group, Pio 20, 40 and 80 mg • kg^{-1} could dose-dependently reverse these activated changes induced by $A\beta_{1-42}$. Pio 40 mg • kg^{-1} could significantly decrease $A\beta_{1-42}$-induced changes in the density ratio of p-MKK4 to total MKK4 from 1.02±0.35 to 0.44±0.06, that of p-JNK1 to total JNK1 from 0.94±0.17 to 0.59±0.03, and that of p-c-Jun to total c-Jun from 4.64±0.41 to 2.48±0.12 (P<0.01). The result of p-JNK and OX-42 expressions examined by double labeling immunofluorescence combined with laser scanning confocal microscope showed that most of p-JNK immunoreactivity co-localized with microglia-speccific protein OX-42. **CONCLUSION** Pio prevents $A\beta_{1-42}$-induced neurotoxicity through suppressing the expression of phosphorylated JNK signal pathway in rat microglial cells.

Key words pioglitazone Alzheimer disease amyloid beta-protain mitogen-activated protein kinase kinase c-Jun N-terminal kinase

DOI: 10.3867/j.issn.1000-3002.2010.03.003

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