Exaggerated Prostaglandin Biosynthesis and Its Influence on Renal Resistance in the Isolated Hydronephrotic Rabbit Kidney

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ABSTRACT Basal and hormone-stimulated prostaglandin biosynthesis was compared in isolated perfused rabbit kidneys with and without ureteral obstruction. At 72 h there was enhanced responsiveness to bradykinin in the ureter-obstructed hydronephrotic kidney. The amount of prostaglandin-like substance released from the perfused kidneys by 25 ng of bradykinin was 533±163 ng from the ureter-obstructed, 28±4 ng from the contralateral, and 26±3 ng from the normal kidney. The enhanced response was also noted with angiotensin II and with norepinephrine. This exaggerated responsiveness by the ureter-obstructed kidney could not be explained by decreased prostaglandin (PG) destruction or by decreased renal peptide inactivation (bradykinin or angiotensin). There was no enhanced PG biosynthesis with exogenous arachidonate, suggesting there was no increase in cyclo-oxygenase activity in the ureter-obstructed kidney. Renal tubular transport of PG from medulla to cortex was apparently not essential for the enhanced PG biosynthesis to hormone stimulation since the same exaggerated responses were noted during perfusion with the ureter ligated. The cyclo-oxygenase inhibitor, indomethacin, increased basal perfusion pressure in the obstructed kidney and enhanced the magnitude and duration of the renal vasoconstriction produced by angiotensin II in the hydronephrotic kidney. These results suggest that the local exaggerated biosynthesis of PG may be occurring in the cortical resistance vessels and may be important to the alteration in blood flow and excretory function that occur in ureteral obstruction.

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INTRODUCTION

Elevation of ureteral pressure in the cat (1) inhibits vasoconstriction elicited by either neuronal stimulation or exogenous catecholamines. Inhibition of prostaglandin biosynthesis by indomethacin, a known inhibitor of the cyclo-oxygenase (2), diminished the inhibitory effects of increases in ureteral pressure. These observations suggested that the effects of ureteral pressure elevations on renal resistance were in part mediated by *de novo* prostaglandin biosynthesis.

Increasing experimental evidence points to a role for prostaglandins in regulating the renal circulation (3). Knowledge of the endogenous factors which control renal blood flow and glomerular filtration is central to the understanding of the basic excretory function of the kidney. Prostaglandin E_2 (PGE_2)[1] exhibits significant vasodepressor function (4), is naturetic (5), and its biosynthesis in ureteral obstruction may contribute to the regulation of regional renal resistance, naturesis, and alterations in excretory function.

The current studies were undertaken to examine the changes in renal prostaglandin biosynthesis occurring in a ureteral obstruction model of hydronephrosis in rabbits.

METHODS

Ureter obstruction. New Zealand male white rabbits weighing 2.5–3.5 kg were anesthetized with pentobarbital sodium (30 mg/kg, i.v.). Complete ureter obstruction was

[1] *Abbreviations used in this paper*: AII, angiotensin II; BK, bradykinin; CLK, contralateral kidneys; HNK, hydronephrotic kidneys; NE, norepinephrine, PG, prostaglandin(s); PGE_2, prostaglandin E_2; PLS, prostaglandin-like substance.

performed through a small abdominal incision by tying a silk suture around the left ureter near the bladder. The wound was closed, bathed in alcohol, and the rabbits were then treated with penicillin G (20,000 U i.m.). The animals were kept in individual cages and had free access to food and water.

Kidney perfusion. 3 days after ligation of the ureter, the animals were anesthetized with pentobarbital sodium (30 mg/kg, i.v.) and treated with heparin (250 U/kg, i.v.). The abdominal cavity was opened, and polyethylene catheters were tied into both renal arteries (PG 160, Clay Adams, Div. of Becton, Dickinson & Co., Parsippany, N. J.), and the kidneys were then removed from the animals. Thus, except where indicated during the perfusion experiments, the ureter of both hydronephrotic (HNK) and contralateral (CLK) kidneys were unobstructed. Both HNK and CLK were separately placed in warming jackets and perfused with oxygenated (95% O_2–5% CO_2) Krebs-Henseleit solution (37°C) and a constant flow rate (12 ml/min); thus, changes in perfusion pressure (measured with a Beckman type-4 327-0121 pressure transducer on a Beckman R-511A recorder [Beckman Instruments, Inc., Fullerton, Calif.]) reflect changes in renal resistance. Renal ischemia was achieved by temporarily diverting (with a three-way stopcock) the flow of perfusion fluid away from the renal artery and directly on to the assay organs.

Superfused organ system. Isolated assay tissues (rat stomach strip and chick rectum) were continuously superfused by the renal venous effluent (6). Both tissues were particularly sensitive to prostaglandins, especially of the E type. A mixture of antagonists was added to the superfusion fluid which rendered the assay tissues insensitive to catecholamines, acetylcholine, serotonin, and histamine (7). Indomethacin (10 μg/min) was also perfused directly over the assay tissues to eliminate the possibility that the assay tissues might release prostaglandins (8).

The response of the perfused kidney to the drug was determined by injecting the agent as a bolus of 0.1–0.2 ml into the Krebs-Henseleit perfusion media just proximal to the arterial cannula (i.e., through the kidney). The direct effect of the agent on the assay organs was tested (as a bolus injection) by adding the agent to the perfusion fluid after it had passed through the kidney (direct testing). Changes in smooth muscle tension were measured with a Harvard smooth muscle transducer (Harvard Apparatus Co., Inc., Millis, Mass.). Prostaglandin release was estimated by comparing contractions of the rat stomach and chick rectum strips to contractions caused by PGE_2 standard on these tissues. The assay organs contracted with a 25–30-s delay after the bolus injection of agonists and were frequently restandardized to known doses of exogenous E_2 directly over the strips to correct for any alterations in sensitivity during experiments. The loss of contractile responses to stimulation with bradykinin (BK), angiotensin II, and norepinephrine after pretreatment of the kidney with indomethacin suggested the substances or substance released into the venous effluent were prostaglandins. Subsequent data obtained after labeling the fatty acid pool with [^{14}C]arachidonic acid indicated that the ^{14}C counts released were essentially all as PGE_2 (see below) and that pretreatment of the kidney with indomethacin inhibited release of any ^{14}C counts as PGE_2.

The agonist hormones were randomly infused with the kidneys with each kidney having a dose-response curve to at least two agonists on any one day.

BK and angiotensin II were kept as stock solutions at concentrations of 1 mg/ml in saline and refrigerated at −20°C. The arachidonic acid was kept at −20°C in n-hexane at a concentration of 5 mg/ml and made up in aqueous solution, pH 9.0–9.5, each day of use.

The agonists (angiotensin II [AII], BK, and norepinephrine [NE]) have direct effects on the tissues. In the case of AII, the results were obtained with AII antagonist [Sar^1 Ile^8]-AII infused directly over the strips. This negated the direct effect of AII on the tissues. Since BK, as well as PGE_2, directly contracts the rat stomach, it was necessary to abolish with indomethacin the prostaglandin (PG) released into the effluent to visualize the direct effects of any unchanged BK coming through the kidney. The difference between these two values gives the amount of PGE_2 released as a consequence of hormone receptor interaction. The correction was only necessary with BK doses greater than 100 mg through the kidney since the kidney appeared to metabolize lesser doses, noted by no contraction of assay organs under the indomethacin-treated kidney. The direct effects of NE at doses used were blocked by phenoxybenzamine.

The data obtained by direct bioassay were correlated with acid lipid extractions of the PG from the venous effluent and bioassay of the extract.

Radiolabeling techniques. The renal phospholipids were prelabeled by infusion of the kidneys with [^{14}C]arachidonate (55 mCi/mmol, Amersham/Searle Corp., Arlington Heights, Ill.) by the procedure previously described (9). Further elucidation of the nature of the prostaglandin-like materials released from the kidney after hormone stimulation was obtained by extracting the renal venous effluent with ethyl acetate after adjustment to pH 3 with formic acid, evaporating the solvent, then chromatographing (with PG standards) the extract on silica gel-G plates in a chloroform:methanol: acetic acid:water solvent (90:8:1:0.8). Spots corresponding to the locus of a PGE_2 standard provided the recovery of a material that contracted the rat stomach and the chick rectum (i.e., the eluted material behaved identically to PGE_2 in the bioassay system).

Genetic hydronephrotic rats. The rats used were a gift of Dr. Denko Susic, University of Tennessee Memorial Research Centre, Knoxville, Tenn. This strain of Memorial Research Centre/Hydronephrosis rats develop congenital hydronephrosis (10). They were studied by superfusing the isolated rat kidney in a cascade as previously described. The rats studied had unilateral hydronephrosis (by gross morphological examination). This was determined by bivalving the kidneys at the end of the experiments. Grossly normal kidneys were compared with grossly abnormal (i.e. HNK) in their response to BK bolus injection through the kidneys. All the results are expressed as mean±SE. Statistical significance was determined by Student's *t* test based on paired data.

RESULTS

Hormone-stimulated PG release. The isolated perfused kidney removed from a rabbit after 3 days of unilateral ureter obstruction (HNK) exhibited a markedly enhanced response to hormone stimulation when compared to CLK and normal kidneys (i.e., from unoperated animals) (Fig. 1 and Table 1). AII was 10 times more potent in the HNK, inducing renal PG release (Fig. 1A). The amounts of prostaglandin-like substance (PLS) released at the doses of 25 and 100 ng were 192±36 and 712±208 ng, respectively, for HNK and 30±6 and 100±18 ng PLS, respectively, for CLK, $P < 0.01$. The response was not

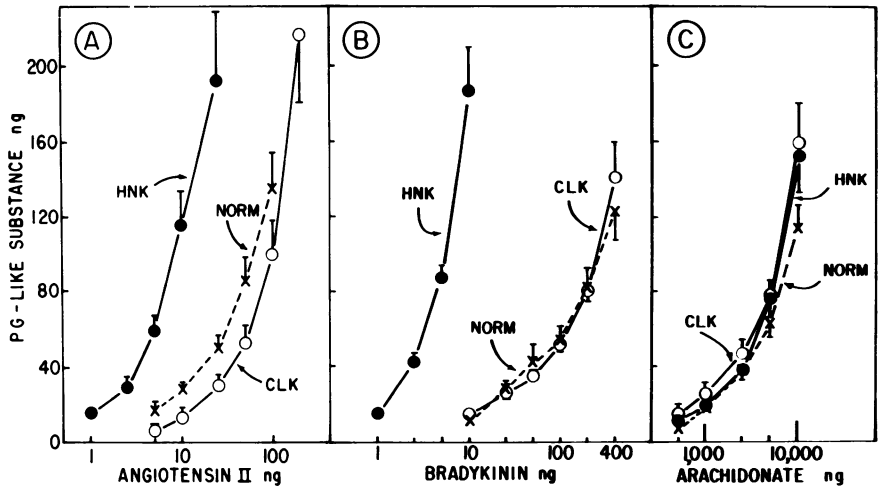

FIGURE 1 (A) Comparison of the angiotensin dose-response curve for renal PG release in HNK (i.e. ureter obstructed for 3 days but untied during the perfusion experiment), CLK (i.e. no ureter obstruction), and normal kidney (Norm, i.e., no prior surgery). At 3 days, the obstructed kidney weight was 50% greater than the CLK or normal control (i.e., 20±0.5 vs. 13±3 g, vs. 12±2 g [n = 12], respectively). The values shown are the mean ±SE, and n designates the number of kidneys. The PG-like activity in the renal venous effluent was calculated from dose-response curves obtained on the rat stomach strips in assays bracketed with a standard PGE_2 dose-response curve. (B) Comparison of renal PG release to BK. (C) Renal conversion of exogenous arachidonate to PGE_2.

significantly different between CLK and normal kidneys. The perfused HNK was extremely sensitive to the PG-releasing action of BK (Fig. 1B). The response to BK was concentration dependent and the dose-response curve was shifted sharply to the left and indicated a 40–50-fold increase in BK potency. The amounts of PLS released by a dose of 25 ng were 533±163 ng for HNK, 28±4 ng for CLK, and 26±3 ng for normal kidney, $P < 0.01$. We found that there was no difference in the BK-stimulated PLS release in ureter-tied vs. ureter-untied (during the perfusion) kidneys. Thus, when comparing the dose of BK needed to release 100 ng of PLS, the ureter-tied HNK required 5±2 ng (n = 4, vs. 6±1 with the ureter-untied [Table I]); whereas the ureter-tied CLK required 150±50 ng (n = 4, vs. 228±27 ng in the ureter-untied CLK [Table II]). Basal release in CLK was 1.7±0.6 ng PGE_2/ml of effluent and in HNK it was 4.3±1.1 ng PGE_2/ml effluent, $P < 0.05$.

A comparison of several humoral stimuli including AII, BK, and NE (four to six times more potent in the HNK), indicate the existence of a generalized enhanced renal sensitivity in the HNK (Table I). The PGE_2-like substance released by hormone stimulation was abolished by indomethacin (1 μg/ml) pretreatment, as indicated by loss of contractile activity of the assay organs.

The experiments presented thus far all relied on

TABLE I
Comparison of Humoral and Nonhumoral Stimuli for Renal PG Biosynthesis

Treatment	Units	Dose needed to release PLS equivalent to 100 ng PGE_2		
		HNK	CLK	Normal
AII (8)	ng	10±2	107±26	115±28
BK (7)	ng	6±1	228±27	271±64
NE (6)	ng	122±27	544±93	755±100
Arachidonate (5)	ng	4,900±1,000	5,900±600	6,800±2,000
ATP (8)	μmole	0.26±0.5	0.52±.08	0.46±0.11
1-min Ischemia (6), *ng PLS released*		305±83	107±27	119±26

The values are the means±SE; the number in parentheses indicates the number of kidneys tested.

TABLE II

Effect of Indomethacin on Renal Perfusion Pressure with and without Maintenance of the Ureter Obstruction during the Perfusion Experiment

	HNK				CLK			
	Ureter untied + INDO		Ureter tied + INDO		Ureter untied + INDO		Ureter tied + INDO	
Basal PP, *mm Hg*								
	41±4	54±8	47±1	62±5	44±3	48±4	45±3	48±3
ΔPP, *mm Hg*								
AII, ng								
10	19±5	25±3	23±10	39±6	17±4	20±11	27±7	21±3
100	47±6	67±5	50±8	78±6	49±7	43±11	56±3	48±13
400	73±9	94±9	70±9	91±9	76±16	85±15	75±3	76±7
n	8	—	4	—	4	—	3	—

Normal kidneys were also tested but were not significantly different from CLK. PP, perfusion pressure; ΔPP, change in perfusion pressure produced by the drug treatment; INDO, 1 μg/ml indomethacin infused continuously through the kidney.

bioassay techniques for the identification of PG-like activity in the renal venous effluent after hormone stimulation. Such assay techniques cannot readily distinguish between such arachidonate metabolites as PGE_2 or $PGF_{2\alpha}$, or such novel products as 6-keto-$PGF_{1\alpha}$ (9). We therefore repeated the above experiments in perfused HNK that we pretreated with [^{14}C]-arachidonic acid to label the renal phospholipid pool (9). Acid-lipid extraction and thin-layer chromatography of the renal venous effluent of such labeled kidneys revealed that [^{14}C]PGE_2 was the primary product after BK treatment (Fig. 2).

Thus was further documented by using two solvent systems: (*a*) benzene:dioxane:acetic acid (60:30:3), and (*b*) chloroform:methanol:acetic acid:water (90:8:1:0.8) for the separation, confirming that PGE_2 was the major arachidonate metabolite released. Indomethacin pretreatment completely abolished the PGE_2 peak in the radiochromatogram. There was a dose-dependent increase of [^{14}C]PGE_2 release with increasing concentrations of BK, which was especially apparent in the perfused HNK (Fig. 3). The enhanced sensitivity for PLS release (Fig. 1) to BK in the ureter-obstructed compared to the contralateral unobstructed kidney is also strikingly evident when comparing the release of [^{14}C]PGE_2 from the prelabeled phospholipid pool (Fig. 3).

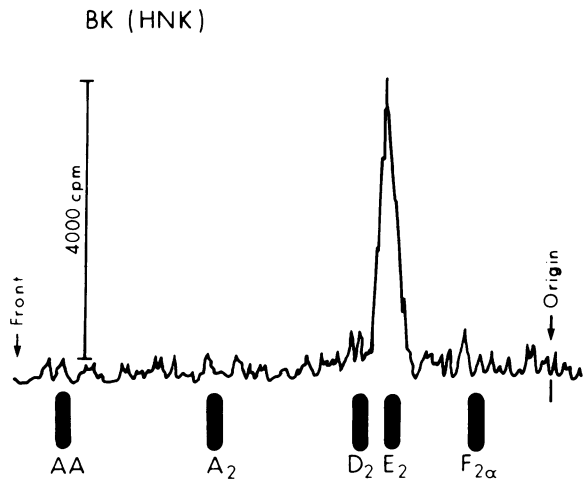

FIGURE 2 Radiochromatogram of the acid-lipid extract of the renal venous effluent after stimulation of a hydronephrotic rabbit kidney with 200 ng of BK. The black spots indicate the migration of known unlabeled standards run on the same plate.

Nonhormonal renal PG stimulation. Renal PG biosynthesis and release also resulted from ATP administration or a brief ischemic episode. The obstructed kidney was more sensitive to these treatments than the CLK and normal kidneys (Table I). PG release induced by exogenously injected arachidonic acid was not different among HNK, CLK, and normal kidneys (Fig. 1C and Table I).

This suggests one of two possibilities: (*a*) that there is no difference in cyclo-oxygenase activity in the HNK as compared with CLK, or normal kidneys, or (*b*) that there is an intrinsic difference between endogenous and exogenously administered arachidonic acid. Further experiments would be necessary to determine if the latter possibility is correct.

Renal perfusion pressure. Angiotensin produced a dose-dependent increase in perfusion pressure in the three types of isolated perfused kidneys (Table II). Indomethacin treatment substantially increased basal perfusion pressure in the obstructed kidney (Table II), and enhanced the magnitude and duration of the renal vasoconstriction produced by AII in the HNK (Fig. 4), but the indomethacin was without effect on the CLK (Table II). Furthermore, there was no significant difference in PLS release or perfusion pressure changes

produced by AII when the ureter was left obstructed, or if the ureter was untied during the time of perfusion (Table II). This experiment suggests that tubular transport of PG to the cortex is not essential for the supersensitivity since there is no bulk fluid transport along the tubule with complete ligation of the ureter.

Congenital hydronephrosis. BK injected as a bolus into the isolated perfused rat kidney with genetic hydronephrosis over a range of 40–400 ng showed a dose-dependent increase in PLS release ($P < 0.02$) (Fig. 5).

Degradation of AII, BK, and PGE_2. Some possible explanations for the enhanced PLS release by the HNK would include a decreased rate of PG metabolism, or a decreased rate of peptide destruction. Therefore, the degradation of AII, BK, and PG was determined in the three kidney types by directly testing the contractile response of the agonists on the assay tissues and comparing the contractile response produced by the agonists injected through the indomethacin-treated kidney (Fig. 6). About 50% of the exogenously administered PGE_2 and about 80% of the exogenous AII was removed by the perfused kidneys in one transit, but there was no difference between the kidney types (Fig. 6A and B). The HNK exhibited a significant reduction (about two to threefold) in BK metabolism compared to CLK and normal kidney (Fig. 6C), but the shift was not enough to account for the 40-fold increase in PLS release produced by BK in the HNK (Table I, Fig. 1).

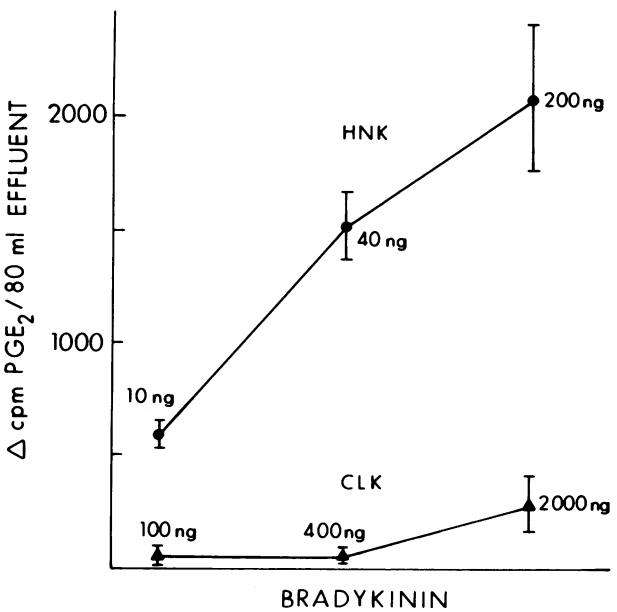

FIGURE 3 Dose-dependent release of [^{14}C]PGE_2 by BK. The renal venous effluent was collected after BK administration during the time when there was demonstrable bioassayable PLS. The pooled effluent was extracted and chromatographed as described in Methods. The values are the means±SE ($n = 4$).

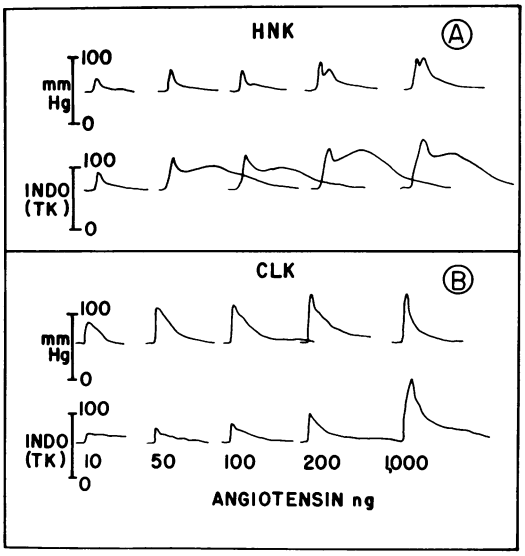

FIGURE 4 The effect of AII on renal resistance in the presence or absence of indomethacin. (A) HNK; (B) CLK; INDO, 1μg/ml indomethacin; TK, continuously infused through the kidney. The duration of increased resistance of the nonindomethacin-treated CLK with the 10-ng dose of AII is 5 min. The duration of increased resistance at the other doses can be compared to this time coordinate.

BK injections less than 100 ng did not appear as intact unchanged peptide in the venous effluent and presumably were completely degraded in the kidney. However, at much lower doses than 100 ng BK, very high concentrations of PLS were released from the HNK. Thus, it is not possible to directly compare the mean effective dose (ED_{50}) for PLS release with the ED_{50} for destruction. Thus, the dose of BK required for 100 ng PLS release is 6±1 ng BK in HNK and 228±27 ng BK in CLK ($P < 0.01$).

DISCUSSION

These results demonstrate that ureteral obstruction initiates an enhanced basal release of PGE_2 which is further exaggerated with peptide hormone stimulation. PG are not stored, but release represents *de novo* biosynthesis. Therefore, ureteral obstruction in some way increases the capacity of the kidney to synthesize PG. BK and AII markedly shift the dose-response curve to the left for the appearance of PG when determined with bioassay or radiochemical techniques (Figs. 1 and 3). These dose-response curves are not strictly comparable since the [^{14}C]arachidonic acid labels only a small portion of the total phospholipid pool which is then only partially released by hormone stimulation. The data, however, do show that the major PG released is PGE_2, and for similar total incorporation of label

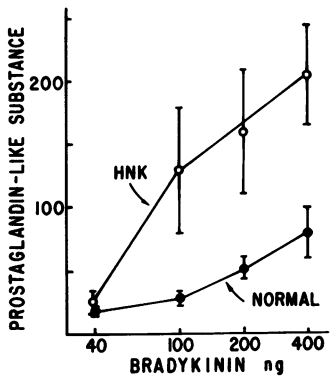

FIGURE 5 BK-induced PG biosynthesis in the congenital hydronephrotic rat. The extent of renal involvement was differentiated after the perfusion experiment by the presence or absence of calyceal dilation and distortion. The values represent the mean±SE (n = 6).

(i.e. ^{14}C counts in the kidney phospholipids), there is a marked release of ^{14}C counts as PGE_2 in the HNK as compared with the CLK. Pretreatment of the labeled kidney with indomethacin inhibited release of radioactive or bioassayable PGE_2.

The observation that exogenous arachidonate produced no enhanced release of PGE_2 in HNK as compared with the CLK suggests that there may be no difference in cyclo-oxygenase activity in the two experimental conditions. The sensitivity for PG release in the HNK could also be the result of enhanced phospholipase A_2 activity or deficient reacylation which determines the availability of endogenous arachidonic acid for the cyclo-oxygenase. An additional possibility is that exogenous arachidonic acid may not mimic the effects of endogenous arachidonate released by the hormone stimulation. Such a situation could occur because of compartmentation of synthetic enzymes or because of differences in concentration achieved when comparing exogenous and endogenous fatty acid.

A marked increase in the number and the triglyceride content of the renal medullary interstitial cell lipid droplets and a decreased rate of $PGF_{2\alpha}$ synthesis have been observed with either ureter obstruction or indomethacin treatment in rabbits (11, 12). Contradictory data, however, are available in the rat (13), where a reduction of lipid granularity of interstitial cells was observed with indomethacin. Medullary interstitial cell lipid droplet triglycerides have been advocated as storage pools for PG precursors (14) and the renal vasoconstriction after chronic ureter obstruction was suggested to be due to loss of vasodilator PG (15). Our data show no loss of vasodepressor PG but in fact we observe a marked enhanced PG release (Fig. 1) which can be demonstrated even after 6 wk of ureter obstruction (data not shown). Indeed the primary renal pool of the PG precursor arachidonic acid is in the phospholipids (11) rather than in the triglyceride stored in medullary lipid droplets. Thus, we believe that there is a clear dissociation between renal PG biosynthesis and the triglyceride content and number of interstitial lipid cell droplets.

The resistance vessels in the kidney reside mainly in the cortex. However, the major area of PG biosynthesis is in the medulla. This suggests that if medullary PG were influencing cortical resistance,

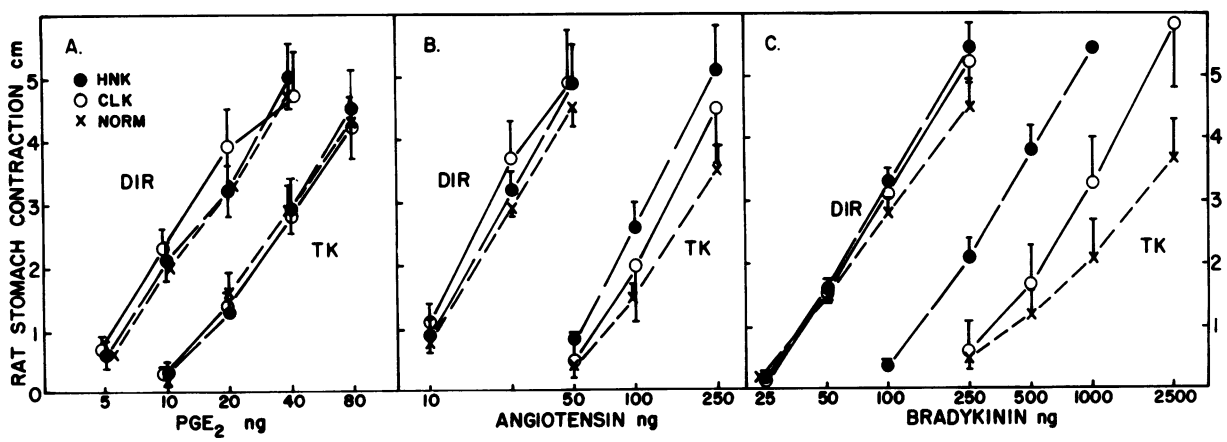

FIGURE 6 Renal clearance of PG, AII, and BK. Standards of PGE_2, AII, or BK were injected directly (DIR) across rat fundal stomach strips and the response was compred to that obtained by injecting the standards through the kidney (TK). The rat stomach strip contracts in response to added PGE_2, AII, or BK. The kidneys were treated with indomethacin, thereby eliminating any renal PLS release and permitting evaluation of the unchanged agonist only. The values represent the mean±SE for five experiments with each agonist.

then some pathway of movement from medulla to cortex had to be involved. There was no difference in sensitivity to hormone stimulation whether the ureter of the HNK was ligated or released during the perfusion experiments (Table II). This observation suggests that tubular movement of PG, which has previously been described (16, 17), was not critical for expression of the enhanced sensitivity. Another suggestion is that the PG synthesized in the medulla are transported via vascular channels, e.g., vasa recta (18), into the cortex. The vasa recta which loop downwards towards the papilla are mainly associated with juxtamedullary and medullary nephrons which constitute only about 20% of the total nephron population (19). These ascending vas recta never really become cortical vessels but instead drain into the venous system (20). This means that they are not in close apposition to cortical resistance vessels. Therefore, in the absence of close anatomical interrelationships to afferent and efferent glomerular arterioles, any PG synthesized in medulla and transported to corticomedullary area by vasa recta would have to diffuse into and around the cortical resistance vessels. This region of the kidney is known to have significant PG dehydrogenase activity (21). These two factors, lack of significant cortical flow of vasa recta and high cortical PG dehydrogenase activity, make it very unlikely that the vasa recta play a significant role in medullary-cortical transport of PG. Since the major resistance vessels are cortical (22), then any PG-like material which influences cortical resistance must either be synthesized locally in the cortex or be transported to the medulla by some other pathway not yet described. Enhanced basal and hormone-stimulated synthesis in the HNK was also evident by the increase in perfusion pressure produced by indomethacin. Indomethacin also enhanced and prolonged the AII-induced vasoconstriction (Fig. 4 and Table II), suggesting that the drug inhibited the synthesis of a vasodilator PG. Cortical biosynthesis of PG has been demonstrated by Larsson and Änggård (22) and others (23). This observation, coupled with the previous demonstrations of PG biosynthesis in blood vessel walls (24–28), would suggest that local synthesis in cortical resistance vessels may be occurring. This would fit very nicely with the concepts of local circulatory control involving PG biosynthesis.

The isolated Krebs perfused rabbit kidney has markedly compromised excretory function (29, 30). It excretes sodium in the same concentration as that of perfusate and does not concentrate urine. This observation makes it very difficult to interpret the enhanced sensitivity in the context of excretory function. However, the finding of enhanced basal and hormone-stimulated release of PGE_2, a potent vasodepressor and naturetic substance, may have several potential functions. Firstly, the PGE_2 may be a protective mechanism initiated to overcome the severe renal vasoconstriction and decrease in glomerular filtration rate normally associated with chronic hydronephrosis (31–35). Secondly, since PGE_2 is known to be naturetic (5), the enhanced PG biosynthesis in hydronephrosis may explain the reduction in sodium reabsorption and naturesis associated with ureter obstruction and could conceivably by involved in the enhanced sodium excretion in postobstructive diuresis. Lastly, since PG have have been shown to inhibit the response to antidiuretic hormone (36); the enhanced release in the HNK may explain in part the reduction in concentrating ability which occurs in obstructive uropathy.

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