Adenosine–catecholamine Interaction in the Renal Vascular Response[1] (35444)

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It is well established by recent studies (1, 2) that intra-arterially administered adenosine or adenosine monophosphate (AMP) increases the resistance of the renal vascular bed while they are potent vasodilators in other organs. Previously Gordon (3) found AMP in the renal venous blood after release of renal arterial occlusion in dogs. Thurau (4) postulated a role of AMP in the autoregulation of renal blood flow from the point of view of nucleotide metabolism. Scott *et al.* (2) detected vasoactive substances like adenosine or AMP in the blood of the renal venous outflow by a bioassay method in dogs and suggested the probable role of adenine nucleotides in the characteristic behavior of the renal circulation. In the present study, we observed enhancement of the renal vascular response to norepinephrine during infusion of adenosine in the dog, suggesting a probable interaction between adenosine and adrenergic mechanisms in the renal circulation.

Methods. Adult mongrel dogs, weighing about 14 kg, were anesthetized with 30 mg/kg of sodium pentobarbital intravenously. The left kidney was exposed retroperitoneally through a flank incision. After giving 500 U/kg of heparin as an anticoagulant, the left renal artery was carefully isolated from surrounding tissues and cannulated with a polyethylene cannula (o.d., 4 mm). The animal's own blood, led from the right femoral artery, was made to flow into the cannuated left renal artery through an electromagnetic flowmeter (Nihon Kohden MF-2). The constant perfusion pressure at 100 mm Hg was attained by the use of a pneumatic resistance in parallel to this circuit and the excess blood was shunted to the femoral vein.

Drugs were injected intra-arterially through a rubber tube connected close to the renal arterial cannula and adenosine solution was infused at a constant rate into the rubber tube by a Harvard infusion pump (Harvard Apparatus Model 600-900). Periarterial stimulation of renal sympathetic nerve fibers (4–6 V, 1 msec, 10 cps for 10 sec) was performed by an electronic stimulator (Nihon Kohden MSE-3R) through a bipolar silver electrode. Responses of the renal circulation to these drugs were observed as changes in renal blood flow which were registered on ink-writing oscillograph (Nihon Kohden WI-180 U).

Results. The rate of the renal blood flow at 100 mm Hg in 24 expts. was 118 ± 26 ml/min (mean and standard error).

Figure 1 illustrates one result typical of 24 expts. The administration of from 3 to 10 μg of adenosine into the renal artery produced a brief vasoconstriction which corresponded to that induced by 1 μg of norepinephrine. While adenosine was infused at the rate of 10 μg/min, the renal blood flow decreased gradually but reverted to the initial level within 15 min. During adenosine infusion, the vasoconstriction induced by a single injection of adenosine was significantly reduced, while the vasoconstrictor response to norepinephrine was clearly enhanced. Immediately after cessation of infusion, these responses to adenosine and norepinephrine promptly returned to what they were before the infusion of adenosine. When adenosine was infused at the rate of 30 μg/min, the renal blood flow promptly decreased but gradually recovered to the initial level with small fluctuations. The response to a single injection of adenosine was definitely reduced, but that to norepinephrine reached the maximum. At a higher infusion rate of adenosine,

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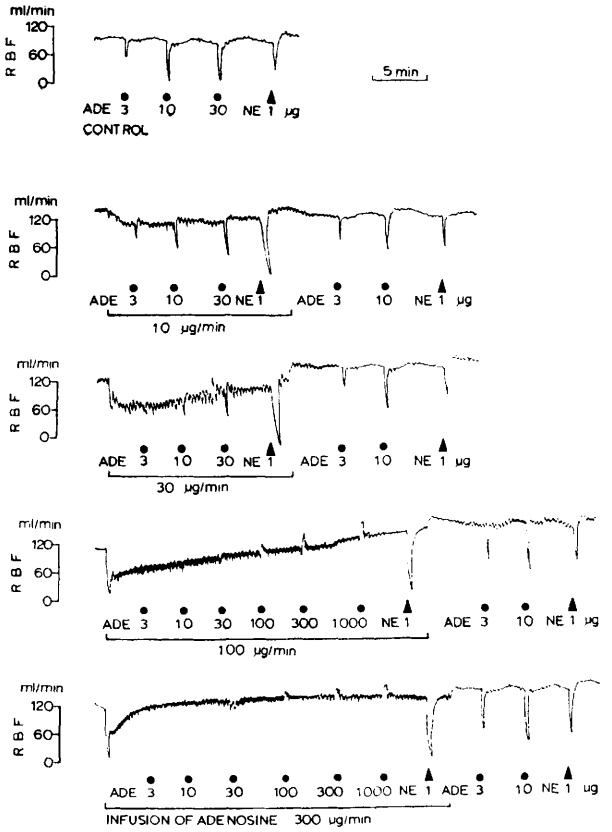

FIG. 1. Potentiation of the effect of norepinephrine (NE) and inhibition of that of adenosine (ADE) by infusion of adenosine: R.B.F., renal blood flow. Doses are presented as µg. It is noteworthy that the effects are present only during the period of infusion.

above 100 µg/min, the initial vasoconstriction was more prompt. The vasoconstrictor effect of adenosine was completely blocked, and vasodilation was observed by a single injection of large amount of adenosine. Meanwhile, the effect of norepinephrine remained at the maximum. Both enhancement of the vasoconstrictor response to norepinephrine and inhibition of that to adenosine were observed only during the period of adenosine infusion.

In Table I, percentage increase of responses to 1 µg of norepinephrine (mean ± standard error) and percentage inhibition of responses to 3 and 10 µg of adenosine are summarized at various infusion rates of adenosine. It shows clearly that the degree of enhancement of the response to norepinephrine depends on the infusion rate of adenosine above 0.3 µg/min until the response reaches a maximum at the rate of 30 µg/min. The vasoconstriction caused by electrical stimulation of the renal nerve was also enhanced during adenosine infusion.

Discussion. It is obvious from these experiments that adenosine has a dual effect in the renal circulation, *i.e.*, vasoconstriction and vasodilation. A large dose of adenosine causes a large vasoconstriction of the renal vascular beds in the initial stage of the response but is followed by relaxation in spite of continuation of adenosine infusion. Thus the vasodilator effect is unveiled only after the vasoconstrictor response is inhibited by continuous infusion at a higher dose of adenosine. Adenosine itself is considered to be the antagonist of its renal vasoconstrictor effect, because the renal artery responds to norepinephrine but not to adenosine. Previously Gaddum (5) observed such desensitization with

5-HT in contraction of guinea pig ileum.

The vasoconstriction induced by norepinephrine was markedly enhanced by an increase of concentration of adenosine in the perfused blood, from approximately 2.5 $\times$ 10^{-9} to 10^{-7} g /ml, while the vasoconstrictor response to adenosine was inhibited. When the latter response was completely inhibited, the former reached a maximum. Both effects disappeared immediately after the interruption of adenosine infusion. The renal vascular beds respond in this way when the renal nerve is electrically stimulated instead of norepinephrine injection. From these observations, it is concluded that not only norepinephrine but also sympathetic stimulation respond more effectively while the renal vascular beds are desensitized to adenosine. In other words, the concentration of adenosine modulates the adrenergic vascular effect in the kidney.

The interaction between adenosine and norepinephrine may be deduced as a probable mechanism for the regulation of the renal circulation. Previously Ono *et al.* (6) observed that, when autoregulation of the renal circulation was lost, it was restored by dipyridamole which is known to potentiate the vascular effect of adenosine. Recently Sakai *et al.* (7) observed that postocclusive vasoconstriction was potentiated by treatment with dipyridamole, while it was blocked by phenoxybenzamine which blocked the vasoconstriction induced by norepinephrine but not that induced by adenosine. Furthermore, Hashimoto *et al.* reported that renal vasoconstrictor responses not only to norepinephrine but also to adenosine were potentiated during intra-arterial infusion of dipyridamole (8). These results suggest that the enhancement of effect of adenosine by treatment with dipyridamole promotes the renal adrenergic mechanism. The adrenergic mechanism is a main factor in the control of renal vascular tone, but adenosine may play the role of modulator through interaction with catecholamines. These observations may help to explain the unique responses of the renal vasculature such as renal autoregulation and postocclusive vasoconstriction.

As mentioned above, infusion with AMP

TABLE I. Percentage Changes of Responses to Norepinephrine, Adenosine, and Nerve Stimulation at Increasing Rates of Adenosine Infusion (mean ± standard error).

	Rate of infusion of adenosine (μg/min)						
	0.3	1	3	10	30	100	300
Norepinephrine, 1 μg ($n = 5$)	+45 ± 4	+118 ± 5	+138 ± 21	+194 ± 52	+248 ± 44	+257 ± 32	+265 ± 45
Adenosine, 3 to 10 μg ($n = 5$)	−0	−0	−13 ± 9	−38 ± 10	−88 ± 9	−94 ± 2	−100
Nerve stimulation ($n = 6$)						+54 ± 10	

acted in almost the same way as adenosine, though a little higher dose of AMP was necessary. Whether it is adenosine or AMP which affects the renal circulation is not certain, because AMP is readily converted to adenosine in the blood stream.

Summary. Renal vasoconstriction induced by intra-arterial administration of 1 μg of norepinephrine or renal nerve stimulation was enhanced during adenosine infusion in concentrations from approximately 2.5×10^{-9} to 10^{-7} g/ml while the vasoconstrictor response to adenosine itself was inhibited. Enhancement of the vasoconstrictor response to norepinephrine and inhibition of that to adenosine were dependent on the infusion rate of adenosine. After interruption of adenosine infusion, the initial responses to norepinephrine and adenosine recovered promptly. Thus it appears that adenosine modulates the adrenergic effect in the renal circulation.

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