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Increased pressor responsiveness of femoral arteries to exogenous norepinephrine in renal hypertensive dogs mediated through α_2 adrenoceptors[1]

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ABSTRACT Changes of perfusion pressure induced by femoral arterial perfusion of norepinephrine (NE) were studied in renal hypertensive dogs made with the method of wrapping both kidneys. The NE threshold dose which induced perfusion pressure increase was lower in hypertensive dogs than that in normotensive dogs. The NE pressor response in low concentration (1, 2, 10 ng · kg^{-1}) was increased in hypertensive dogs, after α_2 adrenoceptors antagonized by idazoxan this increased response had been eliminated. These suggested that increased vasoconstriction by exogenous NE in hypertensive dogs was mediated through the increased reactivity of postsynaptic α_2 adrenoceptors to NE.

KEY WORDS renal hypertension; adrenergic alpha receptor blockaders; femoral artery; norepinephrine; prazosin

The division of vascular postsynaptic α adrenoceptors into α_1 and α_2 subtypes has been recognized. Norepinephrine (NE) has affinity for both these subtypes and vasoconstriction mediated through both adrenoceptors contributes to the basal vascular tone[1].

Increased vascular reactivity to exogenous NE was seen in clinical hypertension and hypertensive animals[2,3]. The reactivity of isolated perfused tail arteries to exogenous NE were increased in spontaneous hypertensive rats (SHR) than that in age-matched Wistar Kyoto rats, and α_2 adrenoceptor antagonist idazoxan inhibited this enhanced reactivity to exogenous NE in SHR[4]. These suggested an increased reactivity to exogenous NE in SHR mediated by postsynaptic α_2 adrenoceptors *in vitro*. The present study scrutinizes the *in vivo* pressor effects of exogenous NE in normotensive dogs and in renal hypertensive dogs with constant femoral artery perfusion before and after α_1 and α_2 adrenoceptors being antagonized. It is our purpose to find whether or not peripheral vascular reactivity to exogenous NE in renal hypertensive dogs increases and, if so, which subtype of adrenoceptors actually mediates this increased reactivity.

MATERIALS AND METHODS

Dogs Healthy mongrel dogs of either sex weighing 14±3 kg were equally divided into 2 groups. Renal hypertension was induced in 10 dogs by wrapping both kidneys with sterile emulsion membrane (0.1 mm)[5]. The other 10 dogs served as normal control. After operation gentamycin 80,000 IU was injected im bid for 2 d. All dogs were fed on an ordinary diet.

Protocol The experiment was carried out 50—80 after surgery. Dogs were anesthetized with ip sodium pentobarbitol 25 mg · kg^{-1}. Both femoral arteries from inguinal ligament to the distal 1/3 of the leg were dissected. A catheter connected with a pressure transducer (Gould P_{50}) was inserted into a femoral artery for monitoring the systemic BP. Another small catheter connected with a pressure transducer was introduced into a branch of medial saphenous artery on the other side for monitoring the perfusion pressure. After iv heparin 700 IU · kg^{-1}, the femoral artery for

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constant perfusion was ligated at 2 cm below the inguinal ligament. A catheter (inner diameter 4 mm) connecting to a constant-flow pump was introduced into the artery proximal to the ligature, and another similiar catheter connecting with the export tube of pump was inserted into the distant end of the ligature. A Y-tube was connecred in midst of the import tube of constant-flow pump for the infusion of drugs. The perfusion pressure was controlled to the systemic BP by regulating the perfusion volume, then the perfusion volume was kept constant during the rest of the experiment. After constant perfusion for 30 min, propranolol (1.0 mg · kg^{-1}) was injected iv.

Normal saline and NE 1, 2, 10, 50, 200 ng · kg^{-1} were injected in bolus (0.5 ml) into the femoral artery succesively, then same doses of NE were given after random intraarterial infused α_1 adrenoceptor antagonist prazosin 60 μg · kg^{-1} (10 ml in 10 min) or α_2 adrenoceptor antagonist idazoxan 0.2 μg · kg^{-1} (10 ml in 10 min). Successive dose of NE was given after perfusion pressure had returned to the basal level. During the whole experiment, perfusion pressure and systemic BP were constantly monitored.

Drugs and solutions The following drugs were infused intraarterially: Prazosin (Pfizer) was dissolved in 5% polypropylene glycol. Norepinephrine (Sigma) and idazoxan (Reckitt & Coleman) were dissolved in normal saline. All solutions were prepared on the day of study and kept at 4℃ until use.

Statistical analysis Results were given as $\bar{x}\pm s$. Changes in perfusion pressure between the 2 groups were analyzed by paired t test.

RESULTS

Before experiments the systemic BP was 21.5± s 2.2 kPa in hypetensive dogs, and 15.8±2.0 kPa in normotensive dogs ($P<0.01$). During the whole experimental period the systemic BP had no significant changes, and intraarterial infusion of saline did not induce perfusion pressure change in the 2 groups. The NE threshold dose inducing perfusion pressure increase was 2 ng · kg^{-1} in normotensive dogs, and 1 ng · kg^{-1} in hypertensive dogs. (Tab 1). After infusion of prazosin this response was inhibited, mainly in 50, 200 ng · kg^{-1}; after infusion of idazoxan mainly in 1, 2, 10 ng · kg^{-1}. To compare with normotensive dogs, NE pressor response in 1, 2, 10 ng · kg^{-1} shown a significant increase in hypertensive dogs. After prazosin, this increased response still remained. There was no significant difference in NE pressor response between normotensive and hypertensive dogs after idazoxan. After both α_1 and α_2 adrenoceptors were blocked, NE intraarterial infusion did not induce significant change of perfusion pressure except 200 ng · kg^{-1}.

DISCUSSION

In the present study, through constant

Tab 1. Perfusion pressure during norepinephrine intraaterial infusion. Pra = prazosin, Ida = idazoxan. $\bar{x}\pm s$, $^*P>0.05$, $^{**}P<0.05$ vs control in the increase of perfusion pressure..

	Pra μg·kg^{-1}	Ida μg·kg^{-1}	n	Norepinephrine/ng·kg^{-1} 1	2	10	50	200
Control			10	15.6±1.6	16.1±1.4	16.7±1.4	17.8±1.8	18.9±2.3
	60		5	15.8±1.9	16.1±1.7	16.6±1.7	17.4±2.0	17.4±2.2
		0.2	5	15.7±2.0	15.6±1.8	16.0±1.9	17.3±1.7	17.9±2.1
	60	0.2	5	15.6±1.6	15.5±1.7	15.8±1.5	16.4±1.8	17.1±2.0
Hypertension			10	22.5±1.5**	23.3±1.9**	23.3±1.8**	24.5±2.1*	25.8±3.0*
	60		5	22.6±1.9**	23.2±1.8**	23.1±2.0**	23.7±1.9*	23.2±2.8*
		0.2	5	21.9±1.7*	22.0±1.9*	21.9±1.9*	23.5±1.7*	24.3±3.0*
	60	0.2	5	21.8±1.8*	21.8±1.8*	21.6±1.7*	22.2±1.5*	23.7±2.6*

infusion to femoral artery, effect of blood flow on the blood pressure was eliminated. Thus, changes in perfusion pressure directly responded changes in peripheral vascular resistance. In our animal model, since local infusion of drugs was used, relatively high dosages could be infused intraarterially without eliciting remarkble systemic hemodynamic effects or direct effects on the central nervous system. Consequently, the changes observed in perfusion pressure were mainly due to the local effect of drugs.

Our previous study[6] had shown that pressor responsiveness of the femoral artery to exogenous NE was predominantly mediated through α_2 adrenoceptors in low dosages and, mediated through α_1 and α_2 adrenoceptors in high dosages only. Pressor response to sympathetic nerve stimulation was mainly mediated through α_1 adrenoceptors. In the present study, increased vasoconstriction to low dosages of exogenous NE in renal hypertensive dogs was evident. After α_2 adrenoceptors blockade this increased responsiveness was eliminated and, α_1 adrenoceptors blockade did not show this effect. It was suggested that increased peripheral vascular reactivity to exogenous NE in hypertensive dogs was still mediated through α_2 adrenoceptors. Another study of ours[7] also showed that the reactivity to endogenous NE in hypertensive dogs was increased, and this increased reactivity was mainly mediated through α_1 adrenoceptors. These results indicated that the adrenergic transmitter-receptor interaction was increased in renal hypertensive dogs.

The value of increased responsiveness of peripheral arteries to exogenous NE in hypertensives was still a controversial issue[2,3]. Our present study showed that NE threshold caused perfusion pressure increase was lower in hypertensive dogs than that in normotensive dogs, and increased reactivity to exogenous NE in hypertensive dogs only presented at low doses. These suggested that increased vascular reactivity to exogenous NE was one of the factors which induced hypertension. It seems to be hardly explainable by structural changes in hypertensives since responsiveness to high dosages NE was the same as control.

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α_2受体介导肾性高血压犬股动脉对外源性去甲肾上腺素的缩血管反应增高

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摘要 肾性高血压犬和正常犬股动脉恒流灌注，观察股动脉内注入不同浓度的去甲肾上腺素(NE)引起的灌流压变化。高血压犬引起升压反应的阈剂量降低，小剂量NE引起的升压反应增高，α_2受体阻滞剂能消除高血压犬这种反应性增高现象。提示高血压犬周围动脉对外源性NE的缩血管反应增强是由于α_2受体对NE的反应性增高所致。

关键词 肾性高血压；肾上腺素能α受体阻滞剂；股动脉；去甲肾上腺素；哌唑嗪