that Dip in doses which did not induce changes in CVR, FVR and peripheral hemodynamics, caused a prominent decrease in VVR. On the one hand, these facts implied that VVR at these doses was unaffected by changes of peripheral vascular resistance, thus the method of measuring VVR in this paper was technically feasible; on the other hand, considering these results together with the previous data *in vitro*[1], we also suggested that Dip affected preferentially the vascular activity, especially the cerebral vasculature. The selective vasodilatory effect of Dip on the cerebral vessels is qualitatively similar to that of Cin and more significantly potent than that of Cin.

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双苯氟嗪对麻醉狗椎动脉的选择性扩张作用

R972.4

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摘要 用恒速泵法比较 Dip 对麻醉狗 VVR，CVR 和 FVR 的作用. Dip 0.1–3 mg·kg^{-1} iv 可显著降低 VVR，强于对 FVR 和 CVR 的降低和 Cin 的作用；两药 1 mg·kg^{-1} iv 仅短暂降低 SBP，DBP，MAP 和 TPR，而对其它血液动力学参数均无显著影响，提示 Dip 对血管床的不同部位有选择性，是一个比 Cin 更强的选择性脑血管扩张剂.

关键词 双苯氟嗪；桂利嗪；血管阻力；血液动力学；椎动脉；冠状血管；股动脉；钙通道阻滞剂

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Blockage of clonidine-induced platelet aggregation in rabbits by procainamide

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ABSTRACT Procainamide was capable of blocking the α_2-adrenergic receptor agonist clonidine-induced platelet aggregation, giving an antagonistic index, pA_2, of 5.0± 0.6 and half antagonistic concentration, A_2, of 10.4 μmol·L^{-1}. Clonidine showed half efficacy concentrations (EC_{50}) of 44, 82, 182, 485, and 662 nmol·L^{-1}, and affinity parameter (pD_2) of 7.4, 7.1, 6.7, 6.3, and 6.2 respectively when different concentrations of procainamide were used as blocking reagent. The results indicated that the mechanism of inhibitory effect of procainamide on clonidine-induced platelet aggregation was to competitively antagonize activating α_2-receptors and others of clonidine on platelet membrane.

KEY WORDS procainamide; clonidine; platelet aggregation; alpha adrenergic receptors

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It was previously found that the α_2-adrenergic receptor agonist clonidine induced blood platelet aggregation and procainamide blocked this aggregation in rabbits[1]. The purpose of this study was to unravel the mechanism of the inhibitory effect of procainamide on clonidine-induced platelet aggregation.

MATERIALS AND METHODS

Procainamide was made by Beijing Pharmaceutical Factory. Clonidine was made by Guilin Pharmaceutical Factory. Aggregometer was made by Beijing Biopharmaceutical Factory (Model BS631).

Preparation of platelet suspension Six ♂ rabbits, weighting 2.2± *s* 0.2 kg were used. Blood was obtained by cardiac puncture. Six volumes of blood were added into one volumne of ACD. Platelet-rich plasma (PRP) was prepared and centrifuged at 1100× *g* for 10 min. Tbe pellet of platelets were washed twice, and then resuspended in Tyrode's solution, in which the number of platelets was usually adjusted to 45×10^7 · ml^{-1} [2].

Experiments of platelet aggregation Turbidimetric tubes, 35 in number (each tube contained platelet suspension 0.5 ml), were divided equally into 5 groups. Group A with clonidine 9, 17, 35, 69, 138, 272, and 552 nmol · L^{-1}. Group B concentrations of clonidine were same as in group A, except that the first tube (9 nmol · L^{-1}) was omitted and a tube of 1105 nmol · L^{-1} was added as the last tube of the group, after procainamide of 8.5 μmol · L^{-1} was added to each tube. From group C through group E, the first tube of each group was omitted and a tube with a concentration of the clonidine doubled that of the last tube in the previous group was added as the last tube, after the concentration of procainamide added in each group was 48.9, 71.3, and 152.7 μmol · L^{-1}, respectively. The curves of clonidine-induced platelet aggregation were recorded in the aggregometer[1,2].

Method of statistical analysis E / mm (the efficacy value) = the peak value / mm of each curve. E_{max} / mm (the maximal efficacy value) = the maximal calculated-value from the E of each group.

In each group, E_{max}, EC_{50} (half efficacy concentration), and pD_2 (affinity index) were calculated from the linear equations which were obtained with the concentrations (C) of clonidine as X and the values of the ratio of C to E as Y according to Scott's method. According to Schild's method, the concentration-efficacy curves were plotted from the linear equations which were obtained with $-\lg C$ as X and the ratio of E to E_{max} as Y. The half antagonistic concentration (A_2) and antagonistic index (pA_2) of procainamide were calculated from the linear equation which was calculated with −lg [procainamide] as X and lg ($r-1$) as Y[3].

RESULTS

Antagonistic action and parameter of procainamide Group A-E linear equations and parameters were $\hat{Y} = -0.3974X + 3.4291$, $r = -0.997$; $\hat{Y} = -0.4262X + 3.5180$, $r = -0.986$; $\hat{Y} = -0.4436X + 3.4812$, $r = -0.984$; $\hat{Y} = -0.4153X + 3.1190$, $r = -0.991$ *and* $\hat{Y} = -0.4119X + 3.0422$, $r = -0.996$.

Procainamide 8.5-152.7 μmol · L^{-1} antagonized significantly the clonidine-induced (9-8837 nmol · L^{-1}) platelet aggregation and shifted the clonidine-induced concentration-dependent platelet aggregation curves of absorbance to the right in a parallel fashion without depression of the maximal response. The concentration-dependent EC_{50} of clonidine was increased, pD_2 was decreased with enhanced concentrations of procainamide (Tab 1, Fig 2).

Tab 1. E_{max}, EC_{50}, and pD_2 on clonidine-induced platelet aggregation in the presence of procainamide according to Scott's method.

Procainamide / μmol · L^{-1}	Concn / nmol · L^{-1}	E_{max} / mm	EC_{50} / nmol · L^{-1}	pD_2
0	9-552	36.1	44	7.4
8.5	17-1 105	33.9	82	7.1
48.9	35-2 209	31.7	182	6.7
71.3	69-4 418	36.1	485	6.3
152.7	138-8 837	35.6	662	6.2

The procainamide parameters, $b = -1.002$, $r = -0.9673$, $pA_2 = 5.0\pm 0.6$, and $A_2 = 10.4$ μmol · L^{-1}, were

derived from Schild's straight line illustration of the coordinate (Fig 2).

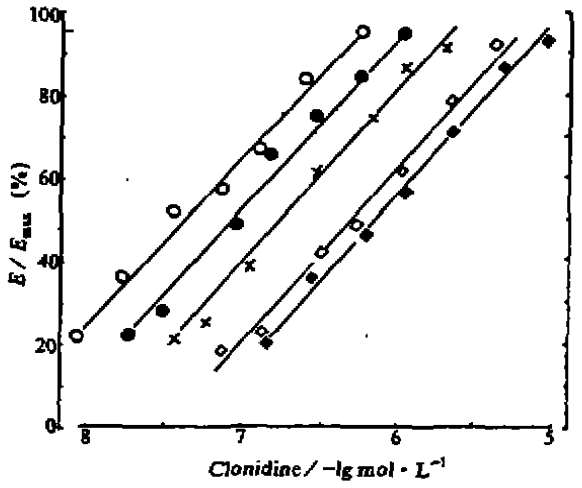

Fig 1. Clonidine-induced platelet aggregation concentration-efficacy curves of absorbance in the presence of procainamide of 0 (○), 8.5 (●), 48.9 (×), 71.3 (□), and 152.7 (■) μmol· L^{-1} (Schild's plot). n= 6 rabbits. $\bar{x}\pm s$.

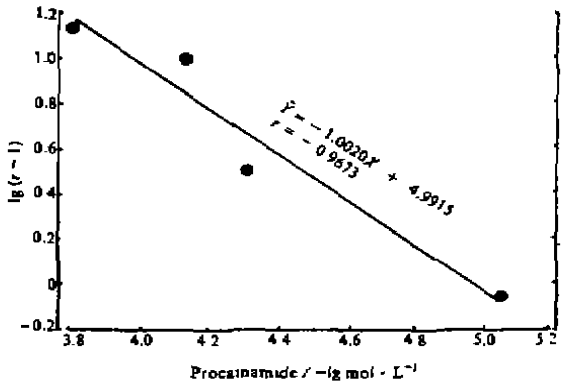

Fig 2. Schild's plot of coordinate of procainamide-antagonized clonidine-induced platelet aggregation. n= 6 rabbits.

DISCUSSION

α_2-adrenoceptors exist in the platelet membrane[4]. Effect of clonidine on presynaptic membrane can also have histamine-like and opiate-related actions in addition to its activating effect on α_2-adrenergic receptor[5]. Therefore, the mechanism of clonidine-induced platelet aggregation may possess factors other than clonidine-activation of α_2-adrenergic receptor on the platelet membrane.

In the experiment, the shift of curves of clonidine to the right was in a parallel fashion and the values of its E_{max} were not changed in the presence of procainamide, proving that procainamide was a competitive antagonist of clonidine-induced platelet aggregation. The mechanism of competitively inhibitory effect of procainamide on clonidine-induced platelet aggregation was mainly the inhibition of the activating effect of clonidine on α_2-adrenergic receptor and others on the platelet membrane.

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普鲁卡因胺阻断可乐定诱导兔血小板聚集作用

R971.2

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提要 普鲁卡因胺能显著地阻断可乐定诱导兔血小板聚集作用, 它的 pA_2 为 5.0± 0.6, 半数拮抗浓度为 10.4 μmol· L^{-1}. 在不同浓度普鲁卡因胺存在, 可乐定的 EC_{50} 为 44, 82, 182, 485 和 662 nmol· L^{-1}, pD_2 为 7.4, 7.1, 6.7, 6.3 和 6.2. 结果提示, 普鲁卡因胺抑制可乐定诱导血小板聚集作用的机制是竞争性地拮抗可乐定激活血小板膜上 α_2 受体等的作用.

关键词 普鲁卡因胺; 可乐定; 血小板聚集; α肾上腺素受体