Korean J Physiol Pharmacol
Vol 2: 77–84, February, 1998

Prostaglandin in Regulations of Renal Blood Flow during Partial Ureteral Obstruction in Dogs

Hoo Bin Song, Hun Mo Yang, and Young Gi Min

Department of Physiology, College of Medicine, Soonchunhyang University, Chunan 330–100, Korea

Ureteral obstruction causes increase in renal blood flow (RBF) and partial impairment of the autoregulation of RBF. Although increased renal prostaglandin production is responsible for the former, it is not clear whether or not it is also responsible for the latter. Therefore, we investigated the role which prostaglandins play in the autoregulation of RBF during an ureteral pressure elevation (40 cmH_2O). Since the major mechanism of RBF autoregulation is the tubuloglomerular feedback, studying the interaction between ureteral pressure and RBF autoregulation may reveal the role of prostaglandin in tubuloglomerular feedback. To pursue the purpose, six anesthetized dogs were prepared for the measurements of RBF, mean sytemic and renal arterial pressure (RAP) and the manipulation of ureteral pressure. The autoregulation curves were determined during both control and elevation of the ureteral pressure, before and after the pretreatment with indomethacin, a cyclooxygenase inhibitor. The desired ureteral pressure was achieved by vertically elevating the water-filled reservoir connected to the ureteral catheter to 40 cm above the kidney level. In response to the elevation of the ureteral pressure, RBF increased from 170 ± 8 ml · min^{-1} to 189 ± 8, and the systemic arterial pressure didn't change significantly. During spontaneous urine flow, RBF autoregulation was abolished when RAP was reduced to 59 ± 3 mmHg. On the other hand, during the ureteral pressure elevation, the autoregulation curves shifted upward and rightward from control, and the pressure when RBF autoregulation was abolished was 74 ± 3 mmHg. The pretreatment of the dogs with indomethacin failed to affect the lower limit of RBF autoregulaion during both control (63 ± 5 mmHg) and the elevated ureteral pressure (77 ± 5 mmHg). Since RBF failed to increase in response to the elevated ureteral pressure, RBF autoregulation curves obtained during the elevated ureteral pressure shifted only rightward from indomethacin control. The results indicate that the increased intrarenal level of prostaglandin or prostaglandin-induced vasodilation does not appear to bear any relation to the reduction in the autoregulatory capacity during partial ureteral obstruction. It seems that the partial impairment of the autoregulation during acute ureteral obstruction is due to the consumption of tubuloglomerular feedback mechanism at spontaneous RAP and that prostaglandin is neither mediator nor effector of tubuloglomerular feedback mechanism.

Key Words: Partial ureteral obstruction, Renal blood flow, Autoregulation, Indomethacin, Prostaglandin

INTRODUCTION

Several recent studies have raised the possibility that eicosanoids participate in the mediation of tubuloglomerular feedback and the regulation of RBF (Franco et al, 1988; Haas et al, 1988; Kauser et al, 1991; Roman & Harder, 1993). Tubuloglomerular feedback responses were shown to be attenuated by certain cyclooxygenase inhibitors and partially restored by systemic infusion of PGI_2 (Boberg et al, 1984) or PGE_2 (Schnerman & Weber, 1982), supporting the role for prostaglandin in the autoregulation. In contrast, in the same study, indomethacin administered to rats on a low-salt diet failed to inhibit

Corresponding to: Hun Mo Yang, Department of Physiology, College of Medicine, Soonchunhyang University, Sangyong dong 366-1, Chunan ChoongNam 330–100, Korea

tubuloglomerular feedback responses even though urinary prostaglandin excretion rates were equally reduced (Schnerman et al, 1979). Franco et al (1988) suggested another pathway for metabolism of arachidonic acid by demonstrating the failure of cyclooxygenase or lipoxygenase inhibitors to block the potentiating effect of arachidonic acid on tubuloglomerular feedback responses. 20-HETE is produced by renal vasculature when incubated with arachidonic acid and is an endogenous P-450 metabolite of arachidonic acid. It plays an important role in tubuloglomerular feedback and may participate in the autoregulation of RBF (Franco et al, 1988; Kauser et al, 1991; Ma et al, 1993). Inconsistencies exist regarding the role of prostaglandin in RBF autoregulation and P-450 metabolite emerged as an arachidonic acid derivative important in regulatng RBF. However, the effect of prostaglandins on tubuloglomerular feedback and renal autoregulation cannot simply be disregarded since the inconsistencies may indicate that the role for prostaglandins within the mechanism is obscured or cancelled out by factors not controlled in the previous experiments.

The regulation of the diameter of preglomerular vasculature according to changes in Cl^- concentration in the early portion of the distal tubule and changes in transmural pressure across the vasculature constitutes the basis of tubuloglomerular feedback and myogenic mechanism, respectively. These mechanisms, especially the former, has been proposed to participate in the mechanisms of the autoregulation of renal blood flow (RBF) and glomerular filtration rate (Holstein-Rathlou, 1987; Kallskog & Marsh, 1990; Sjoquist et al,1984). Since an increase in ureteral pressure impedes glomerular filtration and affects the components of the tubular fluid (Tanner, 1979), it is very likely that tubuloglomerular feedback is involved in ureteral obstruction-induced changes in renal hemodynamics. Taken together, these suggest that impaired autoregulatory efficiency during ureteral obstruction is caused by the change in tubuloglomerular feedback system, as proposed by Navar and Baer (1970). However, the validity of the proposed role of tubuloglomerular feedback depends on whether or not intrarenal prostaglandins increased by ureteral obstruction (Blachshear & Watchen, 1978; Klahr, 1983; Lacy & Schmidt-Nielsen, 1979) do play a role in the autoregulation of RBF and if they do, how they affect it. The significance of prostaglandins in the autoregulation of RBF during ureteral obstruction has not been evaluated previously and, therefore, is the focus of this investigation.

METHODS

Six mongrel dogs of both sexes weighing 11 ± 1 kg were used in this experiment. The dogs were anesthetized with pentobarbital sodium ($20 \sim 30$ mg $\cdot$ kg^{-1}), and catheters were inserted in both femoral arteries and veins. The femoral catheters were advanced into the aorta, and the tip of one catheter was positioned cephalad to and the tip of the other caudal to the origin of the left renal arteries. An externally adjustable silastic occluder was placed around the aorta immediately cephalad to the left renal artery and between the ends of the two arterial catheters. The arterial catheters above and below the occluder were used to monitor the systemic arterial pressure and indirectly the renal arterial pressure (RAP), respectively. The venous catheters were used for the infusion of vehicle or indomethacin. When needed, arterial pressures below the occluder could be precisely reduced to and maintained at desired levels with the continuous control of the inflation of the occluder with a servo-controlled syringe pump, which was in turn connected to a servo unit (Hester et al, 1983). The servo unit was driven by the output of the driver amplifier of the Grass polygraph which continuously monitored the arterial pressure below the occluder. The left ureter was catheterized and the free end of the catheter was connected to a syringe reservoir. Ureteral pressure could be increased to desired levels by elevating the water-air interface and allowing the kidney to excrete against the increased hydrostatic pressure. Finally, the left renal artery was equipped with electromagnetic flow probe for the continuous measurement of RBF by electromagnetic flowmeter (Carolina medical electronics).

Experimental protocol

Saline was infused rapidly at the beginning of surgery (~ 300 ml). Once an adequate urine flow had been obtained ($30 \sim 40$ min), the intravenous infusion was maintained at $8 \sim 12$ ml $\cdot$ hr^{-1} $\cdot$ kg^{-1} b.w.. The systemic arterial pressure, heart rate, and RBF were measured continuously. Experiments were begun only after an adequate recovery period from sugery ($40 \sim 50$ min) as evidenced by stable values for systemic

arterial pressure, heart rate, and RBF. The autoregulation curves were obtained as follows by plotting RBF against the renal artery pressure (RAP): The stable RBF for 30 seconds after an increase following an initial deflection which took ~2 min, if there were any increase, set the criteria for full response to each pressure reduction. RAP was reduced by 10 mmHg step to 20~40 mmHg. Throughout the experiment in a dog, six autoregulation curves were obtained: First, the control curve was determined after stabilization without any additional manipulation. Allowing recovery of RBF after RAP was equalized to the systemic arterial pressure by releasing the inflated occluder, ureteral pressure was gradually increased to the level determined by the vertical height, from the level of renal pelvis, of the top of fluid-filled reservoir. To prevent substantial reflux of urine into the tubules, the reservoir was raised to the height of 40 cm in 5 steps, 7~8 cm at each step: After urine flow against the hydrostatic pressure was established, ureteral pressure was increased to the next step. It took at least 30 min before RBF stabilized at ureteral pressure of 40 cmH_2O and before the second RBF autoregulation curve was determined. After recovery from the reduction in renal perfusion pressure, the ureteral pressure was allowed to return to zero, and another autoregulation curve was obtained and the curve served as a recovery curve.

Experiments were repeated after prostaglandin synthesis was inhibited with indomethacin. Indomethacin was administered intravenously (5 mg · kg^{-1}), followed by a booster injection of 2 mg · kg^{-1}, 70~90 min after the initial dose. The selected dose of indomethacin was 2 mg · kg^{-1} greater than the dose which effectively blocked the response of RBF to an increase in ureteral pressure to 40 cmH_2O in the preliminary experiment. The doses used by other investigators ranged between 3~10 mg · kg^{-1} (Anderson et al, 1975; Baylis, 1987; Krampet al, 1995; Munger & Blantz, 1990).

Statistical analysis

Data are expressed as means ± SE. The control and recovery RBF autoregulation curves (both before and after indomethacin) did not differ from each other and the mean of the two served as control. The significance of differences within and between groups was evaluated using an analysis of variance for repeated measurements followed by a paired *t* test for the data presented in table 1 and Fig. 1. $P<0.05$ was considered statistically significant.

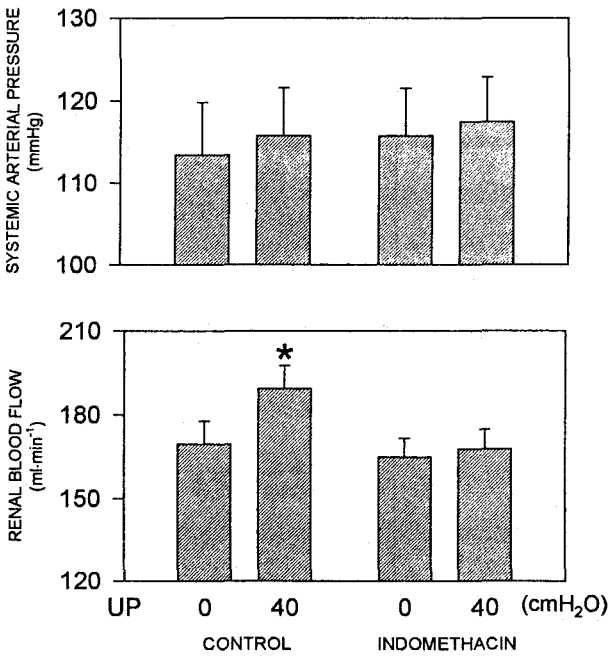

Fig. 1. Renal blood flow and mean systemic arterial pressure during spontaneous urine flow (0) and ureteral pressure of 40 cmH_2O (40), before (CONTROL) and after INDOMETHACIN administrations. UP, ureteral pressure. *$P<0.05$ compared to control values.

Two straight lines were fitted to each autoregulation curve by standard regression technique, and the intersection of these two lines was referred to as the threshold pressure. Ninty five percent of the RBF measured during the spontaneous RAP served as the datum line by which a RAP-RBF datum point is applied to one regression line or the other. The autoregulation curves determined during the elevation of the ureteral pressure demonstrated the mild tendency for RBF to decrease for decreases in RAP which appears to be within the autoregulation range. In this case, an abrupt increase in the slope for a given decrease in RAP was used as the indicator. When it was ambiguous to include a datum in a regression line or the other, it was ignored, and both regression lines were determined without it. Since the threshold pressures differed from dog to dog, the mean autoregulation curves determined with the averages of RBFs from six dogs had no apparent hinge point to sort the plateau from the slope; the individual autoregulation curves were presented in the Fig. 2.

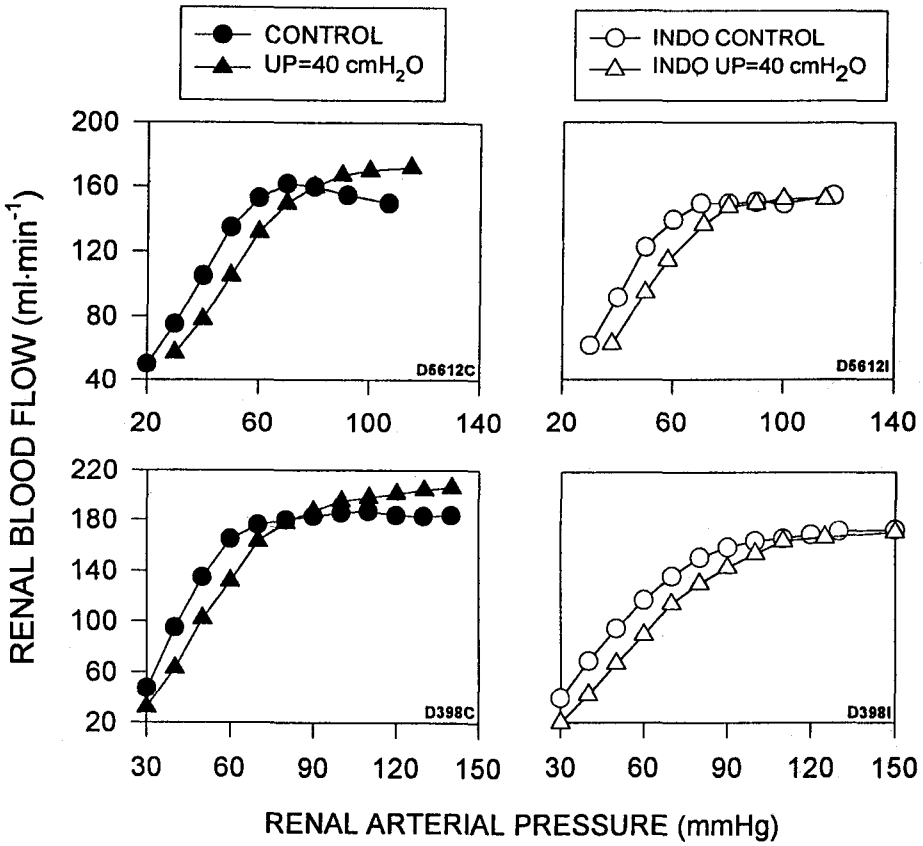

Fig. 2. Autoregulation curves for renal blood flow were obtained in 2 dogs during spontaneous urine flow (circle) and ureteral pressure of 40 cmH_2O (triangle), before (filled symbols) and after (open symbols) indomethacin pretreatment. INDO, indomethacin; UP, ureteral pressure.

RESULTS

Fig. 1 shows the baseline values of systemic arterial pressures and RBF. By the elevation of the ureteral pressure to 40 cm H_2O, RBF was increased from 170 ± 8 ml · min^{-1} to 189 ± 8, but the systemic arterial pressures were not changed significantly. Although indomethacin had no significant effect on both RBF and systemic arterial pressure, it could effectively block the response of RBF to the elevation of ureteral pressure. Increasing ureteral presure did not affect the heart rate. Administration of indomethacin tended to reduce the heart rate from 137 ± 9 beats/min to 133 ± 10 but it was not statistically significant. The sex differences with regard to modulation of vascular tone and heart rate by indomethacin were not observed.

Fig. 2 shows the individual autoregulation curves obtained in 2 dogs during spontaneous urine flow and ureteral pressure of 40 cmH_2O, before and after the administrations of indomethacin. The curves obtained from the other 4 dogs demonstrated similar patterns and were not presented in this Figure. RAP was reduced to 20~40 mmHg depending on the systemic arterial pressure and the fitness of the pneumatic occluder around the renal artery. The autoregulation curves determined at the period of spontaneous urine flow during control conditions assume a typical appearance: RBF was maintained close to the control RBF until the RAP was reduced to 59 ± 3 mmHg (Table 1), below which RBF began to decrease proportionally to RAP. During the elevated ureteral pressure, the elevated RBF was maintained until the RAP was lowered to 74 ± 3 mmHg: When RAP was reduced further, the earlier loss of autoregulatory power caused RBF to become lower at a given RAP than the level observed during spontaneous urine flow. The pretreatment with indomethacin was unable

Table 1. Threshold renal artery pressures at varioius conditions

Ureteral Pressure, cmH_2O	Control		Indomethacin	
	0	40	0	40
Threshold RAP, mmHg	59±3	74±3*	63±5	77±5*

Values are means±SE (n=6). *P<0.05 compared to values for the period of spontaneous urine flow. RAP, renal arterial pressure.

to affect the lower limit of the autoregulatory range determined during spontaneous urine flow and unable to modulate the autoregulatory response reduced by the increased ureteral pressure (Table 1). Since indomethacin prevented RBF from increasing in response to the elevated ureteral pressure, RBF autoregulation curve obtained during the elevated ureteral pressure shifted downward from its pre-indomethacin counterpart and shifted only rightward (but not upward) from indomethacin control.

Since renal interstitial fluid pressure (P_{ISF}) was not measured in the present experiment, the increase in P_{ISF} during ureteral pressure elevation was estimated from the relationship between RAP and RBF. If the degree of maximal vasodilation of the renal vasculature at RAP far below the autoregulatory limit is the same regardless of the ureteral pressure, the difference in RBFs between the two conditions at the same RAP can be attributed to the difference in P_{ISF}. Assuming that RBF of 60 ml · min^{-1} is achieved at RAP of 30 mmHg during spontaneous urine flow and at RAP of 42 mmHg during an increase in ureteral pressure to 40 cmH_2O, the increase in P_{ISF} caused by ureteral pressure elevation was estimated to be 12 mmHg and was significantly greater when prostaglandin synthesis was inhibited with indomethacin (10.0±1.3 mmHg) than when it remained intact (7.5 ±0.8 mmHg).

DISCUSSION

Acute ureteral obstruction is associated with a large increase in intrarenal production of prostaglandins (Klahr et al, 1983), probably through the stimulatory effect of high interstitial pressure on prostaglandin synthesis. As shown in this study and elsewhere, the increase in RBF has been effectively prevented by cyclooxygenase inhibitor which blocks the synthesis of prostaglandin during ureteral pressure elevation. This indicates that prostaglandin is the major mechanism of RBF elevation during ureteral obstruction. Since indomethacin selectively reduces medullary blood flow directly or indirectly through the interaction with adrenomedullin (Jougasaki et al, 1997), increases in blood flow in the medulla contribute to obstruction-induced increase in RBF (Parekh & Zou, 1996). However, the maintenance of RBF during the blockade of prostaglandin synthesis by cyclooxygenase inhibitor occurred despite an increase in the passive renal venous resistance (a part of postaglomerular resistance) which accompanies ureteral pressure elevation. This suggests that some other mechanism was operating, probably through the effect on preglomerular vessels, to restore RBF which should otherwise have been reduced.

Elevated ureteral pressure (40 cmH_2O) reset the autoregulatory plateau at a higher level and increased the lower limit of the autoregulatory range. This means that the autoregulation was not as effective at the elevated ureteral pressure as at spontaneous urine flow. This confirms the finding by Navar and Baer (1970) that the increase in RBF following ureteral pressure elevation was observed only when arterial pressure was within the autoregulatory range. Although indomethacin completely blocked an increase in RBF during ureteral obstruction, the pretreatment of the dog with cyclooxygenase inhibitor could not reverse or worsen the reduced RBF autoregulation caused by an increase in ureteral pressure. This indicates that, as implicated from the selective action of prostaglandins on the medullary blood flow (Parekh & Zou, 1996), prostaglandin-induced preglomerular vasodilation does not share common mechanism with autoregulatory vasodilation. RBF is autoregulated mainly through tubuloglomerular feedback mechanism, and an increase in ureteral pressure impedes glomerular filtration and affects the components of the tubular fluid (Harris & Gill, 1981). Taken together, these suggest that impaired autoregulatory efficiency during ureteral obstruction is caused by changes in tubuloglomerular feedback system, probably by consuming TGF-mediated vasodilatory reserve at the normal renal perfusion pressure. This result reinforces the proposal suggested by Navar and Baer (1970) by excluding the possible role for prostaglanin in RBF autoregulation. It shows indirectly that even under the

condition characterized by enhanced intrarenal production of prostaglandins, the tubuloglomerular feedback operates independently of prostaglandin in term that prostaglandin is not the mediator of tubuloglomerular feedback and does not share a common mechanism or pathway with tubuloglomerular feedback in inducing preglomerular vasodilation. Since the effect of cyclooxygenase inhibitor on the renal autoregulation was absent regardless of the intrarenal concentrations of prostaglandins, the tubuloglomerular feedback does not seem to achieve renal autoregulation by controlling the rate of its release as an effector. Although there are several reports that maximal responses of tubuloglomerular feedback have been shown to be inhibited by intravenous application of indomethacin in the rat (5 mg · kg^{-1}), the inhibition of responses was usually acutely reversible despite the long-lasing inhibition of cyclooxygenase (Schnerman et al, 1979). Furthermore, maximum inhibition of prostaglandin synthesis (as judged from urinary excretion of PGE_2 or PGF_2) could be achieved with a lower dose of indomethacin (Schnerman et al, 1979). Thus, the inhibitory effect of indomethacin on TGF responses demonstrated in several studies may not be related to the specific inhibition of cyclooxygenase.

An increase in ureteral pressure is expected to increase P_{ISF}, which in turn increases the passive renal venous resistance. Kallskog and Wolgast (1975) has shown that, for the increase in ureteral pressure of 20 mmHg, P_{ISF} increased only by ~3 mmHg. Although we did not measure the pressure, the persistance of considerable RBF in the dogs whose RAP was reduced to 30 mmHg (40 cmH_2O) suggests relatively poor transfer of ureteral pressure to P_{ISF}. The estimated P_{ISF} increased by 7.5 ± 0.8 mmHg and 10.0 ± 1.3 mmHg ($p < 0.05$) for ureteral pressure elevation by 40 cmH_2O in control and indomethacin-pretreated dogs, respectively. The increase in P_{ISF} for the ureteral pressure elevation was rather small. It may be accounted for by the inhibitory effect of prostaglandin on the tubular reabsorption (Iino & Brenner, 1981; Stoke & Kokko, 1977) and by the increased P_{ISF} itself favoring peritubular capillary reabsorption. The greater increase in P_{ISF} in response to the ureteral pressure elevation in the indomethacin-pretreated animal appears to be caused by the inhibitory effect of prostaglandin on tubular sodium transport.

P_{ISF} may be related to RBF autoregulation by affecting the transmural pressure - myogenic control of RBF (Bayliss, 1902; Edwards, 1983; Gilmore et al, 1980). The estimated increase in P_{ISF} in response to the elevation of the ureteral pressure was smaller than that the 15 mmHg increase in the lower limit of renal autoregulation could be entirely attributed to it. In addition, the increase in P_{ISF} was greater before than after indomethacin administration. This effect of indomethacin, according to the myogenic theory, should have further impaired the renal autorgulatory capacity. However, indomethacin had no effect on the autoregulation of RBF. Therefore, under the assumption that the estimation of P_{ISF} was correct, these provide tentative evidence against the myogenic control of RBF autoregulation. An innovative experimental protocol that can dissociate the change in the interstitial pressure or the change in distal tubular sodium concentration from the other will provide an definitive evidence for or against the role of tubuloglomerular feedback or myogenic mechanism in the autoregulation.

Under our experimental conditions, renal vasoconstriction or vasodilation could not be demonstrated at the dose of indomethacin of 5 mg · kg^{-1}. Since the renal vascular response to indomethacin has been shown to be dose-dependent, possibilities exist that different doses might produce different results. Doses greater than 3 mg · kg^{-1} usually produces an extensive blockade of the synthesis of prostaglandins and similar depression of plasma PRA or aldosterone concentrations (Kramp et al, 1995). Therefore, the dose-dependency of indomethacin action is not due to differences in the degree of cyclooxygenase inhibition or of the loss of stimulatory action of prostaglandins on the renin-angiotensin-aldosterone system. Possibility exists that the dose-dependency may be due to direct or indirect effect of indomethacin on the lipoxygenase pathway. However, it can be excluded by the finding that inhibition of lipoxygenase pathway with norhydroguaiaretic acid did not alter TGF responsiveness (Franco et al, 1988). Recent observations concerning the cytochrome P-450 may be important in this regard. McGiff (1991) reported that cyclooxygenase inhibition with low concentration of indomethacin did not affect cytochrome P-450-dependent oxygenation. In contrast, high concentrations of indomethacin inhibit the cytochrome P-450 pathway (Capdevila et al, 1988). Indeed, 17-octadecynoic acid, an inhibitor of P-450 pathway of arachidonic acid increased RBF and impaired autoregulation in the rat

(Ai-Ping et al, 1994). This is contrasted with the data obtained in the dog: Cytochrome P-450 blockade by SKF-525 A, miconazole, or 17-octadecynoic acid were all ineffective in altering RBF or RBF autoregulatory efficiency (Pretus et al, 1994). These observations suggest that dose-dependent renal vascular actions may be less in the dog than in the rat. This coincides with the data obtained from our preliminary experiment, where doubling the infusion rate of indomethacin made no difference in the response of RBF. Furthermore, under our experimental conditions in which the synthesis of prostaglandins is enhanced (*i.e.*, during increases in ureteral pressure), *P*-450 dependent action of indomethacin, if any, could easily be overridden by its intended action. This condition would also help reduce the dose-dependent variation in the effect of indomethacin. Since the intravenous doses of both 5 and 10 $mg \cdot kg^{-1}$ indomethacin effectively blocked the increase in RBF in response to partial ureteral obstruction, the lower dose was chosen to avoid unwanted effects of indomethacin but to inhibit cyclooxygenase activity.

We maintained intravenous infusion rate high enough to obtain adequate urine flow. This maintenance of volume status during surgical preparation blunts the stress-induced increase in adrenergic and plasma renin activity and the subsequent production of prostaglandins (Terragno et al, 1977). This seems to be why the administration of indomethacin caused little change in RBF and systemic arterial pressure in the present experiment.

In conclusion, the effect of increased ureteral pressure on RBF autoregulation is independent of increased prostaglandin production. It can be deduced by means of exclusion that the reduced autoregulatory efficiency during partial ureteral obstructions is associated with the consumption of TGF-mediated vasodilation at normal RAPs.

ACKNOWLEDGEMENTS

This study was supported by Research Grant from Soonchunhyang University.

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