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论文

脑5-HT$_{1A/1B}$、α_2受体及腺苷酸环化酶参与了胍丁胺的抗抑郁作用

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摘要：

为了在单胺受体及受体后腺苷酸环化酶(adenylate cyclase，AC)水平探讨胍丁胺(agmatine，AGM)抗抑郁作用的精细机制，采用小鼠悬尾实验和强迫游泳实验观察AGM抗抑郁行为改变。采用放射免疫方法测定大鼠前额皮层突触膜蛋白AC活性。结果表明，AGM(5～40 mg·kg^{-1}，ig)在小鼠悬尾实验和强迫游泳实验模型上均有显著抗抑郁活性。同时伍用β受体/5-HT$_{1A/1B}$受体阻断剂吲哚洛尔(pindolol， PIN， 20 mg·kg^{-1}， ip)、 α_2肾上腺素受体拮抗剂育亨宾(yohimbine， YOH， 5～10 mg·kg^{-1}， ip)或咪唑克生(idazoxan， IDA， 4 mg·kg^{-1}， ip)对AGM(40 mg·kg^{-1}， ig)的抗抑郁活性具有显著拮抗效应； 而β受体阻断剂普萘洛尔(propranolol， PRO， 5～20 mg·kg^{-1}， ip)或5-HT$_3$受体拮抗剂曲匹西隆(tropisetron， TRO， 5～40 mg·kg^{-1}， ip)对AGM(40 mg·kg^{-1}， ig)的抗抑郁活性无显著影响。AGM(0.1～6.4 μmol·L^{-1})与大鼠前额皮层提取的突触膜共孵可剂量依赖地激活AC活性， 而PIN(1 μmol·L^{-1})或YOH(0.25～1 μmol·L^{-1})均显著拮抗AGM(6.4 μmol·L^{-1})对AC的激活作用； 慢性给予大鼠AGM(10 mg·kg^{-1}， ig， bid)或氟西汀(fluoxetine， FLU， 10 mg·kg^{-1}， ig， bid) 2 w也显著增强大鼠前额皮层基础及Gpp(NH)p 预激活的AC活性。本研究表明， 调节脑内5-HT$_{1A/1B}$和α_2等受体功能， 并激活前额皮层AC可能是AGM抗抑郁活性的重要机制之一。

关键词： 胍丁胺 抗抑郁药 悬尾实验 强迫游泳实验 5-HT$_{1A/1B}$受体 α_2-肾上腺素受体 腺苷酸环化酶

5-HT$_{1A/1B}$ receptors, α_2-adrenoceptors and the post-receptor adenylate cyclase activation in the mice brain are involved in the antidepressant-like action of agmatine

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Abstract:

This study is to explore the possible mechanisms of the antidepressant-like effect of agmatine. By using two traditional “behavior despair” model, tail suspension test and forced swimming test, we examined the effects of some monoamine receptor antagonists (including β-adrenergic receptor antagonist propranolol, β-adrenergic receptor antagonist/5-HT$_{1A/1B}$ receptor antagonist pindolol, α_2-adrenergic receptor antagonists yohimbine and idazoxan and 5-HT$_3$ receptor antagonist tropisetron) on the antidepressant-like action of agmatine in mice. Activity of adenylate cyclase (AC) in the synapse membrane from rat frontal cortex was determined by radioimmunoassay. Single dose of agmatine (5-40 mg·kg^{-1}, ig) dose-dependently decrease the immobility time in tail suspension test in mice, indicating an antidepressant-like effect. The effect of agmatine (40 mg·kg^{-1}, ig) was antagonized by co-administration of β-adrenergic receptor antagonist/5-HT$_{1A/1B}$ receptor antagonist pindolol (20 mg·kg^{-1}, ip), α_2-adrenergic receptor antagonists yohimbine (5-10 mg·kg^{-1}, ip) or idazoxan (4 mg·kg^{-1}, ip), but not β-adrenergic receptor antagonist propranolol (5-20 mg·kg^{-1}, ip) and 5-HT$_3$ receptor antagonist tropisetron (5-40 mg·kg^{-1}, ip). Agmatine (5-40 mg·kg^{-1}, ig) also dose-dependently decrease the immobility time in forced swimming test in mice. The effect of agmatine (40 mg·kg^{-1}, ig) was also antagonized by pindolol (20 mg·kg^{-1}, ip), yohimbine (5-10 mg·kg^{-1}, ip), or idazoxan (4 mg·kg^{-1}, ip). Incubation of agmatine (0.1-6.4 μmol·L^{-1}) with the synaptic membrane extracted from rat frontal cortex activated the AC in a dose-dependent manner *in vitro*. While the effect of agmatine (6.4 μmol·L^{-1}) was dose-dependently antagonized by pindolol (1 μmol·L^{-1}) or yohimbine (0.25-1 μmol·L^{-1}). Chronic treatment with agmatine (10 mg·kg^{-1}, ig, bid, 2 w) or fluoxetine (10 mg·kg^{-1}, ig, bid, 2 w)increased the basic activity, as well as the Gpp(NH)p (1-100 μmol·L^{-1}) stimulated AC activity in rat prefrontal cortex. These results indicate that regulation on 5-HT$_{1A/1B}$ and α_2 receptors, and activation AC in the frontal cortex is one of the important mechanisms involving in agmatine’s antidepressant-like action.

Keywords: antidepressant tail suspension test forced swimming test 5-HT$_{1A/1B}$ receptors α_2-adrenergic receptor adenylate cyclase agmatine

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