药学学报 2000, 35(8) 566-570 DOI: ISSN: CN:

论文

NO-cGMP信号转导系统的上调参与阿片类药物耐受和戒断的生化机制

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摘要：

目的 观察阿片激动剂长时程作用对NO-cGMP信号转导系统的影响。方法 选用iNOS cDNA稳定表达的NG-LNCXiNOS细胞，采用NOS活性和cGMP放免测定，Western杂交和NADPH黄递酶组化染色技术。结果阿片类药物长时程作用剂量依赖性增高胞浆相iNOS活性和胞内cGMP含量，药物作用强弱顺序是DPDPE> DADLE>吗啡，EC_{50} 都在nmol.L^{-1}数量级。用纳洛酮急性戒断阿片耐受细胞，造成酶活性和cGMP水平增加更显著。DPDPE长时程作用还引起iNOS基因表达增强和NADPH黄递酶染色阳性细胞增多。结论 提示NO-cGMP信号转导系统上调可能是阿片耐受和成瘾的重要生化改变。

关键词： δ-阿片受体 阿片类依赖 一氧化氮合酶 环磷酸鸟苷 信号转导

UP-REGULATION OF NO-cGMP SIGNAL TRANSDUCTION SYSTEM IS INVOLVED IN THE BIOLOGICAL MECHANISMS OF OPIATE TOLERANCE AND WITHDRAWAL

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Abstract:

AIM To determine the effect of chronic treatment with opioid agonists on NO-cGMP signal system on the basis of successful establishment of a NG-LNCXiNOS cell line expressing iNOS cDNA and a cell model of opioid tolerance and naloxone-precipitated withdrawal. METHODS NOS activity and cGMP content were determined by the conversion of 3H-Arginine to 3H-Citrulline and radioimmunoassay, respectively. Western blot analysis and NADPH diaphorase (NADPH-d) histochemical assay were used to detecte the level of iNOS gene expression and NADPH-d activity which is a histochemical marker for NOS. RESULTS Long-term exposure of NG-LNCXiNOS cells to various opioid agonists enhanced the cytosolic iNOS activity, accompanying the increase in intracellular cGMP content in a dose-dependent manner. The order of potencies was DPDPE>DADLE> morphine. The EC_{50} values of the above indicators were nmol.L^{-1} level. When naloxone induced cell withdrawal, the iNOS activity and cGMP level were dramatically higher than those with agonists alone. Pretreatment of the cells with the more efficacious δ-ligand (DPDPE) for 48 hours also may lead to high-level expression of iNOS protein and elevate the number of NADPH diaphorase-positive cells. CONCLUSION Chronic opioid treatment was shown to up-regulate the NO-cGMP signal pathway, which may reflect an important biochemical change accounting for development of tolerance to and dependence on opiate. Thus, NG-LNCXiNOS cells provide a suitable system for studying the relationship between AC-cAMP and NO-cGMP signal system on the molecular mechanisms of opiate tolerance and dependence.

Keywords: opiate dependence nitric-oxide synthase cyclic GMP signal transduction δ-opioid receptor

收稿日期 1999-10-13 修回日期 网络版发布日期

DOI:

基金项目:

通讯作者: 刘景生

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[J]. 药学学报, 1999,34(7): 484-490

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