Effects of Nicardipine on the Systemic and Renal Hemodynamics in Acutely Elevated Blood Pressure Induced by Vasoactive Agents in Conscious Rabbits

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SUMMARY

The effects of the calcium antagonist, nicardipine, on blood pressure and renal hemodynamics were examined in rabbits with norepinephrine- and angiotensin II-induced elevation of blood pressure. With norepinephrine-infusion, the mean arterial pressure increased from 84±4 to 118±4 mmHg accompanied by decreases in heart rate (10%) and renal blood flow (45%). In contrast to the changes in renal blood flow with norepinephrine-infusion, renal blood flow following angiotensin II-induced elevation of blood pressure was decreased by more than 60% at the same degree of elevation of mean arterial pressure. Both intravenous and intrarenal administration of nicardipine (1 μg/kg) reduced the mean arterial pressure and restored the decreased heart rate and renal blood flow in both norepinephrine- and angiotensin II-infused animals. Intrarenal injection of nicardipine decreased the elevated mean arterial pressure of angiotensin II-induced hypertension more than did intravenous injection (16±2 vs. 11±3 mmHg, p<0.05). Renal nerve denervation did not lead to any significant effects on the mean arterial pressure, heart rate and renal blood flow following intravenous or intrarenal injection of nicardipine in norepinephrine-infused animals. On the other hand, in angiotensin II-induced elevation of blood pressure, the potentiated hypotensive effect of intrarenal injection of nicardipine was lost in renally denervated animals.

In conclusion, the calcium antagonist, nicardipine, was shown to reduce the acutely elevated blood pressure caused by norepinephrine or angiotensin II. In angiotensin II-induced elevation of

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blood pressure, the renal vasculature may play a more important role in both pressor and depressor aspects in the regulation of blood pressure as compared to its role in norepinephrine-induced hypertension.

Additional Indexing Words:
Norepinephrine Angiotensin II Renal blood flow Renal nerve denervation

Since under normal conditions the two kidneys receive 15 to 25% of the cardiac output, the renal vascular resistance influences the total peripheral resistance. In this respect, the renal vasculature has been considered to be, in addition to vasoactive hormones and the water and sodium balance one of the important renal factors in the regulation of blood pressure. Among antihypertensive agents, calcium antagonists, which are potent vasodilators, have been reported to exert various actions on renal function and hemodynamics. Numerous investigations have examined the effects of calcium antagonists on blood pressure and renal function in both physiological and pathological conditions. However, there have been few papers dealing with the direct actions of calcium antagonists on the renal vasculature in pathological conditions. It is of interest therefore to examine their direct effects on the renal vasculature through the intrarenal administration of a calcium antagonist to rabbits with acutely elevated blood pressure induced by two vasoactive agents, norepinephrine and angiotensin II.

Methods

Experiments were carried out on female Japanese white rabbits weighing between 2.4 and 3.3 kg. The animals were maintained on a normal chow diet and tap water ad libitum for 7 days. Twelve hours before the experiments, food was withheld but water was allowed ad libitum. Anesthesia was induced with intravenous pentobarbital sodium (30 mg/kg), and maintenance doses of the anesthetic given as needed. Two polyethylene catheters (Intramedic, Clay Adams, New Jersey, USA) were placed in the femoral artery (PE 90) for recording the mean arterial pressure and heart rate and in the femoral vein (PE 20) for infusion of agents. In half of the animals, a PE 20 catheter was inserted into the opposite femoral vein, and the remaining animals were prepared for insertion of a renal catheter.

Implantation of the renal catheter was performed in a similar manner to that described by Smits et al with some modifications. Briefly, following midline laparotomy, the left renal artery and suprarenal artery were located.
The latter artery was carefully freed from the connective tissue over a length of 10–12 mm. To prevent damage of the periarterial renal nerve bundle, the connective tissue around the renal artery was dissected as little as possible. After confirmation that the suprarenal artery originated from the renal artery, a PE 10 catheter (Intramedic) was slipped into it and secured to the vessel. To prevent any disturbance of renal blood flow, insertion of the catheter tip into the renal artery was carefully avoided. For blood flow measurements, an electromagnetic flow probe of appropriate diameter (model FC, Nihon Kohden, Tokyo, Japan) was placed around the left renal artery. The flow probe was connected to an electromagnetic flow meter (model MF-27, Nihon Kohden) at the time of the experiment. After completion of implantation of the renal catheter and renal flow probe, the kidney in half of the animals was carefully denervated by dissection of all visible nerve fibers and application of phenol in 10% alcohol. The tips of the three catheters and blood flow meter were tunneled within the subcutaneous tissue to the back of the neck.

Experimental protocols:
Experiments were performed in a conscious unrestrained condition at least 2 days after surgery.

Exp. 1. Effects of intrarenal or intravenous injection of nicardipine on mean arterial pressure, heart rate and renal blood flow in non-denervated and denervated normotensive control rabbits.

Saline was infused at a rate of 0.1 ml/min using a Harvard infusion pump (model 975, Harvard Apparatus Co., Inc., Massachusetts, USA). After stabilization of the mean arterial pressure, heart rate and renal blood flow, recordings were carried out for 10 min. Nicardipine (a gift from Yamanouchi Pharmaceutical Co., Tokyo, Japan) was then administered via the vein (1 μg/kg) or the renal artery (1 μg/kg) and during the next 30 min recordings were performed.

Exp. 2. Effects of intravenous or intrarenal injection of nicardipine on mean arterial pressure, heart rate and renal blood flow in non-denervated and denervated animals following norepinephrine- or angiotensin II-induced elevation of blood pressure.

Norepinephrine (Sankyo Pharmaceutical Co., Tokyo, Japan) or angiotensin II (Protein Research Foundation, Osaka, Japan) at doses ranging from 2.0 to 4.0 μg/kg/min and from 80 to 110 ng/kg/min, respectively, was infused. These doses elevated the mean arterial pressure to 120 mmHg. After stabilization of the mean arterial pressure at approximately 120 mmHg for 20 min, nicardipine was administered via the vein (1 μg/kg) or the renal artery (1 μg/kg) and during the next 30 min recordings were performed.
Statistics:
All values are expressed as means±SE. Statistical analysis was performed by Student’s t-test for paired and unpaired data. Correlation coefficients were determined by linear regression. P<0.05 was considered as significant.

RESULTS
Neither intravenous nor intrarenal injection of nicardipine produced any significant changes in mean arterial pressure and heart rate in non-denerverated normotensive rabbits, in spite of a significant increase in renal blood flow after its intrarenal injection (Table I). In denervated animals, although the basal renal blood flow increased, no significant changes were observed after the administration of nicardipine (Table I).

Intravenous infusion of norepinephrine increased the mean arterial pressure to approximately 118±4 mmHg (+25%), decreased the heart rate by 10% and the renal blood flow by 45%. The elevated mean arterial pressure was significantly reduced to the same degree by both intravenous and intrarenal injection of nicardipine and was accompanied by an increase in the previously decreased heart rate. The decreased renal blood flow was significantly increased by intrarenal, but not by intravenous, infusion of nicardipine (Fig. 1).

The changes in mean arterial pressure, heart rate and renal blood flow before and after intravenous or intrarenal injection of nicardipine in non-denerverated angiotensin II-infused animals are also shown in Fig. 1. Intravenous infusion of angiotensin II increased the mean arterial pressure to approximately 118±4 mmHg (+25%), and decreased the renal blood flow.

Table I. Effects of Intravenous (IV) or Intrarenal (IR) Injection of Nicardipine on Mean Arterial Pressure (MAP), Heart Rate (HR) and Renal Blood Flow (RBF) in Non-denerverated and Denervated Normotensive Control Animals

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nicardipine (1 μg/kg)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>IV</td>
<td>IR</td>
<td></td>
</tr>
<tr>
<td>non-denerverated (n=6)</td>
<td></td>
<td>MAP (mmHg)</td>
<td>82±2</td>
<td>77±4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (beats/min)</td>
<td>258±5</td>
<td>266±7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RBF (ml/min)</td>
<td>28±2</td>
<td>28±3</td>
</tr>
<tr>
<td>denervated</td>
<td></td>
<td>MAP</td>
<td>80±2</td>
<td>78±3</td>
</tr>
<tr>
<td>(n=6)</td>
<td></td>
<td>HR</td>
<td>260±4</td>
<td>264±6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RBF</td>
<td>34±4</td>
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Values are expressed as means±SE. * p<0.05 as compared with control values. n=number of animals.
by 60% without any significant changes in heart rate. After intravenous and intrarenal injection of nicardipine, the elevated mean arterial pressure was reduced with marked restoration of renal blood flow. Especially in angiotensin II-induced elevation of blood pressure, intrarenal injection of nicardipine produced an increase in the decreased renal blood flow by 230% (11±4 to 24±2 ml/min) and a decrease in mean arterial pressure by 14% (118±4 to 102±4 mmHg). These changes were significantly greater than those following intravenous injection on nicardipine (Fig. 1). The heart rate was not changed by either angiotensin II administration or nicardipine injection.

Renal nerve denervation did not lead to any significant effects following intravenous and intrarenal injection of nicardipine on the mean arterial pressure, heart rate and renal blood flow in norepinephrine-induced hypertension (Fig. 2). On the other hand, in angiotensin II-induced elevation of blood pressure, renal nerve denervation abolished the potentiated effects of
Fig. 2. Changes in mean arterial pressure (MAP), heart rate (HR) and renal blood flow (RBF) before (open bars) and after (hatched bars) intravenous (IV) or intrarenal (IR) injection of nicardipine (NC) in denervated norepinephrine (NE)-induced or angiotensin II (Ang II)-induced hypertensive rabbits. n=number of animals. Values are expressed as mean±SE. NS=non significant. * p<0.05, ** p<0.01.

the intrarenal injection of nicardipine on mean arterial pressure and renal blood flow as compared to intravenous injection of nicardipine (Fig. 2). In angiotensin II-induced elevation of blood pressure, the fall in mean arterial pressure was significantly correlated with the change in renal blood flow after intrarenal injection of nicardipine to animals without renal nerve denervation (r=−0.68, p<0.05, n=12).

**DISCUSSION**

Both intrarenal and intravenous injection of nicardipine reduced the blood pressure in conscious unrestrained rabbits with norepinephrine- and angiotensin II-induced elevation of blood pressure, but not that of normotensive controls. The depressor effect of intrarenal injection of nicardipine on the elevated blood pressure was greater than that of intravenous injection following angiotensin II- but not norepinephrine-infusion. This action is
mainly followed by restoration of renal blood flow. In addition, renal denervation abolished the greater depressor effect of intrarenal injection of nicardipine in angiotensin II-induced elevation of blood pressure.

Studies of the effects of calcium antagonists on norepinephrine-induced vasoconstriction have shown conflicting results. Some investigators have reported that calcium antagonists reverse norepinephrine-induced vasoconstriction, whereas others failed to demonstrate such a reversal. Since the discrepancies may arise from different experimental conditions, such as the choice of conscious or anesthetized animals, the type of animals employed and the calcium antagonists administered, it is difficult to compare and evaluate all the previously reported data. In the present study, we employed conscious unrestrained rabbits which received nicardipine. It is generally agreed that calcium antagonists reduce blood pressure through their potent vasodilating action, although intrarenal hemodynamic actions have been proposed as one of the other possible antihypertensive mechanisms. Following norepinephrine-infusion, the depressor effects of intrarenal and intravenous administration of nicardipine were not significantly different. Further, after renal denervation, there were no significant differences in blood pressure, heart rate and renal blood flow between these two routes of administration. Therefore, in so far as the antihypertensive effects of nicardipine on norepinephrine-induced elevation of blood pressure are concerned, the renal vasculature does not seem to play a major role.

In contrast to the conflicting data for the effects on norepinephrine-induced vasoconstriction, in all studies in which exogenous angiotensin II was administered, calcium antagonists increased the renal blood flow and GFR. Our findings are in good agreement with these previous results. Further, both intrarenal and intravenous administration of nicardipine significantly increased the suppressed renal blood flow in angiotensin II-induced elevation of blood pressure compared to that following norepinephrine-infusion. These results may be due to the different mechanisms of vasoconstriction between norepinephrine and angiotensin II.

In comparison with the effects of norepinephrine on renal blood flow, angiotensin II revealed a more potent vasoconstricting action on the renal vasculature, since at the same levels of elevated blood pressure, the renal blood flow was significantly reduced in angiotensin II-induced elevation of blood pressure. These findings are similar to the report of Goldberg and Schrier. The depressor effects of calcium antagonists on angiotensin II-induced elevation of blood pressure were greater with intrarenal administration than with intravenous administration. Further, the degree of fall in blood pressure in angiotensin II-infusion was significantly correlated with the
changes in renal blood flow after intrarenal injection of nicardipine. These findings suggest therefore that vasodilation of the renal vascular bed contributes to the depressor action of nicardipine in angiotensin II-induced hypertension.

As was the case in norepinephrine-induced elevation of blood pressure, after renal nerve denervation there were no significant differences in changes of blood pressure between intrarenal and intravenous administration of nicardipine in spite of the same degree of reduction in renal blood flow. This implies that in the renal vasculature the resistance vessels may be strongly regulated by the renal sympathetic tone. Guo and Abboud\textsuperscript{20} have demonstrated that angiotensin II impairs reflex decreases in heart rate and lumbar sympathetic nerve activity during hypertension but not reflex increases in them during hypotension. Furthermore, Clapham\textsuperscript{16} has demonstrated that the ability of nifedipine to inhibit pressor responses to neuronally released norepinephrine, as well as pressor responses to angiotensin II, contributes to the efficacy of this drug as an antihypertensive in SHR. In these respects, the interaction between the sympathetic nervous system and angiotensin II in the renal vasculature may be more important for the control of the vascular tone in the regulation of blood pressure than has previously been considered.

However, before any final conclusion can be drawn, further investigations are needed of the complex relationships and individual roles in the regulation of blood pressure among the baroreceptors, sympathetic nervous system, and renin-angiotensin system as well as the antihypertensive actions of calcium antagonists on the kidney.

In summary, the calcium antagonist, nicardipine, was shown to reduce the acutely elevated blood pressure caused by norepinephrine and angiotensin II. In angiotensin II-induced hypertension, the renal vasculature may play a more important role in the regulation of blood pressure in both pressor and depressor aspects as compared to its role in norepinephrine-induced hypertension.

**References**