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3,6-(二甲氨基)-二苯骈碘杂六环依地酸盐对豚鼠乳头状肌动作电位的影响

R965.2

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摘要 IHC-72 12.7、25.4 和 50.8 μmol·L^{-1} 显著降低动作电位的 APA，OS，RP 和 V_{max}，延长 APD；25.4 和 50.8 μmol·L^{-1} 使高 K$^+$除极慢反应动作电位的 APA 由 76± 5 mV 分别降低至 74± 6 和 67± 6 mV (P 均<0.05)，V_{max} 由 12± 3 V·s^{-1} 分别降至 9± 2 和 7± 2 V·s^{-1} (P 均<0.01)，并且明显延长 APD；IHC-72 25.4 和 50.8 μmol·L^{-1} 还抑制 $BaCl_2$ 诱发异常节律的 APA 和 MDP. 结果提示，IHC-72 抑制 Ca^{2+}，Na^+和 K^+的跨膜转运.

IHC-72

关键词 3,6-(二甲氨基)-二苯骈碘杂六环；乳头状肌；动作电位

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Selective vasodilatory effect of dipfluzine on vertebral artery in anesthetized dogs

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ABSTRACT Dipfluzine (Dip) is a novel calcium antagonist first developed by Department of Chemistry, Beijing University. The effects of Dip on hemodynamics and vascular resistance in vertebral (VVR), coronary (CVR), and femoral (FVR) arteries were compared with those of cinnarizine (Cin) in anesthetized dogs. Dip iv decreased dose-dependently VVR at 0.1, 0.3, 1, and 3 mg·kg^{-1}, CVR at 3 mg·kg^{-1}, and FVR at 1 and 3 mg·kg^{-1}. The fall of VVR by Dip iv was more remarkable than that by Cin at the matching doses. The systolic, diastolic, and mean blood pressure and total peripheral resistance were temporarily reduced equally by both of them at 1 mg·kg^{-1} iv; while Dip and Cin produced no obvious changes in heart rate, cardiac index, stroke index, LVP, and dP/dt_{max} at all doses. These results suggested that Dip possessed a high selectivity at different sites of the vasculature and was a more potent selective cerebral vasodilator than Cin.

KEY WORDS dipfluzine; cinnarizine; vascular resistance; hemodynamics; vertebral artery; coronary vessels; femoral artery; calcium channel blockers

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Our previous study using isolated blood vessels *in vitro* demonstrated that dipfluzine (Dip), a novel diphenylpiperazine calcium antagonist first developed by Department of Chemistry, Beijing University, China, was a more selective and more potent vasodilator on cerebral vessels than cinnarizine (Cin)[1]. But it remained uncertain whether these properties of Dip existed *in vivo*. The present study was to examine the selectivities of Dip and Cin on vascular resistance in various sites of the vasculature in anesthetized dogs, and to examine the peripheral hemodynamics in doses reducing the vascular resistance in cerebral arteries.

MATERIALS AND METHODS

Chemicals Dip and Cin (purities of both >99.85%), synthesized by Department of Chemistry, Beijing University, were dissolved in 2% tartaric acid solution containing 20% dimethylacetamide (solvent). Drugs were injectd into femoral vein in a volume of 0.1 ml·kg^{-1}. Same volume of the solvent was used as control.

Vascular resistance Twelve mongrel dogs of

either sex weighing 15± *s* 3 kg were used for measuring vascular resistance in vertebral (VVR), coronary (CVR), and femoral (FVR) arteries by perfusion at a constant rate[2]. The rate of perfusion in various animals was different and adjusted to make perfusion pressure equal to mean blood pressure. The lowest value of vascular resistance within 30 min after perfusion was used for comparison between the 2 groups.

Hemodynamics Twelve mongrel dogs of either sex weighing 17± *s* 3 kg were anesthetized with pentobarbital sodium (30 mg · kg^{-1} iv). The right femoral artery and vein were cannulated for measuring blood pressure (BP) and for drug administration, respectively. The heart was exposed through the left 4th intercostal space and suspended in a pericardial cradle. A saline-filled polyethylene catheter was inserted into the left ventricle through a stab wound in the apex and connected to a pressure transducer (MPU-0.5). The left ventricular pressure (LVP) and its dP/dt_{max} were determined by electronic differentiation of the LVP pulse. The root of aorta was put into an electromagnetic flowmeter (MF-26) probe for measuring aortic blood flow (ABF). BP, LVP, dP/dt_{max}, and ABF were monitored with polygraph (RM-6200). Through an A-D convertor, the 4 channels of signals were collected and analyzed by microcomputer using a program designed by our department. Heart rate (HR), systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) were recorded automatically. Cardiac index (CI), stroke index (SI), and total peripherial resistance (TPR) were calculated[3]. All the hemodynamic data were printed in digits at 0, 1, 5, 10, 15, 20, 25, and 30 min.

Experimental protocol In each study, 12 dogs were divided into 2 groups and injected iv Dip and Cin, respectively. Doses of both drugs were 0 (solvent), 0.03, 0.1, 0.3, 1, and 3 mg· kg^{-1} in vascular resistance experiments and 0, 0.1, 0.3, and 1 mg· kg^{-1} in hemodynamic experiments. Drugs were injected iv at 35-min intervals.

Results were expressed as $\bar{x}\pm s$ and compared using *t* test.

RESULTS

Vascular resistance Dip caused a significant decrease in FVR at 1 and 3 mg· kg^{-1} ($P<0.05$ or 0.01) and in CVR at 3 mg· kg^{-1} ($P<0.05$), but Cin did not. VVR was dose-dependently lowered by Dip 0.1, 0.3, 1, and 3 mg· kg^{-1} iv ($P<0.01$) and by Cin 1 and 3 mg· kg^{-1} iv ($P<0.05$). The decrease in VVR caused by Dip was more remarkable than that by Cin ($P<0.05$ or 0.01). The order of the decreases in vascular resistance with Dip and Cin were VVR > FVR > CVR (Tab 1). VVR responses occurred

Tab 1. Effects of iv dipfluzine and cinnarizine on vertebral vascular resistance, coronary vascular resistance, and femoral vascular resistance in anesthetized dogs. $n=6$, $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **0 mg· kg^{-1}**. $^{+}P>0.05$, $^{++}P<0.05$, $^{+++}P<0.01$ *vs* **cinnarizine.**

Drugs / mg· kg^{-1}		FVR / kPa	CVR / kPa	VVR / kPa
Dipfluzine	0	18.0± 1.1^{+}	17.7± 1.1^{+}	17.9± 1.3^{+}
	0.03	17.7± 1.2^{**+}	17.7± 1.1^{**+}	16.1± 2.1^{**+}
	0.1	17.1± 1.5^{**+}	17.5± 1.6^{**+}	14.7± 1.6^{***++}
	0.3	16.7± 1.3^{**+}	17.1± 1.6^{**+}	12.5± 1.7^{***+++}
	1.0	15.7± 1.6^{***+}	16.4± 1.7^{**+}	11.1± 2.7^{***+++}
	3.0	15.2± 1.9^{***+}	15.7± 1.7^{***+}	11.6± 2.1^{***++}
Cinnarizine	0	17.7± 1.7	17.7± 1.7	17.9± 1.9
	0.03	17.7± 1.7*	17.7± 1.7*	17.9± 1.9*
	0.1	17.3± 1.7*	17.7± 1.7*	17.6± 2.0*
	0.3	17.2± 1.7*	17.5± 1.7*	16.4± 1.9*
	1.0	16.4± 2.0*	17.1± 1.6*	15.5± 1.7**
	3.0	16.4± 2.0*	17.1± 1.7*	14.4± 2.1**

within 1 min after Dip iv and reached the peak within 2 min, then gradually returned to the original level. The response was prolonged as the dose of Dip increased (Tab 2).

Hemodynamics Dip and Cin 0.1 and 0.3 mg · kg^{-1} did not alter any hemodynamic parameter in anesthetized dogs. All the slight transient increases in CI, SI, LVP, and dP/dt_{max} and slight transient decreases in HR and ABF appeared 1–5 min after Dip and Cin 1 mg · kg^{-1} iv were non-significance. Both drugs at 1 mg · kg^{-1} decreased the SBP, DBP, MAP, and TPR ($P<0.05$ or 0.01), but these responses were rapidly lessened within 5 min (Tab 3).

DISCUSSION

The present study showed that Dip in all doses, like Cin, did not significantly affect the hemodynamics in anesthetized dogs except for transient lowering of SBP, DBP, MBP, and TPR at 1 mg · kg^{-1}. Since cerebral circulation in the dog exists anastomotic communication between carotid and vertebrobasilar arteries, the changes in intra-cranial and extra-cranial vascular resistance may be partly intermingled. However, the present study showed

Tab 2. Effect of iv dipfluzine 0.03–3 mg · kg^{-1} on vertebral vascular resistance in 6 anesthetized dogs. $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **0 min.**

Time / min	0	0.03	0.1	0.3	1	3 mg · kg^{-1}
0	17.7± 1.1	17.9± 1.3	17.9± 1.1	17.9± 1.1	18.1± 0.7	17.7± 1.3
1	17.9± 1.2*	16.7± 1.6*	15.9± 1.9**	15.5± 1.7**	14.8± 1.2***	14.8± 1.3***
2	18.0± 1.1*	16.1± 2.1*	14.7± 1.6***	12.5± 1.7***	11.1± 2.7***	11.3± 2.8***
3	18.0± 1.3*	16.8± 2.1*	15.9± 1.7**	14.8± 2.0***	12.1± 1.7***	12.5± 1.7***
4	17.9± 1.3*	17.3± 1.6*	16.5± 1.3*	16.4± 1.1**	13.3± 1.5***	12.8± 1.2***
5	18.1± 1.2*	17.7± 1.3*	17.3± 0.9*	17.2± 0.7*	15.5± 0.8***	13.5± 0.8***
10	17.7± 1.7*	17.9± 1.9*	17.6± 0.8*	17.7± 1.3*	16.0± 0.9***	13.9± 2.7**
15	17.9± 1.9*	17.9± 2.1*	17.6± 1.3*	17.7± 1.6*	15.9± 1.2***	13.9± 2.7**
20	18.1± 0.8*	18.0± 1.7*	17.7± 1.8*	17.9± 1.5*	16.0± 1.1***	13.3± 2.1***
25	17.7± 1.3*	17.7± 1.3*	17.9± 2.3*	17.7± 1.7*	17.3± 1.1*	13.3± 2.1***
30	17.9± 1.1*	17.7± 2.1*	17.9± 2.0*	18.0± 1.3*	17.7± 1.3*	14.4± 1.6***

Tab 3. Effects of dipfluzine and cinnarizine 1 mg · kg^{-1} iv on hemodynamics of anesthetized dogs. $n=6$, $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **0 min.**

Parameter	Drug	0 min	1 min	5 min	10 min	20 min	30 min
SBP / kPa	Dip	16.3± 2.5	12.7± 2.1**	16.1± 3.2*	16.0± 3.5*	15.9± 3.9*	15.3± 3.2*
	Cin	16.4± 2.4	12.7± 3.1**	14.7± 5.1*	15.6± 5.1*	15.2± 4.7*	14.1± 3.5*
DBP / kPa	Dip	8.5± 1.6	5.6± 2.4***	8.5± 1.7*	8.7± 2.0*	8.3± 2.1*	8.1± 1.9*
	Cin	9.3± 2.9	4.7± 1.7***	9.3± 3.2*	9.2± 3.3*	8.5± 2.8*	8.1± 2.3*
MAP / kPa	Dip	11.9± 1.6	9.2± 1.3***	10.7± 1.9*	12.0± 2.3*	11.7± 2.4*	11.3± 2.1*
	Cin	12.3± 3.3	8.7± 2.0**	11.1± 3.6*	12.3± 3.6*	11.6± 3.3*	11.1± 2.7*
TPR/kPa· min· L^{-1}	Dip	15.6± 6.3	9.3± 3.2**	14.1± 7.3*	16.2± 10.9*	16.8± 10.6*	14.3± 7.8*
	Cin	16.6± 6.3	10.0± 4.5**	16.6± 9.4*	17.0± 11.2*	15.7± 11.0*	15.2± 11.2*
HR / beat · min^{-1}	Dip	127± 28	110± 25*	116± 26*	121± 28*	120± 28*	118± 28*
	Cin	133± 31	128± 33*	130± 31*	126± 31*	126± 31*	125± 31*
ABF / L · min^{-1}	Dip	1.73± 0.38	1.83± 0.67*	1.79± 0.39*	1.57± 0.52*	1.52± 0.41*	1.63± 0.42*
	Cin	1.87± 0.51	1.90± 0.29*	1.89± 0.52*	1.87± 0.60*	1.87± 0.56*	1.93± 0.65*
LVSP / kPa	Dip	14.9± 2.9	13.7± 4.8*	16.9± 5.3*	16.9± 5.2*	15.7± 4.8*	14.0± 3.1*
	Cin	14.0± 3.9	12.3± 4.7*	13.9± 4.0*	13.5± 4.1*	13.9± 4.7*	14.1± 4.5*

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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124-127 (7)

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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