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论文

一种新的α_{1A}肾上腺素受体选择性拮抗剂—Sertindole

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摘要:

本工作分别在稳定表达α_{1A},α_{1B}和α_{1D}肾上腺素受体(adrenoceptor,AR)的人胚胎肾脏细胞(human embryonic kidney 293,HEK 293)和大鼠离体血管上,用放射配体结合实验和离体血管收缩功能实验方法以确定sertindole对α_1-AR亚型的选择性拮抗作用。结果显示sertindole与克隆α_{1A}-AR的亲和性分别是与克隆α_{1B}-AR和克隆α_{1D}-AR的69倍和132倍。Sertindole拮抗去甲肾上腺素引起的主动脉和肾动脉收缩反应的pA_2值分别与其对α_{1D}和α_{1A}亚型的pKI值相符。分别稳定表达3种亚型受体的HEK293细胞膜标本经与sertindole预温育30min后,受体与^{125}IBE2254结合的B_{max}值显著降低,KD值无显著变化;而在 sertindole 存在条件下,α_1-AR3种亚型与^{125}IBE2254 结合的KD值显著增大,但B_{max}值无显著改变。上述结果表明sertindole为不可逆性竞争性α_1-AR拮抗剂,并有α_{1A}亚型选择性。

关键词: α_1肾上腺素受体 拮抗剂 受体亚型 Sertindole

SERTINDOLE, A NOVEL α_{1A}-ADRENOCEPTOR SELECTIVE ANTAGONIST

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Abstract:

The antagonism effect of sertindole on α_1-AR subtypes was studied by combining radioligand binding saaays in three cloned α_1-AR subtypes stably expressed in human embryonic kidney 293 cells and contractile response experiment in isolated rat blood vessels,The results showed that the affinity for sertindole in the cloned α_{1A}-AR(pK18.90±0.17) was 69-fold (pK_1 7.06±0.09) and 132-fold (pK_1 6.78±0.07) higher that for the cloned α_{1D}-AR,respectively.The pA_2 values for sertindole in antagonizing NE-induced vasoconstriction in isolated rat aorta and renal artery were shown to fit well to the pK_1 values on cloned α_{1D}- and α_{1A}-AR,respectively.Pretreatment of membrane preparations with sertindole for 30 min significantly reduced the maximal binding capacities (B_{max}) of ^{125}IBE2254 to the three cloned α_1-AR subtypes without alteration of affinities(KD values). In the presence of sertindole,the B_{max} of ^{125}IBE2254 binding to the cloned α_1-ARs were not significantly changed,while the K_D values were significantly incressed .Thus,sertindole is a selective irreversible compitive α_1-AR antagonist with α_{1A} subtype.

Keywords: Antagonist Receptor subtype Sertindole α_1-Adrenoceptor

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