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Effect of nicardipine on the relationship of renal blood flow and of renal vascular resistance to perfusion pressure in dog kidney

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Abstract—The effect of nicardipine, a Ca channel blocker, on autoregulation of renal blood flow and perfusion pressure-vascular resistance relationship has been investigated in perfused kidneys of anaesthetized dogs. In control animals excellent autoregulation of renal blood flow and pressure-dependent elevation of vascular resistance were observed above 100 mmHg of perfusion pressure. However, intra-arterial infusion of nicardipine at doses of 3 and 10 $\mu g\ min^{-1}$ showed dose-dependent impairment of the autoregulatory response and of elevation of vascular resistance. Infusion of nicardipine (2·5 $\mu g\ min^{-1}$) into the renal artery also inhibited renal vasoconstriction induced by YC-170, a Ca channel activator. These results suggest that the inhibitory effect of nicardipine upon renal autoregulation may be due to its Ca^{2+} channel blocking action.

Ca channel blockers are useful as antihypertensive agents, because they relax vascular smooth muscle, thereby producing a reduction of peripheral vascular resistance. In the kidney, increase of renal vascular resistance is necessary for sustaining elevated systemic blood pressure (Guyton et al 1970). We have observed in dog kidney, that acute increase of perfusion pressure caused the elevation of renal vascular resistance (Ogawa & Ono 1986; Ogawa et al 1987). This phenomenon is based on an autoregulatory function in renal vasculature. Therefore, the effect of Ca channel blockers on autoregulatory function of renal vasculature is of interest.

In the present study, we examined the effect of nicardipine (Takenaka et al 1985) a potent Ca antagonist, on the autoregulation of renal blood flow, and analysed the relationship between perfusion pressure and renal vascular resistance. In addition, we have studied the effect of nicardipine on the decrease in renal blood flow induced by YC-170 (2-(2-pyridyl)ethyl 4-(*O*-chlorophenyl)-2,6-dimethyl-5-phenyl-carbamoyl-1,4-dihydropyridine-3-carboxylate), a Ca channel activator (Takenaka et al 1988).

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Materials and methods

Preparation for autoregulation study. Five mongrel dogs of either sex, 14·3–24·0 kg, were used. Sedation was induced with morphine hydrochloride (2 mg kg^{-1} s.c.) and the animals anaesthetized with α-chloralose (40 mg kg^{-1} i.v.) and urethane (400 mg kg^{-1} i.v.). The left renal artery was exposed retroperitoneally, cannulated and perfused with blood from the carotid artery by means of a Harvard peristaltic pump (Model 1215). An initial dose of 500 units kg^{-1} of sodium heparin was given as anticoagulant. Perfusion pressure was regulated and adjusted by means of a Starling pneumatic resistance from which excess blood was conducted to the left jugular vein. Renal blood flow was measured with an electromagnetic flowmeter (Narco RT-500). Kidney perfusion pressure and femoral artery pressure were measured with transducers (Statham P23Db).

Renal blood flow was allowed to stabilize for 30 min at the basal perfusion pressure of 100 mmHg; perfusion pressure was then changed stepwise between 60 and 200 mmHg. Infusion of drug was started at the basal perfusion pressure of 100 mmHg, and pressure-flow relation was examined.

Preparation for studying the effect of nicardipine on YC-170-induced renal vasoconstriction. Five mongrel dogs of either sex, 10·0 to 15·4 kg, were anaesthetized with sodium pentobarbitone (30 mg kg^{-1} i.v.) and artificially ventilated after the administration of decamethonium bromide (0·25 mg kg^{-1} i.v.) to induce paralysis of the skeletal muscle. Systemic blood pressure was measured with a pressure transducer (Statham P23Db) at the right brachial artery. A flank incision was made and the left kidney was exposed through a retroperitoneal approach. A non-cannulating electromagnetic flow probe (Narco RT-500, 2·5–3·0 mm in diameter) was placed around the renal artery adjacent to the aorta for measurement of renal blood flow. Nicardipine and YC-170 were infused into the renal artery proximal to the flow probe.

The first period was the control phase during which vehicle, 0·4 mL min^{-1}, was infused into the renal artery. Nicardipine was then infused into the renal artery at 2·5 $\mu g\ min^{-1}$ during the

second period. Intrarenal injection of YC-170 was applied during two periods, starting 10 min after the commencement of the vehicle (control period) or nicardipine infusion. Animals received two graded bolus injections of YC-170 (0·3 and 1·0 mg).

Drugs and data analysis. Nicardipine hydrochloride was dissolved in 0·9% NaCl (saline). YC-170, 20 mg, was dissolved in 1 mL of 1 M HCl, diluted to 1 mg mL^{-1} with saline and adjusted to pH 4 by addition of $NaHCO_3$.

Renal vascular resistance was calculated by dividing perfusion pressure by renal blood flow.

The efficiency index of autoregulation (ARI) was calculated according to the formula of Semple & DeWardener (1959):

$$ARI = \frac{(RBF_2 - RBF_1)/RBF_1}{(P_{RA2} - P_{RA1})/P_{RA1}}$$

where the renal blood flow changes to RBF_2 from the initial value of RBF_1 when renal perfusion pressure is altered to P_{RA2} from the initial value of P_{RA1}.

Differences were considered significant at $P<0·05$, using Student's *t*-test for paired data for single comparisons and analysis of variance for multiple comparisons. When multiple comparisons were made with a single control, Dunnett's test was used to determine significant levels. Data are presented as means ± s.e.m.

Results

The control observation showed excellent autoregulation of renal blood flow (Fig. 1), the autoregulatory index being less

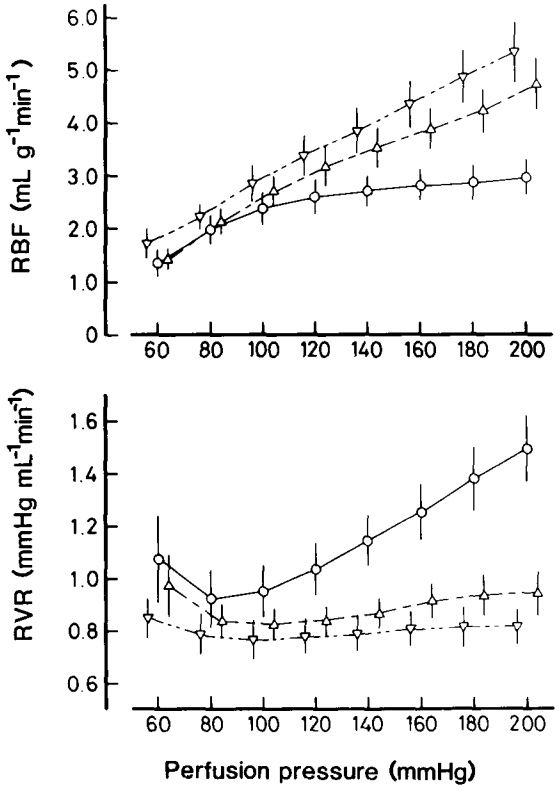

FIG. 1. Effect of nicardipine on the relationship of renal blood flow (upper panel) and of renal vascular resistance (lower panel) to renal perfusion pressure (n = 5). Symbols and vertical bars represent means ± s.e.m., respectively. ○——○ Control, △——△ during infusion of nicardipine (3 μg min^{-1}) and ▽——▽ during infusion of nicardipine (10 μg min^{-1}).

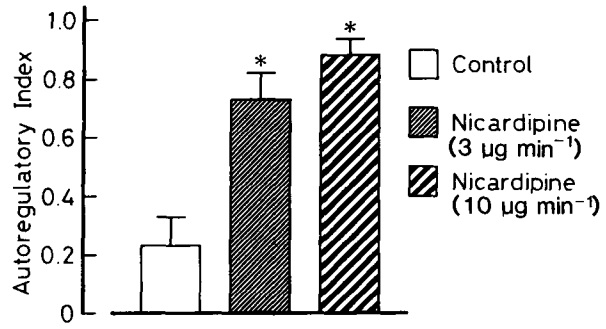

FIG. 2. Effect of nicardipine on the autoregulatory index of renal blood flow (n = 5). Autoregulatory index for a range of perfusion pressures (120–200 mmHg) are shown. Bars show means ± s.e.m. *$P<0·01$, compared with control values.

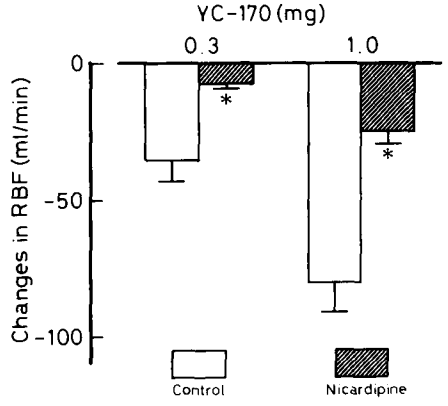

FIG. 3. Effect of intra-arterial infusion of nicardipine on the decrease in renal blood flow (RBF) induced by intra-arterial injection of YC-170. Bars show means ± s.e.m. (n = 5). *$P<0·05$, compared with control values.

than 0·3 in the range of 120–200 mmHg (Fig. 2). Partial autoregulation was also observed between 100 and 120 mmHg of perfusion pressure. Autoregulation was not present below 100 mmHg of perfusion pressure. Renal vascular resistance rose sharply in response to an increase of perfusion pressure over the autoregulatory range of 100–200 mmHg (Fig. 1).

An intra-arterial infusion of nicardipine (3 and 10 μg min^{-1}) made the renal blood flow markedly pressure-dependent at all perfusion pressures (Fig. 1), i.e. nicardipine impaired the autoregulation. Autoregulatory indices were higher than those of the control period (Fig. 2) and dependent upon the dose. The absolute change of renal vascular resistance between 100 and 200 mmHg of perfusion pressure during nicardipine infusion was significantly decreased from 0·54 ± 0·10 mmHg mL^{-1} min at the control period to 0·11 ± 0·06 mmHg mL^{-1} min at 3 μg min^{-1} ($P<0·01$) and to 0·05 ± 0·02 mmHg mL^{-1} min at 10 μg min^{-1} ($P<0·01$), respectively.

Renal blood flow increased from 98 ± 14 mL min^{-1} to 110 ± 18 mL min^{-1} ($P<0·05$), 10 min after the start of nicardipine infusion at 2·5 μg min^{-1}. The application of YC-170 (0·3 to 1·0 mg) produced a dose-dependent reduction in renal blood flow. During nicardipine infusion, the decrease in renal blood flow produced by YC-170 was markedly suppressed (Fig. 3).

Discussion

The kidney has a remarkable ability to maintain blood flow despite changes in renal perfusion pressure, a phenomenon

called autoregulation. Autoregulation is due to an automatic adjustment of the renal vascular tone to the change of perfusion pressure. The present experiments showed that nicardipine, a Ca channel blocker, abolished autoregulation of renal blood flow and depressed the change of renal vascular resistance. Previously, we obtained similar results using other Ca channel blockers, such as verapamil (Ogawa & Ono 1986), nifedipine (Ogawa & Ono 1987) and diltiazem (Ogawa et al 1987). Furthermore, we observed that the inhibitory effects of these Ca channel blockers on autoregulation were antagonized by simultaneous infusion of Bay k 8644 (methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate), a Ca channel activator (Ogawa & Ono 1986, 1987; Ogawa et al 1987). Recently, we showed that TMB-8 (8-(*N,N*-diethylamino)octyl-3,4,5-trimethoxybenzoate), an inhibitor of intracellular Ca^{2+} release, had no effect on autoregulation of renal blood flow (Ogawa & Ono 1988a). Therefore, the inhibitory effect of nicardipine on autoregulation appears to be due to its Ca channel blocking action. Indeed, nicardipine markedly inhibited renal vasoconstriction caused by YC-170 (Takenaka et al 1988), a Ca channel activator, in this experiment.

Sakamoto et al (1978) reported that nicardipine has an inhibitory activity upon cyclic (c) AMP phosphodiesterase. We have previously reported that both forskolin which activates adenylate cyclase and IBMX which inhibits cAMP phosphodiesterase had no effect on autoregulation of renal blood flow (Ogawa & Ono 1988b). Therefore, the inhibitory effect of cAMP phosphodiesterase by nicardipine seems not to be involved in the abolition of autoregulatory function.

In conclusion, it is considered that nicardipine inhibits autoregulatory pressure-dependent elevation of renal vascular resistance by its Ca channel blocking action. Guyton et al (1970) reported that increased renal vascular resistance is necessary for sustaining elevated systemic blood pressure. The inhibitory effect of this Ca channel blocker on autoregulation of renal blood flow may be a factor in its hypotensive effect.

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Serum protein binding of noscapine: influence of a reversible hydrolysis

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Abstract—The binding of the antitussive drug noscapine to human serum, pure albumin and α_1-acid glycoprotein has been investigated by ultrafiltration and equilibrium dialysis, using radiolabelled noscapine. The binding in serum pooled from volunteers was $93 \pm 0{\cdot}2\%$ (at 100 ng mL^{-1}). After incubation for 24 h the binding decreased to about 85% (ultrafiltration $87{\cdot}0 \pm 1{\cdot}0\%$; equilibrium dialysis $84{\cdot}3 \pm 1{\cdot}2\%$), because of the conversion of noscapine to noscapinic acid. Only unbound drug underwent this hydrolysis, and as noscapine is extensively bound in healthy volunteers, this elimination process is probably unimportant. The major binding protein of noscapine was albumin ($K = 3060\ M^{-1}$, $n = 5{\cdot}62$), but the binding to α_1-acid glycoprotein was also substantial ($K = 31500\ M^{-1}$, $n = 1{\cdot}73$). The interindividual variation in binding was low and binding was linear at the concentrations observed after therapeutic doses (0–500 ng mL^{-1}).

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Noscapine is a phthalideisoquinoline alkaloid with cough suppression as its only pronounced pharmacological effect. Its antitussive effect is of the same order of magnitude as that of codeine in both healthy volunteers (Empey et al 1979) and patients with chronic bronchitis (Matthys et al 1985).

The lactone ring on the noscapine molecule can undergo a pH-dependent reversible hydrolysis to noscapinic acid (Fig. 1). The two forms are present in approximately equal concentrations in buffer solutions of physiological pH (Pawelczyk & Zajac 1975). However, Johansson et al (1983) could not detect noscapinic acid in whole blood or albumin solution spiked with noscapine and incubated to equilibrium. They proposed that this difference between buffer and blood/albumin solution was due to strong binding of noscapine to proteins. In this case, the inability to detect noscapinic acid would imply high protein binding inconsistent with a previously reported figure for binding in serum of 65% (Idänpään-Heikkilä 1968).