Different Effects of Various Vasodilators on Autoregulation of Renal Blood Flow in Anesthetized Dogs

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Abstract—In order to examine whether the autoregulation of renal blood flow is equally influenced by all kinds of vasodilators, kidney perfusion experiments were performed in anesthetized dogs. The perfused kidney usually showed excellent autoregulation of blood flow over the perfusion pressure between 120 and 200 mmHg. Renal blood flow was increased by the renal arterial infusion of diltiazem (100 μg/min), papaverine (10 mg/min) or nicorandil (300 μg/min) (at the basal perfusion pressure of 100 mmHg) and was maintained at an increased level while the infusion was continued. On the other hand, renal blood flow was increased only transiently by the infusion of nitroglycerin (50 μg/min), and the blood flow gradually decreased to the basal level in spite of the continuous infusion. Infusions of diltiazem and papaverine abolished the autoregulation of renal blood flow besides the vasodilator effect, but infusions of nitroglycerin and nicorandil have no effect on the autoregulation. Furthermore, sodium nitroprusside (30 μg/min) and sodium nitrite (5 mg/min), which are assumed to produce vasodilation through cyclic GMP, also have no effect on the autoregulation of renal blood flow. In conclusion, all the vasodilators do not influence the renal blood flow autoregulation, and vasodilation caused by cyclic GMP is unconnected with the myogenic mechanism regulating the renal blood flow.

The autoregulation of renal blood flow is the maintenance of a stable blood flow level in spite of fluctuation in the renal perfusion pressure. The presently accepted mechanism of the autoregulation is the myogenic response of the vascular smooth muscle adjusting the vascular tone to the change of perfusion pressure. This myogenic theory is supported by the evidence that the autoregulation is effectively abolished by vasodilators, such as papaverine, aminophylline, verapamil and nifedipine (1–3).

Kii et al. (4) reported that infusion of acetylcholine into the renal artery produced potent vasodilation on canine kidney, but failed to impair the autoregulation. We have obtained similar results with acetylcholine (N. Ogawa and H. Ono, unpublished results) and also with prostaglandin E2 and bradykinin (5). Thus, there are vasodilators devoid of potency to abolish the autoregulation of renal blood flow. In other words, some substances produce vasodilation without affecting the myogenic response of the renal vasculature.

The present study is to examine whether or not there exists a common mechanism among vasodilators which do not impair the autoregulation of renal blood flow.

Materials and Methods
Twenty-seven mongrel dogs of either sex, weighing 11–17 kg, fed on a pellet dog food (CD-5, Clea Japan Co.) were anesthetized with α-chloralose (40 mg/kg) and urethane (400 mg/kg) intravenously, preceded by sedation with morphine hydrochloride (2 mg/kg, s.c.). Pressure-controlled perfusion experiments were performed with the left kidney. Details of the procedure have been described previously (5). The left renal artery was cannulated and perfused with blood con-
ducted from the carotid artery. An initial dose of 500 U/kg of sodium heparin was given as anticoagulant. When necessary, smaller doses of α-chloralose and urethane were supplemented, and sodium heparin was supplemented constantly by 100 U/kg/hr. Perfusion pressure was controlled by the use of a Starling’s pneumatic resistance. Perfusion pressure and systemic blood pressure in the femoral artery was measured with electric manometers (transducers: Statham P23Db and carrier amplifiers: San- ei 1206B). Renal blood flow was measured by an electromagnetic flowmeter (Narco RT-500). A test drug solution was infused into a rubber tube connected close to the shank of the renal arterial cannula by the aid of an infusion pump (Harvard Apparatus 901).

Renal blood flow was allowed to stabilize for 30 min at the basal perfusion pressure of 100 mmHg; then perfusion pressure was changed stepwise between 60 and 200 mmHg. After the control observation of the blood flow responses to the stepwise changes of perfusion pressure between 60 and 200 mmHg, the infusion of a drug was started at the basal perfusion pressure of 100 mmHg, and pressure-flow relation was examined again.

Following drugs were studied: diltiazem hydrochloride (Tanabe), papaverine hydrochloride (Nakarai), nitroglycerin (NGA-800128, 0.5 mg/ml aqueous solution, Nippon Kayaku), nicorandil (Chugai), sodium nitroprusside (30 μg/min) and sodium nitrite (5 mg/min). The increase of blood flow reached a maximum within 3 min after the onset of the infusion and was sustained at an increased level during the infusion. Mean systemic blood pressure was significantly decreased by the infusion of each one of these drugs. The infusion of nitroglycerin (50 μg/min), however, produced only a transient vasodilation, and the initial vasodilation was nullified in spite of continuous infusion, though a decrease in the systemic blood pressure was obvious and sustained. Then, the effect of nitroglycerin on the renal autoregulation was examined at the infusion rate of 50 μg/min. The infusion of 100 μg/min of diltiazem did not cause a significant increase of blood flow below the perfusion pressure of 80 mmHg. The infusion of papaverine and nitro-compounds except nitroglycerin caused vasodilation at all ranges of perfusion pressure.

**Autoregulation of renal blood flow:** Control observation usually confirmed excellent autoregulation of the renal blood flow between 120 and 200 mmHg of the perfusion pressure and partial autoregulation between 100 and 120 mmHg. The blood flow changed pressure-dependently below 100 mmHg.

Figure 1 illustrates the effects of diltiazem (30 and 100 μg/min) and papaverine (10 mg/min) on autoregulation of renal blood flow. Autoregulation of renal blood flow was clearly abolished by diltiazem and papaverine. Simultaneous infusion of CaCl₂ (30 mg/min) restored the autoregulation impaired by 30 μg/min of diltiazem, but it was not effective.

**Results**

**Systemic blood pressure and renal blood flow:** Table 1 shows the mean values for mean systemic blood pressure and renal blood flow at the perfusion pressure of 100 mmHg, before and during infusion of drugs. Renal blood flow was increased by the intra-arterial infusion of diltiazem (100 μg/min), papaverine (10 mg/min), nicorandil (300 μg/min), sodium nitroprusside (30 μg/min) and sodium nitrite (5 mg/min). The increase of blood flow reached a maximum within 3 min after the onset of the infusion and was sustained at an increased level during the infusion. Mean systemic blood pressure was significantly decreased by the infusion of each one of these drugs. The infusion of nitroglycerin (50 μg/min), however, produced only a transient vasodilation, and the initial vasodilation was nullified in spite of continuous infusion, though a decrease in the systemic blood pressure was obvious and sustained. Then, the effect of nitroglycerin on the renal autoregulation was examined at the infusion rate of 50 μg/min. The infusion of 100 μg/min of diltiazem did not cause a significant increase of blood flow below the perfusion pressure of 80 mmHg. The infusion of papaverine and nitro-compounds except nitroglycerin caused vasodilation at all ranges of perfusion pressure.
Table 1. Mean systemic blood pressure and renal blood flow before and during the infusion of a drug at basal perfusion pressure of 100 mmHg

| Drug               | Mean systemic blood pressure (mmHg) | Renal blood flow (ml/g/min) |
|--------------------|------------------------------------|-----------------------------|
|                    | control during infusion J decrease | control during infusion J increase |
| Diltiazem (n=5)    |                                    |                             |
| 30 µg/min          | 120±12 106±15 14±6 3.59±0.29 3.77±0.18 0.18±0.24 |
| 100 µg/min         | 100±15 20±4 4.24±0.27 0.65±0.22 |
| Papaverine (n=5)   |                                    |                             |
| 10 mg/min          | 88±7 60±8 29±3 3.03±0.44 3.38±0.45 0.34±0.03 |
| Nitroglycerin (n=4) | 121±4 108±6 14±2 3.88±0.50 3.91±0.56 0.03±0.10 |
| 50 µg/min          |                                    |                             |
| Nicorandil (n=4)   | 123±5 107±5 16±1 3.17±0.58 4.08±0.55 0.91±0.15 |
| 300 µg/min         |                                    |                             |
| Sodium nitroprusside (n=6) | 136±11 118±12 18±3 2.96±0.12 3.95±0.20 0.99±0.15 |
| 30 µg/min          |                                    |                             |
| Sodium nitrite (n=4) | 144±13 111±15 33±2 3.22±0.52 3.64±0.52 0.42±0.02 |

Values are means±S.E., and J shows actual changes. *: P<0.05 compared with the control (paired t-test); b: P<0.05 compared with J increase value caused by the infusion of 10 mg/min of papaverine (Student's t-test).

Fig. 1. Effects of (A) diltiazem (○—○: control, △——△: 30 µg/min, ▲—▲: 100 µg/min, ▼——▼: simultaneous infusion of 30 mg/min of CaCl₂ and 30 µg/min of diltiazem, n=5) and (B) papaverine (○—○: control, △——△: 10 mg/min, n=5) on the pressure-flow curves in perfused dog kidney. Symbols and vertical bars represent means and S.E., respectively. *shows a significant difference from the corresponding value of the control (P<0.05).
on restoring the autoregulation impaired by papaverine (not shown in the figure). Figures 2 and 3 illustrate the effects of nitroglycerin, nicorandil, sodium nitroprusside and sodium nitrite on the autoregulation of renal blood flow. The infusion of nicorandil (300 μg/min), sodium nitroprusside (30 μg/min) or sodium nitrite (5 mg/min) caused an increase in renal blood flow at all ranges of perfusion pressure, but did not impair the autoregulation, shifting the pressure-flow curve upward. Nitroglycerin (50 μg/min) also could not abolish the autoregulation in addition to the lack of sustained vasodilation as stated above, though the change in the systemic blood pressure obviously showed the effectiveness of the drug. Pressure-flow curves before and during infusion of nitroglycerin overlapped each other.

ARI's before and during the infusion of the vasodilators are shown in Table 2. The control ARI is in all experiments were less than 0.5 between 100 and 120 mmHg and less than 0.3 between 120 and 200 mmHg, indicating an effective autoregulation. ARI's during infusion of nitroglycerin, nicorandil, sodium nitroprusside and sodium nitrite were also less than 0.3 between 120 and 200 mmHg, showing that the autoregulation was not influenced. On the other hand, the ARI's during infusion of diltiazem were increased at any perfusion pressure range. This effect was dose-related and ARI became nearly 1.0 with the infusion of 100 μg/min of diltiazem, showing a complete abolition of the autoregulation. ARI's during simultaneous infusion of CaCl₂ (30 mg/min) with diltiazem (30 μg/min) recovered to the control value for 140–200 mmHg of perfusion pressure. ARI's were also increased by 10

Fig. 2. Effects of (A) nitroglycerin (○—○: control, △—△: 50 μg/min, n=4) and (B) nicorandil (○—○: control, △—△: 300 μg/min, n=4) on the pressure-flow curves in perfused dog kidney.

Fig. 3. Effects of (A) sodium nitroprusside (○—○: control, △—△: 30 μg/min, n=5) and (B) sodium nitrite (○—○: control, △—△: 5 mg/min, n=4) on the pressure-flow curves on perfused dog kidney.
| Drug                        | 60–80 | 80–100 | 100–120 | 120–140 | 140–160 | 160–180 | 180–200 |
|----------------------------|-------|--------|---------|---------|---------|---------|---------|
| Diltiazem (n=5)            |       |        |         |         |         |         |         |
| Control                    | 1.18±0.65 | 0.46±0.12 | 0.39±0.09 | 0.23±0.07 | 0.19±0.07 | 0.20±0.10 | 0.31±0.14 |
| 30 µg/min                  | 1.27±0.49 | 0.93±0.17 | 0.65±0.09 | 0.60±0.03 | 0.55±0.08 | 0.61±0.12 | 0.87±0.25 |
| 100 µg/min                 | 1.01±0.25 | 1.05±0.13 | 0.79±0.07 | 0.80±0.15 | 0.98±0.20 | 1.09±0.26 | —        |
| 30 µg/min + CaCl₂ (30 µg/min) | —     | 1.37±0.42 | 1.03±0.16 | 0.72±0.13 | 0.42±0.12 | 0.29±0.10 | 0.27±0.09 |
| Papaverine (n=5)           |       |        |         |         |         |         |         |
| Control                    | 1.30±0.12 | 0.86±0.08 | 0.42±0.05 | 0.12±0.03 | 0.01±0.04 | 0.02±0.05 | 0.11±0.09 |
| 10 mg/min                  | 0.97±0.05 | 0.83±0.03 | 0.81±0.04 | 0.79±0.05 | 0.75±0.07 | 0.70±0.08 | 0.69±0.07 |
| Nitroglycerin (n=4)        |       |        |         |         |         |         |         |
| Control                    | 1.82±0.54 | 1.19±0.15 | 0.42±0.09 | 0.13±0.08 | 0.04±0.13 | 0.00±0.00 | 0.00±0.00 |
| 50 µg/min                  | 1.37±0.12 | 1.03±0.12 | 0.41±0.11 | 0.27±0.05 | 0.10±0.06 | 0.00±0.00 | 0.00±0.00 |
| Nicorandil (n=4)           |       |        |         |         |         |         |         |
| Control                    | 0.88±0.13 | 0.78±0.26 | 0.34±0.16 | 0.06±0.08 | 0.07±0.07 | 0.21±0.14 | 0.24±0.10 |
| 300 µg/min                 | 1.00±0.13 | 0.79±0.16 | 0.52±0.20 | 0.29±0.16 | 0.16±0.05 | 0.28±0.11 | 0.28±0.13 |
| Sodium nitroprusside (n=5) |       |        |         |         |         |         |         |
| Control                    | 1.51±0.24 | 0.78±0.19 | 0.42±0.16 | 0.17±0.16 | 0.18±0.20 | 0.02±0.04 | 0.16±0.10 |
| 30 µg/min                  | 0.98±0.09 | 0.67±0.12 | 0.39±0.12 | 0.15±0.07 | 0.04±0.03 | 0.11±0.06 | 0.31±0.17 |
| Sodium nitrite (n=4)       |       |        |         |         |         |         |         |
| Control                    | 1.34±0.22 | 0.83±0.18 | 0.47±0.17 | 0.16±0.12 | 0.04±0.02 | 0.02±0.05 | 0.11±0.04 |
| 5 mg/min                   | 1.20±0.12 | 0.78±0.13 | 0.42±0.21 | 0.08±0.09 | 0.04±0.02 | 0.01±0.05 | 0.13±0.05 |

Values are means±S.E. * shows a significant difference from the corresponding control value (P<0.05).
mg/min of papaverine infusion up to 0.7–0.8, indicating that the autoregulation was considerably impaired.

**Discussion**

Analysis of pressure-flow curves and the indexes of autoregulation (ARI) showed that autoregulation of renal blood flow was impaired by diltiazem and papaverine; and it was not impaired by nitroglycerin, nicorandil, sodium nitroprusside and sodium nitrite. This lack of influence of the latter agents on the autoregulation can not be accounted for by any insufficiency of the doses used because, as shown Table 1, the increase of renal blood flow at the perfusion pressure of 100 mmHg with the used doses of nicorandil, sodium nitroprusside and sodium nitrite were comparable to or even greater than the increase produced by papaverine or by diltiazem. Thus, the different influence of these agents on the autoregulation suggests the presence of diversified mechanisms for renal blood flow regulation.

The Ca antagonist diltiazem, which blocks the Ca influx across various cell membranes, has a potent vasodilator action (7–9). Papaverine is a potent phosphodiesterase inhibitor and induces the accumulation of cyclic AMP (10). On the other hand, nitroglycerin and sodium nitroprusside raise cyclic GMP levels in bovine tracheal smooth muscle (11), in guinea pig taenia coli (11) and in rat ductus deferens (12). Furthermore, nitro-compounds concentration-dependently relax bovine coronary arterial smooth muscle (13) and rat aorta (14) in close association with an increase of cellular cyclic GMP level. The vasodilation of nicorandil has also been reported as cyclic GMP-related (15). It thus appears that vasodilation mediated by cyclic GMP does not influence the autoregulatory mechanism. This is also consistent with the fact that acetylcholine did not influence the autoregulation (reference 4 and our unpublished observation), since Furchgott and Zawadzki (16) have shown that acetylcholine-induced relaxation of arterial strip was dependent on an intact endothelial cell layer, and other investigators have shown that the endothelium—derived relaxant factor (obtained in relation to acetylcholine) activated guanylate cyclase in vascular smooth muscle (17).

The nature of autoregulation of renal blood flow is generally accepted to be the myogenic response of the vascular smooth muscle. The myogenic theory has been deduced from the fact that the autoregulation is abolished by the intra-arterial infusion of a vasodilator papaverine (3). Ca antagonists such as verapamil and nifedipine also have been known to abolish renal autoregulation through their effects on the vascular smooth muscle (1). In the present experiment, another Ca antagonist, diltiazem, provided the similar result. Furthermore, this inhibitory effect of diltiazem was antagonized by simultaneous infusion of excess calcium as it was with verapamil and nifedipine (1). Thus, the influx of calcium through the cell membrane of renal vascular smooth muscle is contributing to the renal vasculature in adjusting its tone to the change of perfusion pressure.

The effect of papaverine was not antagonized by simultaneous infusion of CaCl₂ solution (2). The same result is obtained in the experiment used aminophylline (2), which is also known to be a potent phosphodiesterase inhibitor (18). It is generally assumed that cyclic AMP plays an important role in the relaxation of vascular smooth muscle. Bhalla et al. (19) suggested that cyclic AMP might promote relaxation by stimulating the removal of calcium from the cytoplasm. It is conceivable that increased cyclic AMP can overcome the CaCl₂ infusion resulting in lowering the cellular calcium. Furthermore, it was discussed that papaverine and theophylline had no quantitative correlation between cyclic AMP level and the degree of relaxation (20). It is also considered that these drugs may affect renal blood flow autoregulation by means of mechanisms that do not depend on phosphodiesterase inhibition.

The fact that all vasodilators do not abolish the autoregulation of renal blood flow may arise from differences among the site and mechanism of action of each vasodilator. For the time being, the authors cannot give any good explanation, but the following matters should be considered. The vascular
segment responsible for the renal autoregulation must be located proximally to the afferent arteriole (21–23). Some differences are known in the effect of vasodilators on renal function. Thomas et al. (24) reported that papaverine increased renal blood flow, but decreased glomerular filtration rate in dogs. Treatment with Ca antagonists is reported to increase the glomerular filtration rate and urine flow besides the renal blood flow in dogs and human patients (25, 26). Bastron and Kaloyanides (27) reported that the infusion of sodium nitroprusside into the renal artery of the isolated dog kidney increased the renal blood flow and did not change the glomerular filtration rate in the intact kidney. The nitro-compounds may not have paralyzed the afferent arteriole, but may act on a blood vessel other than the afferent arteriole, though there is no evidence to support this point. Furthermore, Ohmura et al. (28) showed that sodium nitroprusside counteracted the inhibitory effect of halothane on autoregulation of renal blood flow. It is also reported that acetylcholine increased renal blood flow without changing the glomerular filtration rate (29). Therefore, Abe and Okahara (30) suggest that Ca antagonists dilate mainly the afferent arteriole and acetylcholine dilates both afferent and efferent arterioles.

The present experiment has indicated that all kinds of vasodilators do not inhibit the autoregulation of renal blood flow. In addition, it is suggested that vasodilators which relax smooth muscle through cyclic GMP increase do not influence the autoregulation.

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