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论文

γ-羟基丁酸受体在大鼠局灶性脑缺血再灌注损伤中的作用

靳榕;蒋新颖;马行;谷淑玲;戴体俊

徐州医学院 1. 药理学教研室, 2. 附属医院检验科; 3. 江苏省麻醉学重点实验室, 江苏 徐州 221002

摘要:

研究γ-羟基丁酸(gamma-hydroxybutyric acid，GHB)受体在大鼠局灶性脑缺血再灌注损伤中的作用及其机制。选用GHB受体选择性激动剂NCS-356和特异性拮抗剂NCS-382作为工具药，采用改良的Longa法制备大鼠大脑中动脉栓塞(MCAO)模型。缺血2 h再灌注2 h后，动物进行Longa法行为功能评分；再灌注24 h后，部分动物用TTC染色法测定大鼠脑梗死体积；部分动物应用流式细胞仪测定神经细胞内游离钙离子浓度；分光光度法测定缺血侧大脑皮质中总一氧化氮合酶(tNOS)、诱导型一氧化氮合酶(iNOS)活性和一氧化氮(NO)含量；放射免疫法测定大鼠缺血侧大脑皮层环磷酸鸟苷(cGMP)含量。Isc/R组大鼠行为功能评分、脑梗死体积、神经细胞内游离Ca^{2+}浓度、cGMP和NO含量、tNOS及iNOS活性均显著高于假手术组；NCS-356 160 μg·kg^{-1}(N_1)、NCS-356 320 μg·kg^{-1}(N_2)、 NCS-356 640 μg·kg^{-1}(N_3)和尼莫地平600 μg·kg^{-1}(Nim)组的上述各指标均不同程度地低于Isc/R组，而NCS-382 640 μg·kg^{-1}+NCS-356 640 μg·kg^{-1} (NCS-382+N_3)组则能显著对抗N_3组的作用。激动GHB受体对大鼠局灶性脑缺血再灌注损伤具有一定的保护作用，其作用机制可能与降低神经细胞内游离Ca^{2+}浓度，减少NO及cGMP含量有关。

关键词： γ-羟基丁酸受体 脑缺血 再灌注损伤 一氧化氮 环磷酸鸟苷

Effect of gamma-hydroxybutyric acid receptor on focal cerebral ischemia-reperfusion injury in rats

JIN Rong; JIANG Xin-ying; MA Xing; GU Shu-ling; DAI Ti-jun

Abstract:

This study is to investigate the effect of gamma-hydroxybutyric acid receptor (GHBR) on focal cerebral ischemia-reperfusion injury in rats and its mechanism. NCS-356 (the agonist of GHBR) and NCS-382 (the antagonist of GHBR) were adopted as the tool medicine. The ripe male Sprague-Dawley rats weighing 240-280 g were randomly divided into seven groups: sham operation group (sham), ischemia-reperfusion group (Isc/R), NCS-356 160 μg·kg^{-1} group (N_1), NCS-356 320 μg·kg^{-1} group (N_2), NCS-356 640 μg·kg^{-1} group (N_3), NCS-382 640 μg·kg^{-1} + NCS-356 640 μg·kg^{-1} group (NCS-382+N_3), and nimodipine (Nim) 600 μg·kg^{-1} group. The middle cerebral artery occlusion (MCAO) model referring to Longa's method with modifications was adopted. The effect of GHBR on behavioral consequence of MCAO rats was studied after 2 h of ischemia-reperfusion. After 24 h of ischemia-reperfusion, part of animals were used to measure the cerebral infarction volume by TTC staining; ischemic cortex of another part of animals were used to measure the content of intracellular free calcium by flow cytometry, the tNOS, iNOS activity and the content of NO by spectrophotometric method, the content of cGMP by radioimmunoassay. The neurological function score and infarction volume rate in Isc/R group rats increased significantly than that in sham group; The content of intracellular calcium ($[Ca^{2+}]_i$) of cortex neuron and cGMP, the activities of tNOS and iNOS, and the content of NO in Isc/R group were higher than that in sham group obviously (P<0.01); These consequence we mentioned of N_1, N_2, N_3 and Nim group were lower than that of Isc/R. NCS-382 + N_3 group could significantly antagonize the above effect of N_3. Thus, NCS-356 has protective effects against ischemia-reperfusion brain injury by activating GHBR. The neuroprotective effect of GHBR is related with decreasing the content of $[Ca^{2+}]_i$, NO, cGMP and tNOS, iNOS activity in MCAO rats.

Keywords: brain ischemia reperfusion injury nitric oxide cyclic guanosine monophosphate gamma-hydroxybutyric acid receptor

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作者简介:

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