药学学报 1999, 34(2) 90-94 DOI: ISSN: CN:

论文

羟苯氨酮强心作用的生化机理研究

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摘要：

目的：研究羟苯氨酮(oxyphenamone, Oxy)强心作用的生化机理。方法：采用Na^+,K^+-ATP酶活性和cAMP-PDE活性、肌浆网Ca^{2+}-ATP酶活性和cAMP含量以及心肌肌原纤维Ca^{2+},Mg^{2+}-ATP酶活性等测定法，研究Oxy对它们的影响，并与milrinone和MCI-154作比较。 结果：Oxy对Na^+,K^+-ATP酶和PDE无抑制作用，也不影响心肌cAMP含量，但能显著增强心肌肌原纤维对Ca^{2+}的敏感性，高浓度时轻度抑制心肌肌浆网Ca^{2+}-ATP酶活性。结论：Oxy的强心作用方式不同于强心苷、β受体激动剂和PDE抑制剂等强心药,可能为一种新的钙增敏性强心药物。

关键词： 羟苯氨酮 钠，钾-三磷酸腺苷酶 磷酸二酯酶 钙-三磷酸腺苷酶 环-磷酸腺苷 钙增敏剂

BIOCHEMCAL MECHANISM OF THE POSITIVE INOTROPIC EFFECT OF OXYPHENAMONE

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Abstract:

AIM: To investigated the biochemical mechanisms of the positive inotropic effect of oxyphenamone (Oxy). METHODS: The assays of Na^+,K^+-ATPase activity, cAMP dependent phosphodiesterase(cAMP-PDE) activity and Ca^{2+}-ATPase activity in sarcoplasmic reticulum(SR) isolated from cardiac muscle, cAMP level in cardiac muscle and the cardiac myofibrillar Ca^{2+},Mg^{2+}-ATPase activity were adopted and compared with those of strophanthin-G（Str） and milrinone（Mil）. RESULTS: Oxy at its effective concentration, showed no remarkable inhibition on Na^+,K^+-ATPase and cAMP dependent phosphodiesterase (cAMP-PDE) activities, while in parallel experiments Na^+,K^+-ATPase and cAMP-PDE activities were significantly inhibited by Str and Mil. Their IC50 values were found to be 2.0 μmol.L^{-1}, and 85 μmol.L^{-1}, respectively. Oxy did not affect the cAMP level in cardiac muscle of guinea pig. However, Mil at 30 μmol.L^{-1} in control experiments increased the cAMP level by 73.6%. These results suggest that the mechanism of the positive inotropic effect of Oxy differs from that of glycosides, PDE inhibitors and β-adrenergic agonists. Oxy at 100 μmol.L^{-1} inhibited Ca^{2+}-ATPase activity significantly in cardiac sarcoplasmic reticulum. Its IC_{50} value was 200 μmol.L^{-1}. The result suggests that Oxy at high concentration exerts inhibitory effect on the Ca^{2+} uptake by SR. This mechanism may be partly responsible for the positive inotropic effect of Oxy. Oxy at 50 μmol.L^{-1} shifted the relationship curve between p$Ca^{2+}$and myofibrillar Ca^{2+},Mg^{2+}-ATPase activity to the left without affecting the maximum enzyme activity. When pCa 7, Oxy increased the myofibrillar Ca^{2+},Mg^{2+}-ATPase activity in a concentration dependent manner and EC_{50} value was about 10 μmol.L^{-1}. MCI-154 at 100 μmol.L^{-1} and some new derivatives of Oxy with positive inotropic effect enhanced the Ca^{2+} sensitivity. Mil at 100 μmol.$L^{-1}$and some new derivatives of Oxy with no positive inotropic effect showed no effect at all. Solaro and Kitada found a positive correlation between the increase of myofibrillar Ca^{2+},Mg^{2+}-ATPase activity and the enhancement of Ca^{2+} sensitivity of the contractile protein system. CONCLUSION: These results demonstrate that the biochemical mechanism of the positive inotropic effect of Oxy is different from these of the cardiac glycosides, PDE inhibitors and β-adrenergic agonists, therefore, it may be a novel cardiotonic agent, a calcium sensitizer.

Keywords: Na^+,K^+-ATPase phosphodiesterase Ca^{2+},Mg^{2+}-ATPase cAMP calcium sensitizers oxyphenamone

收稿日期 1998-04-09 修回日期 网络版发布日期

DOI:

基金项目:

通讯作者:

作者简介:

参考文献:

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