

ADAPTIVE EFFECT AND WITHDRAWAL SYNDROME OF PROPRANOLOL IN RELATION TO NOREPINEPHRINE AND EPINEPHRINE

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ABSTRACT Two distinct phases of changes in the urinary and myocardial norepinephrine (NE) were observed in rats after sc injection of propranolol $\times 7$ d. The 1st phase was up-regulation of NE. The 2nd phase was down-regulation of NE and designated as an adaptive effect which may be related to its antihypertensive effect. No adaptive effect on urinary E during medication was found. After withdrawal there was a significant rebound in NE and E, which might be the cause to lead to coronary accident in patients with severe ischaemic heart disease by acting on the hypersensitive β -receptor in myocardium.

KEY WORDS propranolol, pharmacodynamics, substance withdrawal syndrome, norepinephrine, epinephrine

In antihypertensive therapy, the β -receptor is immediately blocked after propranolol medication, but the blood pressure is lowered only several days' lag, the reason was unknown.^(1,2) Another important clinical problem of propranolol is a rebound phenomenon which often happened in patients with coronary diseases after sudden cessation of medication.^(3,4) We explored changes in catecholamines during and after the medication in the hope of throwing light on the mode of the drug effect.

METHODS

Ninety-six rats weighing $198 \pm SD$ 21 g

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were injected sc propranolol 12.5 mg/kg bid $\times 7$ d. Rat was kept in metabolic cage for collecting 24 h urine into a flask in which 0.2 ml of 6 N HCl was added to prevent catecholamines from degradation. The total urinary excretion of norepinephrine (NE) and epinephrine (E) was measured by fluorometric assay during medication and post-medication on d 1, 2, 4, 6 and 8. The levels of NE and E in heart were determined on d 2 and 7 of medication, and on d 2, 4, 6 and 8 of post-medication. Rats were killed at 12 h after the last sc.

NE and E were extracted by alumina from urine or acidic butanol from myocardium.⁽⁶⁾ The iodine oxidation technique⁽⁸⁾ was adopted for fluorometric assay. The double wavelengths of 450/520 and 387/470 on perkin-Elmer Model MPF-44 b spectrofluorometer were used. The net fluorescent readings of NE and E in sample was calculated. $[NE] = (R - aR') / (1 - ab)$. $[E] = R' - bNE$.

The interference coefficient of E with NE is referred as a ($a = 0.4$). The interference coefficient of NE with E is referred as b ($b = 0.035$). R' and R are the readings of the same sample at the wavelengths of 450/520 and 387/470 nm, respectively.

The internal standard of the assay was 100 ng each of NE and E. Epinephrine bitartrate and norepinephrine hydrochloride were products of Sigma.

RESULTS

The total urinary excretion of NE was $0.9 \pm SD$ 0.4 $\mu\text{g}/24$ h in rats before medication. A marked peak of NE, up to 423% of the normal ($p < 0.01$), was noticed on d 2 of

tor⁽⁹⁻¹²⁾ a sudden rebound of endogenous NE and E resulting from abrupt cessation of propranolol might lead to dramatically deteriorate the balance between oxygen consumption and the blood supply via the diseased coronary vessels and might be dangerous in patients with severe coronary insufficiency.

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心得安的适应效应及停药现象和去甲肾上腺素与肾上腺素的关系

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提要 大鼠 sc 心得安 25 mg/kg/d \times 7 d, 尿及心肌中 NE 有 2 相性改变。第 1 相中 NE 向上调节。第 2 相中 NE 向下调节, 称适应性效应。心得安的降压作用可能与降低 NE 的适应性效应有关。E 未见明显适应性改变。停药后内源性 NE 及 E 骤然反跳性升高, 作

用于增敏了的 β -受体, 可能是使缺血性心脏病病人引起症状反跳的原因。

关键词 心得安; 药效学; 停药现象; 去甲肾上腺素; 肾上腺素