of tablets in the small intestine were available for 4 subjects taking the light breakfast and 4 subjects taking the heavy breakfast (Table 2). Here there are no differences that can be attributed to the size of the breakfast and the mean transit time is about 3 h. This relative constancy in small intestinal transit time has been discussed in detail elsewhere by Davis et al (1986a).

Interestingly, the transit of single units through the ileocaecal sphincter, can, in some cases, result in one tablet moving to the ascending colon with the other remaining at the ICJ. Periods of stagnation at the ICJ (and also at the hepatic splenic flexure of the colon) are not uncommon and can be observed with single and multiple unit dosage forms (Khosla & Davis, unpublished) and with faecal masses in constipation. The differential transit of two single units through the ICJ indicates that the sphincter in this region may have some form of limiting function in controlling the transit of chyme from the small to large bowel. This role has been discussed in recent contributions from the Mayo Clinic (Quigley et al 1984).

Conclusions. Two large units administered together can either empty together (or within 1 h of each other) or at widely different times. The transit of two single units through the ileocaecal junction can also occur on a differential basis.

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Modulation of cyclic AMP and autoregulation of renal blood flow, analysed by the use of forskolin and 1-methyl-3-isobutylxanthine

NOBUYUKI OGAWA, HIROSHI ONO, *Department of Pharmacology and Toxicology, Hatano Research Institute, Food and Drug Safety Center, Kanagawa 257, Japan*

Abstract—We have examined the effects of forskolin and 1-methyl-3-isobutylxanthine (IBMX) in relation to cyclic (c)AMP metabolism and renal blood flow autoregulation in anaesthetized dogs. Control observations usually showed excellent autoregulation of renal blood flow over the renal perfusion pressure range of 120–200 mmHg, when the perfusion pressure was changed, stepwise, between 60 and 200 mmHg. Renal blood flow was increased by the infusion of forskolin (10 μg min^{-1}) and IBMX (100 μg min^{-1}) at the basal perfusion pressure of 100 mmHg, and maintained an increased level while the infusion was continued. Forskolin and IBMX did not inhibit autoregulation, though they shifted the perfusion pressure range evoking autoregulation. These data indicate that vasodilators which may produce the activity through modulating the cAMP level in vascular smooth muscle do not influence the establishment of autoregulation of renal blood flow.

Kidney is known to show autoregulation which maintains a stable renal blood flow level in spite of fluctuation of perfusion pressure. As the explanation of this mechanism, Thurau & Kramer (1959) have assumed the myogenic theory based on the experimental result that papaverine, by its "smooth muscle paralysing action", abolished renal blood flow autoregulation. We have expanded the theory demonstrating that intra-arterial infusion of Ca antagonistic vasodilators, such as verapamil, nifedipine and diltiazem, inhibited renal blood flow autoregulation (Ono et al 1974; Ogawa & Ono 1986a). We recently discovered, however, that certain vasodilators, such as nicorandil, sodium nitroprusside, sodium nitrite, prostaglandin E_2 and bradykinin had no effect on renal blood flow autoregulation despite causing an increase in renal blood flow (Ogawa & Ono 1985, 1986a).

Correspondence to: Nobuyuki Ogawa, Dept of Pharmacology and Toxicology, Hatano Research Institute, Food and Drug Safety Center, 729-5, Ochiai, Hadano, Kanagawa 257, Japan.

Thus, not all kinds of vasodilators inhibit renal blood flow autoregulation, and the inhibitory activity of some vasodilators has a different mechanism of action from their vasodilator activity.

In the present study, we have studied the effects of forskolin, which stimulates adenylate cyclase (Seamon & Daly 1981), and IBMX, which inhibits phosphodiesterase (Wells et al 1975), on renal blood flow autoregulation.

Materials and methods

Healthy mongrel dogs of either sex (n = 15), 9–15 kg, were sedated with morphine hydrochloride (2 mg kg^{-1} s.c.) and anaesthetized with α-chloralose (40 mg kg^{-1}) and urethane (400 mg kg^{-1}) intravenously. A femoral artery and vein were cannulated for the measurement of systemic blood pressure and administration of further anaesthetic and heparin. Pressure-controlled perfusion experiments were performed using the left kidney. Details of the procedure have been described previously (Ogawa & Ono 1985). The left renal artery was cannulated and perfused with blood from the carotid artery. An initial dose of 500 u kg^{-1} of sodium heparin was given as anticoagulant. Perfusion pressure was controlled by the use of a Starling's pneumatic resistance. Perfusion pressure and systemic blood pressure were each measured conventionally by means of a

Statham P23Db transducer and San-ei 1206B carrier amplifier. Renal blood flow was measured by a Narco RT-500 electromagnetic flowmeter. Drug solutions were infused via a catheter inserted close to the shank of the renal arterial cannula, by means of a Harvard Apparatus 901 infusion pump.

Experimental protocols

Series 1. Renal blood flow was allowed to stabilize for 30 min at the basal perfusion pressure of 100 mmHg, after which perfusion pressure was changed stepwise between 60 and 200 mmHg. Perfusion pressure was then returned to 100 mmHg and the dimethyl sulphoxide (DMSO, vehicle) infused continuously into the renal artery at the rate of 50 μL min^{-1}. The second pressure-flow study was made during this infusion.

Series 2. These experiments were identical to those of Series 1 except that forskolin (Nippon Kayaku Co. Ltd.) was incorporated into the DMSO vehicle to give an infusion rate of 10 μg min^{-1}.

Series 3. Identical to Series 1 except that IBMX (Sigma) was incorporated in the DMSO vehicle to give a renal artery infusion rate at 100 μg min^{-1}.

Calculation. The efficiency index of autoregulation (ARI) as described by Semple & DeWardener (1959) was calculated as

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

where P_{RA1} and P_{RA2} define a range of perfusion pressure and RBF_1 and RBF_2 are the respective measured blood flow at the limits of perfusion pressure. ARI approaching 0 indicates excellent autoregulation.

Statistical analysis. Results are expressed as means ±s.e. Student's *t*-test for paired observations was used to determine statistical significance. A value of $P < 0.05$ was considered statistically significant.

Results

Control observations usually showed excellent autoregulation in the perfusion pressure range between 120 and 200 mmHg, and partial autoregulation between 100 and 120 mmHg (Table 1). Renal blood flow was pressure-dependent below 100 mmHg. DMSO alone, at the rate of 50 μL min^{-1} into the renal artery, did not alter renal blood flow and autoregulatory function (Tables 1, 2).

Renal blood flow was increased by the intra-arterial infusion

Table 1. Changes of the renal blood flow in response to changes of the perfusion pressure during infusion of DMSO, forskolin or IBMX.

	Renal perfusion pressure (mmHg)							
	60	80	100	120	140	160	180	200
DMSO (n = 5)								
Control	1·82 ±0·34	2·64 ±0·41	3·28 ±0·52	3·60 ±0·56	3·71 ±0·58	3·73 ±0·57	3·73 ±0·56	3·73 ±0·55
50 μL min^{-1}	1·90 ±0·29	2·82 ±0·41	3·47 ±0·50	3·79 ±0·56	3·88 ±0·58	3·89 ±0·58	3·89 ±0·57	3·89 ±0·57
Forskolin (n = 5)								
Control	1·83 ±0·16	2·63 ±0·29	3·30 ±0·41	3·70 ±0·48	3·82 ±0·49	3·84 ±0·50	3·86 ±0·50	3·86 ±0·52
10 μg min^{-1}	2·42* ±0·16	3·27* ±0·22	4·03* ±0·30	4·67* ±0·40	5·08* ±0·46	5·20* ±0·47	5·29* ±0·46	5·40* ±0·45
IBMX (n = 5)								
Control	1·93 ±0·26	2·64 ±0·27	3·11 ±0·28	3·37 ±0·27	3·50 ±0·28	3·53 ±0·29	3·55 ±0·28	3·57 ±0·28
100 μg min^{-1}	2·46* ±0·31	3·40* ±0·37	4·02* ±0·43	4·40* ±0·46	4·65* ±0·47	4·75* ±0·49	4·84* ±0·48	4·90* ±0·48

Values are means ±s.e. and represent as mL g^{-1}, kidney weight min^{-1}. • Shows a significant difference from the corresponding control value ($P < 0.05$).

Table 2. Changes in the efficiency index of autoregulation (ARI) of renal blood flow during infusion of DMSO, forskolin or IBMX.

	Renal perfusion pressure (mmHg)						
	60–80	80–100	100–120	120–140	140–160	160–180	180–200
DMSO (n = 5)							
Control	1·52 ±0·31	0·98 ±0·23	0·51 ±0·19	0·17 ±0·08	0·05 ±0·04	0·02 ±0·02	0·01 ±0·03
50 μL min^{-1}	1·56 ±0·48	0·92 ±0·15	0·45 ±0·13	0·13 ±0·05	0·02 ±0·03	0·01 ±0·02	0·00 ±0·00
Forskolin (n = 5)							
Control	1·30 ±0·22	1·00 ±0·17	0·59 ±0·09	0·18 ±0·05	0·04 ±0·05	0·04 ±0·04	0·01 ±0·03
10 μg min^{-1}	1·08 ±0·20	0·94 ±0·15	0·77* ±0·11	0·50* ±0·05	0·16 ±0·03	0·15 ±0·07	0·19 ±0·10
IBMX (n = 5)							
Control	1·19 ±0·21	0·74 ±0·07	0·44 ±0·18	0·23 ±0·16	0·07 ±0·05	0·05 ±0·02	0·05 ±0·05
100 μg min^{-1}	1·13 ±0·11	0·78 ±0·09	0·49 ±0·13	0·30* ±0·17	0·15* ±0·06	0·16 ±0·06	0·14 ±0·08

Values are means ±s.e. *Shows a significant difference from the corresponding control value ($P < 0.05$).

of forskolin (10 μg min^{-1}) and IBMX (100 μg min^{-1}) at the basal perfusion pressure of 100 mmHg. The increase of blood flow reached a maximum within 3 min after the onset of the infusion and sustained an increased level during infusion. The infusion of forskolin (10 μg min^{-1}) and IBMX (100 μg min^{-1}) increased renal blood flow at all ranges of perfusion pressure, but the autoregulation was not impaired (Table 1).

ARIs before and during the infusion of the vasodilators are shown in Table 2. The control ARIs in three groups were less than 0·6 between 100 and 120 mmHg, showing partial autoregulation, and were less than 0·3 indicating nearly effective autoregulation between 120 and 200 mmHg. ARIs during infusion of forskolin were significantly increased at the perfusion pressure range of 100–140 mmHg, but were less than 0·2 above 140 mmHg showing that autoregulation was not influenced. ARIs during infusion of IBMX were also significantly increased at perfusion pressure range of 120–160 mmHg, but were less than 0·2 above 160 mmHg.

Discussion

The study of Thurau & Kramer (1959) which demonstrated the effect of papaverine on renal autoregulation, provided strong support for the myogenic theory of autoregulation. The present authors have confirmed the effect of papaverine (Ogawa & Ono 1986a) and shown a similar effect of aminophylline (Hashimoto et al 1980). The spasmolytic activity of papaverine has been ascribed to its inhibitory action on phosphodiesterase (Kukovetz & Pöch 1970). However, the potent phosphodiesterase inhibitor IBMX did not inhibit autoregulation in spite of obvious vasodilation. Forskolin also did not inhibit autoregulation. Thus, the inhibitory effects of papaverine and aminophylline on renal flow autoregulation may not be due to an increase in cyclic (c)AMP level induced by phosphodiesterase inhibition and further work in this area is required.

We have shown many examples of vasodilators which do not inhibit the autoregulation of renal blood flow: nitro-compounds, prostaglandin E_2 and bradykinin all increase renal blood flow but have no inhibitory effects upon autoregulation (Ogawa & Ono 1985, 1986a).

Previous work from the authors (Ogawa & Ono 1986b, 1987) suggests that Ca channels play an important role in the establishment of renal blood flow autoregulation. Ca antagonists, such as verapamil, nifedipine and diltiazem inhibited renal autoregulation; these inhibitory effects were antagonized by simultaneous infusion of $CaCl_2$ or Bay K 8644 (methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate) a Ca channel activator (Ono et al 1974; Ogawa & Ono 1986a,b, 1987). Papaverine is known to have a Ca current blocking action in addition to the phosphodiesterase inhibitory effect (Kadlec et al 1973). However, the present authors observed that the inhibitory effect of papaverine on renal autoregulation was not antagonized by simultaneous infusion of Bay K 8644 (Ogawa & Ono 1987).

Calmodulin inhibitors, such as trifluoperazine and chlorpromazine have been shown to abolish renal blood flow autoregulation (Ogawa et al 1987). These inhibitory effects of trifluoperazine and chlorpromazine on renal autoregulation were not antagonized by simultaneous infusion of Bay K 8644 or $CaCl_2$ (Ogawa et al 1987). It may be readily conceivable that the increase in Ca influx through Ca channels is of no use for the establishment of renal blood flow autoregulation if the intermediating calmodulin is non-competitively blocked. The effect of trifluoperazine and chlorpromazine on renal autoregulation seems similar to that of papaverine. Kukovetz et al (1981) have indicated that papaverine and theophylline caused relaxation and rise in the cAMP level in bovine coronary artery, but that there was no consistent correlation among the potencies for relaxation. Therefore, the inhibitory effect of papaverine on renal blood flow autoregulation may be due to an activity other than the inhibitory effect upon phosphodiesterase, papaverine may have a calmodulin inhibitory action in renal vasculature. Premen et al (1985) also observed renal blood flow autoregulation during aminophylline infusion at a dose which inhibited the change of renal blood flow induced by adenosine. Nevertheless, the present study offers no support for the hypothesis that papaverine and aminophylline abolish renal autoregulation by phosphodiesterase inhibition.

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