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Participation of renal cortical prostaglandins in the regulation of glomerular filtration rate

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The intimate linkage between glomerular filtration rate (GFR) and sodium chloride excretion requires close control of glomerular hemodynamics in order to maintain body fluid and electrolyte homeostasis. Other papers in this symposium have dealt with evidence that prostaglandins (PG's) may influence sodium excretion by direct transport effects. This paper will be confined to evidence for PG's participation in the hemodynamic control of GFR. Numerous experimental studies over the past years have identified single factors exerting GFR control and have elucidated their interplay in various conditions. Perturbations that induce changes in filtration forces result in a complex array of regulatory mechanisms that tend to minimize deviations from the set value. The final setting of glomerular vascular tone and therefore of renal blood flow (RBF) and GFR results from an interaction of general intrinsic and specifically intrarenal myogenic mechanisms with local hormonal systems. Initial studies of the role of PG's in this system were contradictory and at times difficult to interpret. It is now becoming clear that some of the apparent contradictions were a consequence of the complex interaction of the vasoconstrictor and vasodilator systems of the kidney whereas others reflected methodologic difficulties both in measurements of PG's and in the use of PG synthesis inhibitors. Although contradictions remain, evidence has accumulated that points to an important and occasionally central role of PG's in the control of vascular resistance and thereby of GFR.

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Cortical formation of prostaglandins

Formation of glomerular filtrate is an exclusive task of the renal cortex. Until about 10 years ago renal cortical tissue was not believed to generate PG's, but it is now clear that PG's are formed and can therefore act in the cortex without being transported there from synthetic sites in the medulla [1–3]. Because PG's in general appear to act close to their site of synthesis, formation within the renal cortex makes it more likely that modulations in PG synthesis and degradation exert a local regulatory function. Microsomal fractions from renal cortical tissue convert arachidonate and PGG_2 predominantly to 6-keto-$PGF_{1\alpha}$, the relatively stable metabolite of prostacyclin PGI_2 [4]; this compound is found in the renal cortex in greater amounts than other arachidonate metabolites [5]. Endothelial cells of all arteries and arterioles as well as epithelial cells of Bowman's capsule and mesangial cells of the glomerular tuft (at least in some species) have been identified as the cortical sites of localization of PG cyclooxygenase [6]. In agreement with the anatomical localization of PG synthetase is the finding that microdissected renal arteries and arterioles convert arachidonate into 6-keto-$PGF_{1\alpha}$, PGF, and PGE, with the PGI_2 metabolite being the major product [7]. Isolated glomeruli of the rat generate primarily PGE_2 and PGF_2, but small amounts of PGI_2 and thromboxane B_2 are also formed [8, 9]. In contrast, proximal and distal tubules do not seem to possess cyclooxygenase [6] and are not able to generate PG's [7], which agrees with the apparent absence of a direct transport effect in these tubular structures. Although it was initially concluded that certain arachidonate metabolites were exclusive products of either the cortex or the medulla, more sensitive and specific methods have forced revision of this conclusion. The localization within different

regions of the kidney of synthesis of specific PG's appears to be less sharply demarcated than was originally thought [10, 11].

Influence of prostaglandins on resting vascular tone

Renal cortical PG's are apparently not involved to a significant extent in determining the resting tone of renal resistance vessels. In conscious normovolemic animals, rates of urinary PG excretion and rates of PG secretion into the vascular bed are relatively low [12, 13]. This is in a way analogous to the low tonic stimulation that the kidney vasculature receives normally through sympathetic efferents and to the low basal rates of renin secretion. As a reflection of the low level of PG release under control conditions, administration of inhibitors of PG synthesis, the most studied being the nonsteroidal antiinflammatory drugs (NSAID), is not followed by marked changes in renal resistance: in the normal awake state, both RBF and GFR are generally unaltered by these drugs [12, 14–22]. For several reasons, however, it is not possible at present to exclude totally an influence of PG's on resting renal vascular tone even in conscious normovolemic animals. PG's are formed by the kidneys in this state [12, 13, 21]. Furthermore, a modest reduction of RBF [15, 23] or GFR [19] by NSAID has occasionally been observed in conscious dogs. Finally, there are doubts about the adequacy of the inhibition of PG synthesis: basal levels of PG formation were found not to be blocked at all [12] or only incompletely [18, 21] by NSAID administration, and the stimulation of PGE excretion by water immersion could not be prevented by indomethacin even though base-line PGE excretion was reduced [24]. The main problem is that rates of urinary excretion or vascular secretion are only a rather crude index of the activities of PG's at cellular sites of synthesis. This is particularly true for PG's generated in the cortex, because they are assessed against the background of the much greater amounts of PG's originating in the renal medulla. Similarly, the degree of inhibition of biosynthetic activity by NSAID may not be homogenous within different regions of the kidney [25]. As long as PG synthesis as well as local metabolism and inhibition cannot be assessed directly, uncertainties will remain about the role of these compounds in intracortical physiologic events.

Protective effect of prostaglandins

In marked contrast to the modest contribution of PG's to the resting tone of renal resistance vessels is the important role that must be attributed to PG's whenever maintenance of appropriate renal perfusion and formation of filtrate is threatened. Renal release of PG's or PG-like material is elevated following a reduction of renal perfusion pressure [26–29], and in hypovolemic states induced either by blood loss [30, 31], low sodium chloride diet [3, 32–34], or anesthesia-laparatomy [12, 13] even without marked changes of arterial pressure. PG synthesis is also increased in glycerol-induced renal failure [35], in endotoxin-induced shock [30, 36], and during elevated ureteral outflow resistance [37, 38]. Administration of NSAID to anesthetized and laparotomized animals is followed by an increase of renal vascular resistance [12, 14, 20, 39–44]. The deterioration of glomerular function can under some conditions be quite dramatic. For example, hemorrhagic hypotension inducing a 30% reduction of arterial pressure in anesthetized-laparatomized dogs was associated with only modest reductions of RBF and GFR with the PG system intact; however, a large fall of GFR was observed when indomethacin was administered [45]. Marked deterioration was also demonstrated in salt-depleted animals during partial renal arterial constriction [46] and in glycerol-induced renal failure [47]. Hypoxemia in fetal lambs induced by hypoxic breathing of the ewe for 5 to 7 min did not reduce RBF unless PG synthesis was inhibited [48]. During partial chronic unilateral constriction of the ureter, GFR of both single nephrons and whole kidney were well maintained; but, after the administration of indomethacin or meclofenamate, both glomerular plasma flow and GFR fell significantly [49]. Protection of glomerular function by PG's could also be demonstrated during infusion of angiotensin II (AII). Although AII alone had only a small effect on GFR, a marked reduction was observed when NSAID were given together with AII [50]. From these and similar studies, one may conclude that increased synthesis of vasodilatory PG's is required to effectively counteract other mechanisms that would cause resistance to rise and RBF and GFR to fall.

Prostaglandins and autoregulation

It has been a logical suggestion to implicate PG's in the reduction of renal vascular resistance during reduction of renal perfusion pressure, a phenomenon generally referred to as autoregulation of RBF or GFR. Initial studies in isolated dog kidneys indeed supported such a role for PG's [27]. Results from more recent experiments in both dog and rat have led to the prevailing opinion that PG's are not

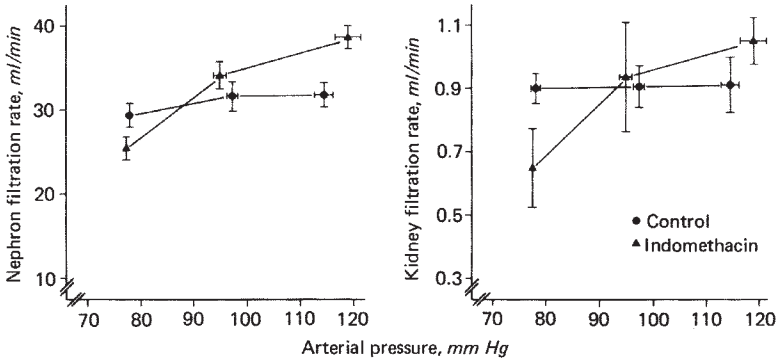

Fig. 1. *Relationship between nephron filtration rate* (left) *and kidney filtration rate* (right) *and mean arterial pressure in control rats* (circles) *and rats treated with indomethacin* (triangles). Values are the means ± SEM.

involved to a significant extent in autoregulatory adjustments [43, 51–55]. Because in most of these studies only RBF was measured [43, 52–55] we reinvestigated the response of kidney GFR and nephron GFR (SNGFR) to reduced renal perfusion pressure. In rats in which the laparatomy-induced reduction of plasma volume was ameliorated by plasma replacement, reduction in arterial pressure to about 75 mm Hg was associated with excellent autoregulatory responses (Fig. 1). Sensitivity of SNGFR to changes in arterial pressure (ΔSNGFR/ΔAP) was 0.006 nl·min^{-1}·mm Hg^{-1} during pressure reduction from 115 to 95 mm Hg and 0.126 nl·min^{-1}·mm Hg^{-1} during pressure reduction from 95 to 77 mm Hg. The SNGFR – AP slope in the nonautoregulating pressure range 77 to 57 mm Hg (0.58 nl·min^{-1}·mm Hg^{-1}) may be taken as an estimate of the sensitivity of SNGFR to changes in arterial pressure in the absence of compensatory resistance changes. From this estimate, we calculate that completeness of autoregulation was 99% and 78% in the upper (115 to 95 mm Hg) and lower (95 to 77 mm Hg) pressure ranges, respectively. In the presence of indomethacin (2 mg/kg plus 5 mg/kg per hour), SNGFR became more pressure dependent: sensitivity increased significantly to 0.15 nl·min^{-1}·mm Hg^{-1} in the pressure range 115 to 95 mm Hg and to 0.47 nl·min^{-1}·mm Hg^{-1} in the pressure range 95 to 75 mm Hg (Table 1 and Fig. 1). Completeness of autoregulation was reduced to 75% and only 21% in the two pressure ranges, respectively. We estimate that in the pressure range from normal to 95 mm Hg, at least 25% of the observed regulatory adjustment is in some way PG-dependent, whereas in the pressure range 95 to 77 mm Hg PG-dependency increases to at least 80%. It appears that inhibition of PG synthesis is associated with a reduced capability of renal resistance vessels to dilate following reduction of arterial pressure and

Table 1. Relationship between SNGFR and arterial pressure (sensitivity), completeness of autoregulation of SNGFR, and contribution of prostaglandins to autoregulatory adjustments in rats

	Pressure range		
	115 to 95 mm Hg	95 to 77 mm Hg	77 to 55 mm Hg
Sensitivity (ΔSNGFR/ΔAP), *nl · min^{-1} · mm Hg^{-1}*			
Control	0.006	0.126	0.61
Indomethacin	0.15	0.47	0.56
Completeness of autoregulation			
Control	99%	78%	—
Indomethacin	75	21	—
Contribution of prostaglandins to autoregulation	25%	80%	—

that this dependency of autoregulatory capacity on PG's is most pronounced in the lowest pressure range associated with maintained function. Our results also show that at some pressure glomerular function decreases with identical slopes whether PG's are synthetised or not (Fig. 2). The pressure at which this occurs, however, is significantly lower with the PG system intact. Similarly, protection of renal circulation during hemorrhagic hypotension by PG's has been shown to be limited to a certain pressure range. If hemorrhage is great enough, neither a protective effect of PG synthesis stimulation by arachidonate [56] nor a deleterious effect of NSAID [44] on renal function is observed.

Mechanism of protective action of prostaglandins

Direct intrarenal vascular effects. Although there are strong arguments for the concept that variations in the synthesis and release of PG's protect GFR by maintaining RBF, the mechanisms for this action are not fully understood. The possibility that the influence of PG's on renal perfusion is a reflection

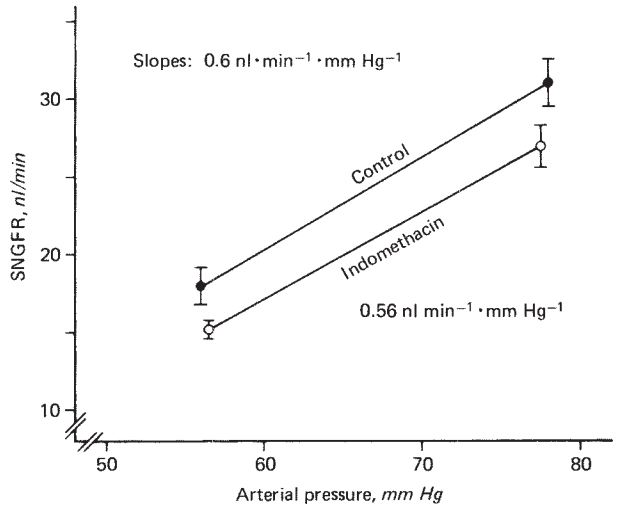

Fig. 2. *Relationship between filtration rate of single nephrons and mean arterial pressure in the nonautoregulating pressure range of 77 to 55 mm Hg.* Values are the means ± SEM.

of cardiac actions of these agents will not be considered in detail in this paper. One should keep in mind, however, that administration of NSAID [19, 23, 46] is often associated with bradycardia, and that reduced cardiac output may contribute to the deterioration of glomerular function following NSAID.

In those situations in which enhanced PG synthesis is accompanied by a reduced renal vascular resistance, such as during reduction of renal perfusion pressure by aortic constriction, the beneficial influence of PG's could be explained by the vasodilatatory properties of these agents. It is well established that both PGE_2 [57–65] and PGD_2 [65] induce vasodilatation when infused into the kidneys of dogs or rabbits, whereas $PGF_{2\alpha}$ probably has no vascular effect [61, 63, 66, 67]. Similarly, infusion of arachidonate leads to an increase of blood flow that is most pronounced in the inner cortex [66–68]. Species dependency of the renal vascular effect of PGE_2 and PGD_2 has been suggested by several reports that these PG's as well as arachidonate increase renal vascular resistance in the rat [69–71]. These results are controversial, however. PGE_1 infused into rat kidneys in vivo reduces both afferent and efferent arteriolar resistance, resulting in an increase in plasma flow through individual glomeruli [72]. PGI_2 is the only major arachidonate metabolite that induces unequivocal reductions of renal vascular resistance in both dogs and rats [65, 71, 73, 74]. The simplest explanation for the protective effect of PG's on renal function would be that a challenging event stimulates the synthesis of vasoactive PG's in renal cortical vessel walls and that their local action results in the reduction of resistance required to maintain organ perfusion and function.

In circumstances in which enhanced PG synthesis is accompanied by increased renal vascular resistance, a role for vasoconstrictor metabolites of arachidonate such as endoperoxides [75] and thromboxanes can be considered. Thromboxane formation appears to be elevated in hydronephrotic kidneys [76], and imidazole, an inhibitor of thromboxane synthesis, ameliorates the vasoconstriction that follows release of ureteral obstruction [77]. Another condition in which thromboxane is formed is in glycerol-induced acute renal failure [78], and it has therefore been implicated in the increased vascular resistance in this condition. It is difficult at present to evaluate the importance of the vasoconstrictor PG's.

Interaction of prostaglandins with vasoconstrictor influences. A number of experimental findings are not simply explained by the direct vascular effects of PG's. This evidence indicates that most challenging events activate vasoconstrictor and vasodilator systems simultaneously and that the final setting of renal resistance represents the net effect of these excitatory and inhibitory influences. Whether or not a vasodilatory effect of PG's is observed depends in part on the activity of the opposing vasoconstrictor influences. Thus, for example, during hemorrhagic hypotension an intact PG system does not prevent net vasoconstriction; rather, it attenuates the impact on kidney function of vasoconstrictor systems activated at the same time. One would thus predict that blockade of vasoconstrictor effects might lead to improvement in the reduced kidney function resulting from inhibition of PG synthesis. And in fact, NSAID have been shown to have a deleterious effect on GFR and RBF during hemorrhagic hypotension, but to be without effect when the kidneys were denervated and received an AII antagonist [45]. These results identify the sympathetic nervous system and the renin-angiotensin system as main vasoconstrictor elements acting in the renal vasculature. In agreement with this are the observations that blockade of PG synthesis augments the vasoconstrictor response to administration of AII [15, 28, 53, 79], to catecholamines [15, 80–82], and to nerve stimulation [69, 82]. Support for simultaneous opposing actions of endogenous PG vasodilator and AII vasoconstrictor systems is also furnished by the observations that

by and large when NSAID's induce vasoconstriction vasodilatation is noted with AII antagonists [83–86].

Activation of renin-angiotensin system by prostaglandins. Prediction of the resultant net effect on vascular resistance is complicated further by the fact that vasodilator and vasoconstrictor systems are not only activated at the same time, but that they appear to activate each other. Coactivation of antagonistic systems by PG's may explain why indomethacin has been observed in some instances to be without discernible effects on kidney function in anesthetized laparotomized animals [28, 49, 53]. Assuming that PG's not only have a direct relaxing effect on vascular smooth muscle, but also stimulate generation of agents mediating vasoconstriction, then the effect of PG synthesis blockade and PG administration is not necessarily predictable. Recent preliminary results illustrate this particular issue [87]. In this study, infusion of PGI_2 into rat kidneys was followed by an increase of efferent arteriolar resistance rather than by the expected decrease. This vasoconstriction could be converted into vasodilatation by simultaneous administration of the AII antagonist saralasin. Thus, application of the vasodilator PGI_2 resulted in net vasoconstriction apparently because of coactivation and action of endogenous AII. The vasodilator property of PGI_2 became predominant only after blocking the effect of AII. This result is in all likelihood a functional consequence of the increased renin release that is initiated by exogenous [46, 88] or endogenous PG's [89–91]. Although PG endoperoxides [75, 91] and PGD_2 [65, 93] have been shown to elevate renin release, PGI_2 is the arachidonate metabolite that most consistently exerts this effect [93–96]. Because AII in turn increases PG synthesis [38, 97–100], the PG-angiotensin interrelationship should theoretically possess the properties of an autoregenerative or positive feedback system. The factors controlling unlimited self-augmentation within the PG-angiotensin cycle are not fully identified. Rapid local metabolism of the vasoactive compounds may be important in limiting active concentrations [101]. Although it contributes to our difficulty in untangling the complexities of the control of RBF, the simultaneous coactivation of vasoconstrictor and vasodilator systems may have functional advantages for the kidney. In the case of a challenge to extracellular volume, for example, the simultaneous intrarenal activation of angiotensin and PG's permits angiotensin to exert its extrarenal effects (maintenance of arterial blood pressure, release of mineralocorticoids, stimulation of thirst, and so on) without compromising renal function by its intrarenal vasoconstrictor action.

Interaction of prostaglandins with catecholamines. It has been mentioned already that another vasoconstrictor system that interacts with renal PG's is the catecholamine-sympathetic nervous system. Both catecholamines and nerve stimulation elevate renal PG synthesis and release [38, 102–105]. As already pointed out, PG's attenuate the vasoconstrictor effect of nerve stimulation and catecholamines, and conversely, NSAID's augment it [15, 69, 80–82]. The mechanism of this interaction may in part be related to the reduction of transmitter release from presynaptic vesicles associated with PG administration [106, 107]. Experimental evidence elucidating the functional importance of the antagonistic effect of PG's on nerve-induced vasoconstriction is relatively scarce. As mentioned earlier, the marked deterioration of renal function induced by NSAID during severe hemorrhagic hypotension could be partly prevented by protecting against endogenous AII with saralasin, but full protection was seen only when in addition the kidneys were denervated [45].

The interdependency of vasoactive mechanisms becomes even more complex when one takes into account the older result that catecholamines and renal nerves stimulate renin release [108–111], an effect that is in all likelihood mediated through β-receptors [111–113]. This interrelationship is illustrated by studies on the effect of hemorrhage on renin release and glomerular function [45]. It was found that during mild hemorrhage, in contrast to severe hemorrhage, administration of NSAID had no marked deleterious effect on glomerular function [114]. The moderate reduction in RBF and GFR observed could be prevented by giving the adrenergic antagonist propranolol in addition to NSAID. The protective effect of NSAID and propranolol is probably explained by blockade of the increase in renal renin secretion normally induced by hemorrhage. Propranolol alone or NSAID alone did not prevent an augmented renin release. One may conclude from these results that during less severe stimulation renin release is to a relatively larger extent driven by PG's. Removal of PG's by NSAID under such circumstances, particularly in combination with removal of other factors promoting renin release, can then be expected to assist in maintaining glomerular function. In contrast, during severe

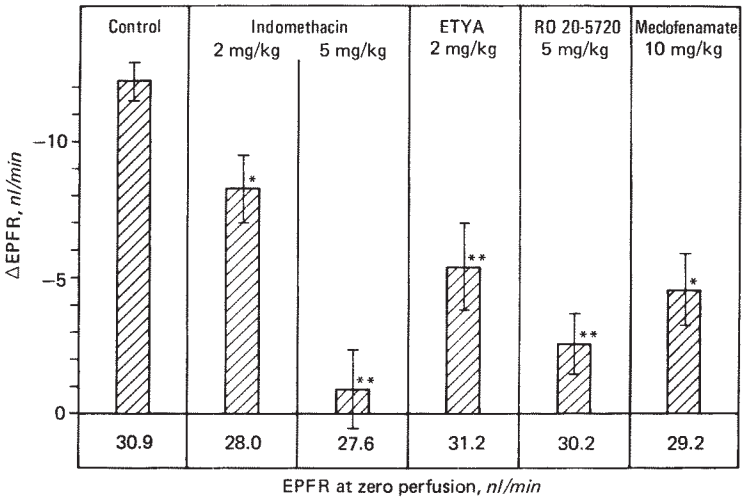

Fig. 3. *Changes in early proximal flow rate (EPFR) induced by elevating perfusion rate in the loop of Henle from 0 to 40 nl/min in rats before (control) and after the i.v. administration of four different inhibitors of PG synthesis.* Values are the means ± SEM, and asterisks indicate changes significantly different from control [126].

degrees of vasoconstrictor influences, renin release is driven mainly by factors independent of PG's, for example by reduced perfusion pressure and increased sympathetic nerve impulses. Removal of PG's by NSAID would then augment net vasoconstriction because the vascular effects of sympathetic nerves and AII are unopposed by PG's and because, in view of other strong drives for renin release, the beneficial effect of PG blockade on renin release becomes negligible.

Interaction of prostaglandin and kallikrein systems. Net balance of vasomotor effects at the level of glomerular arterioles may be tipped toward vasodilatation by another effect of PG's. It has been shown that PG's activate renal kallikrein [115, 116] and thereby the level of the potent vasodilators kallidin and bradykinin. In turn, bradykinin induces an increase of PG synthesis [29, 38, 117–120], probably by activation of phospholipase A [121]; conversely, aprotinin, a nonspecific inhibitor of proteases, reduces urinary output of both kallikrein and PGE [122]. Because bradykinin is a vasodilator, it may be a factor associated with maintaining RBF and GFR under conditions in which intrarenal formation of angiotensin and other vasoconstrictors is elevated. In fact, angiotensin itself may stimulate the release of kallilrein, thereby limiting its vasoconstrictor potency within the kidney [123]. This is also supported by parallel changes of urinary or plasma kallilrein levels with plasma renin activity during acute [124] or chronic [125] changes in salt intake. The exact nature of the interrelationship between bradykinins and PG's is difficult to evaluate at the present time. It appears, however, that their effects are additive and not mediated through each other, because bradykinin vasodilatation is observed after NSAID administration [119, 120].

Role of prostaglandins in feedback control of GFR

Recent evidence indicates that the PG system participates in the glomerular vascular response to changes in flow past the macula densa [126, 127]. An inverse relationship between tubular flow rate and SNGFR has been demonstrated by several laboratories [128–130]: when flow past the macula densa is elevated, SNGFR falls, and when flow decreases, SNGFR rises. The response to increased tubular flow has been shown to be mediated by vasoconstriction of the afferent arteriole [131, 132]. It is probable that the response to decreased flow involves vasodilatation at the same vascular site, although this has not been established.

We have recently found that formation of PG's is required for feedback responses to be elicited [126, 127]. Although normally an elevation of tubular urine flow from 0 to 40 nl/min induces a 40% reduction of SNGFR, feedback responses were significantly reduced during inhibition of PG synthesis. As shown in Fig. 3, this effect was demonstrated with four different agents. In sodium-chloride-depleted rats in which endogenous synthesis is probably elevated, higher doses of inhibitors were required to induce feedback inhibition. In animals treated with indomethacin, intraaortic infusion of PGI_2 (Fig. 4) or PGE_2, but not PGF_2, was noted to restore the capability of glomerular vessels to change their resistance in response to increases in loop of Henle flow rate [127]. This finding, like the

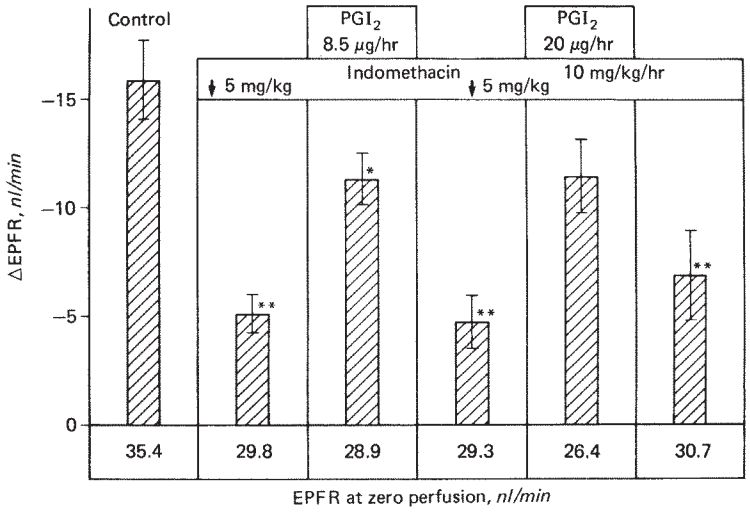

Fig. 4. *Changes in early proximal flow rate (EPFR) induced by elevating perfusion rate in the loop of Henle from 0 to 40 nl/min in rats before (control), during the i.v. administration of indomethacin, and during superimposed intraaortic infusion of PGI_2 in two different doses.* Values are the means ± SEM, and asterisks indicate changes significantly different from control.

studies described earlier [87], represents an instance of a paradoxical effect of the vasodilator PGI_2. Its infusion into an animal in which PG synthesis is inhibited leads to the restoration of a vasoconstrictor response.

It is unclear at present how PG's are integrated into the mechanism of tubuloglomerular coupling. It is possible that PG's are necessary for vessels to be responsive to the tubular signal, but that PG's are not directly involved in the change of vascular tone. The demonstration that alterations of vascular resistance may be produced through the feedback mechanism when PG's are infused into animals in which endogenous synthesis is inhibited suggests that variations in endogenous synthesis are not responsible for the response. It seems likely that instead PG's are necessary for the interaction with some other vascular mediator. It has been shown that the vasodilator response to furosemide, which may be feedback mediated, can be prevented by prior administration of indomethacin [133, 134], whereas the vasoconstrictor response to hypertonic sodium chloride, which is feedback mediated [135], could not be blocked by this drug [136]. This would suggest a dual mechanism for feedback mediation: the vasodilator response (to reduced loop of Henle flow rates) being dependent on PG's but the vasoconstrictor response (to elevated loop of Henle flow rates) being independent of them. This, however, is only speculative at this point.

It has been known for some time that the tubuloglomerular feedback mechanism does not produce symmetrical responses to changes in tubular flow. In animals in a control hydropenic state, increases in tubular flow produce rather marked decreases in filtration rate, but decreases in flow result in more modest increases in filtration rate [137, 138]. The mechanism is thus positioned to stabilize filtration rate in response to such challenges as a sudden increase in arterial pressure which, if unopposed, would lead to marked loss of salt and water. The mechanism is probably less potent in face of a challenging event that tends to reduce GFR. Thus, it seems likely that the protective effect of PG's in some of the conditions discussed above, such as hemorrhagic hypotension, is not primarily a consequence of their role in the feedback mechanism. This conclusion can only be tentative, however. Feedback sensitivity in the low-flow range is increased by a number of manipulations, such as a low sodium chloride diet [139], and it is possible that in some of the conditions discussed, such changes in sensitivity could lead to a much larger contribution of the feedback mechanism than would be predicted from measurements in animals in a control state.

Localization of prostaglandins effects

Some information is available that permits localization of the vascular sites of the interaction of PG's with other intrarenal hormones. The major resistance vessels in the renal vasculature are the afferent and efferent arterioles and possibly the interlobular arteries [140]. RBF is controlled by changes of the sum of these resistances, but the rate of glomerular filtration is a more complex function of total intrarenal resistance. Computer modelling of glomerular function leads to the prediction that

changes in afferent arteriolar resistance induce parallel and inverse changes of both RBF and GFR [141–144] largely independent of the initial conditions of filtration dynamics. Changes in efferent arteriolar resistance will also be accompanied by inverse changes of plasma flow. GFR, however, is predicted to have a biphasic response to changing efferent resistance: in a low resistance range it will increase with increasing resistance, but in a high resistance range the relationship will become inverse with increasing resistance, causing decreasing filtration. Furthermore, the effect of efferent resistance changes depends on the initial filtration conditions. If equilibrium of filtration forces is achieved by the end of the glomerular capillary tuft, then the increase of GFR with increased efferent resistance will be relatively small.

Afferent arteriole. During certain severe interventions, such as hemorrhage in the presence of NSAID, RBF and GFR change in parallel, suggesting that the resistance increase is localized to a predominant extent in preglomerular resistance vessels [31, 45]. Micropuncture studies have confirmed this expectation. Administration of exogenous AII and indomethacin [50], or administration of indomethacin to salt-depleted animals [145] are situations in which afferent resistance rises and glomerular plasma flow and SNGFR fall markedly and in parallel. PGE_1 infusion is associated with a decrease of both pre- and post-glomerular resistances, indicating that the afferent arteriole is one of the target tissues of angiotensin-PG interaction, particularly during strong stimulation of both systems.

Recent evidence has shown that feedback control of glomerular hemodynamics, which as discussed above requires PG's, is predominantly exerted at the level of the afferent arteriole [131, 132]. Some effect on the efferent arteriole or the glomerular capillary tuft, particularly in response to reduced flow rates through the loop of Henle, cannot be excluded, however.

Efferent arteriole. In several studies in anesthetized laparatomized animals in which NSAID reduced RBF [42, 44] and exogenous PG's increased it [57–61, 63, 65], a change of GFR was not observed. A similar finding was reported for single nephrons where indomethacin induced a fall in nephron plasma flow, but left SNGFR unaltered [50]. One explanation for these results is that the vasoconstrictor influence uncovered by PG synthesis inhibition is acting under these circumstances predominantly at the level of the efferent arteriole. A number of lines of evidence indicate that AII has such a predominant action on efferent resistance. In isolated kidneys, both the administration of AII and the administration of renin substrate were associated with reduced renal plasma flow and increased GFR [146]. Infusion of angiotensin in a dose that increased arterial blood pressure by 10% induced a much greater increase of efferent than afferent resistance [147, 148]; the difference was even more pronounced when the rise of arterial blood pressure was prevented [147]. Although afferent arteriolar resistances were not significantly different between salt-depleted and salt-loaded rats, efferent resistance was significantly higher during salt depletion [145], a state associated with elevated renin release. This higher efferent resistance and the concomitant increase of glomerular capillary pressure had the consequence that SNGFR was the same as it was in salt-loaded rats even though plasma flow was reduced. It appears that at a relatively low level of renin and PG activity the efferent arterioles are the main sites of their interaction. When PG's are removed, efferent arterioles constrict somewhat [145]. The result of this constriction may be maintenance of GFR despite reduction of RBF. Because the dependency of GFR on efferent resistance is biphasic, however, efferent arteriolar vasoconstriction protects GFR only in a limited range of resistances. Administration of NSAID to salt-depleted rats in one study, for example, increased efferent resistance more than it did afferent resistance, and the degree of efferent vasoconstriction was unable to preserve SNGFR because the fall of glomerular plasma flow outweighed the increase of glomerular capillary pressure [145]. Thus, it appears to be a role of PG's to counteract vasoconstrictor actions also at the efferent arteriolar level. The effect of such an action of PG's on maintenance of glomerular function is limited. Increases of efferent arteriolar resistance are beneficial for GFR maintenance only in a narrow resistance range and when afferent resistance is not augmented at the same time. NSAID administration in states of stimulated vasoconstrictor and PG systems will therefore create a degree of efferent vasoconstriction that is associated with reduced GFR, in particular because afferent resistance also increases. Thus, RBF and GFR will be dissociated only within certain limits of isolated or predominant efferent resistance changes.

Glomerular capillary tuft. The filtration coefficient K_f, the product of filtration area and hydraulic permeability of the glomerular capillaries, is another determinant of the rate of filtration that appears

to be modulated by the rate of formation of intrarenal hormones. Therefore, it has to be considered as a possible site of interaction of PG's with other hormonal factors. Infusion of PGE_1 induced a reduction of K_f to half normal [72], an effect shared by other vasodilator substances, for example by bradykinin [72]. Although PG's and AII have antagonistic actions at the glomerular resistance vessels, they seem to have the same effect on K_f because exogenous AII also reduces K_f [147, 148]. The reduction of K_f was noted even with angiotensin doses that did not change afferent or efferent arteriolar resistances [148]. This result may have a structural correlate in the changes observed by electron microscopy in both in vivo glomeruli [149] and in cultured glomerular cells [150]. Recent results suggest that the PG effect on K_f is in fact angiotensin mediated. Infusion of PGI_2, which induced an increase of efferent arteriolar resistance as mentioned earlier, was associated with a reduction of K_f [87]. This PGI_2-induced decrease of K_f could be reverted to control by simultaneous administration of saralasin [87]. Furthermore, the decrease of K_f observed in salt depletion and unilateral ureteral constriction, where both AII and PG production are elevated, was not affected by NSAID, suggesting that the alteration of K_f in these cases was not PG dependent [49, 145]. Further support for the conclusion that PG's do not appear to modify K_f directly comes from the observation that PGE_2 does not produce structural changes of cultured glomerular cells [150]. In view of these findings and in view of the fact that GFR is relatively independent of K_f under conditions at or close to filtration pressure equilibrium, it is unlikely that any of the influences of PG's on filtrate formation are a reflection of K_f modifications.

Summary

Figure 5 summarizes the effects of the various control systems on renal resistance vessels and on the glomerular tuft. The interrelationships between these systems discussed in this paper are indicated. Although the scheme as presented is already difficult to untangle, it is probably still a simplification. Factors waiting to be studied in more detail and possibly to be integrated as controlling variables include other arachidonate intermediates and metabolites such as free radicals, endoperoxides, leukotrienes, and vasoconstrictor PG's, histamine, adenine nucleotides, and adenosine, cyclic AMP and ionized calcium, mineralocorticoids and vasopressin, endogenous inhibitors of kallikrein, renin,

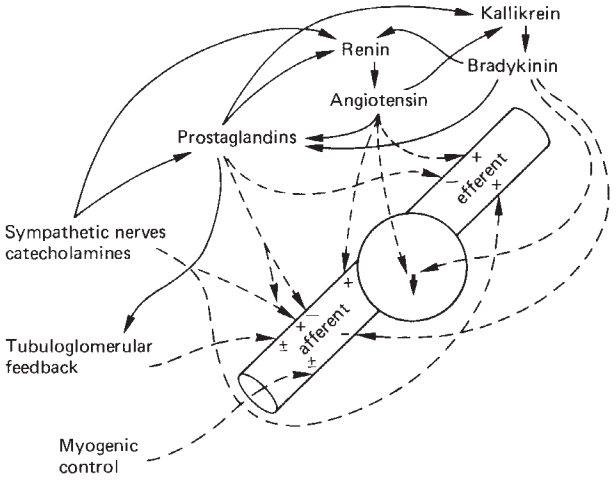

Fig. 5. *Excitatory (+) and inhibitory (−) effects of intrarenal hormonal and other regulatory systems on afferent and efferent arterioles and on the glomerular tuft* (broken lines) *and their relationships of mutual activation* (solid lines). The scheme disregards the anatomical localization of the systems as well as the compartments of formation of the vasoactive compounds.

and PG synthesis, and the enzymes responsible for their metabolism.

The following conclusions seem justified at this time: *(1)* Prostaglandins are synthetized in the renal cortex, with sites of localization including the arterial tree. The main, but not exclusive, product is PGI_2. Local cortical PG's can therefore influence glomerular arteriolar resistance and affect RBF and GFR. *(2)* Prostaglandins are not major determinants of the resting tone of renal resistance vessels in normovolemic animals. *(3)* Prostaglandins protect glomerular function in potentially hazardous situations such as salt depletion, hemorrhage, endotoxin shock, and hydronephrosis. PG's participate in adjustments of renal vascular resistance that are responsible for autoregulation of GFR during reduced renal perfusion pressure. *(4)* Prostaglandins exert this effect in part by their own vasodilatory properties; in some instances, a direct vascular effect of vasoconstrictor PG's is possible. *(5)* Prostaglandins exert their protective effect largely by interaction with other intrarenal hormonal systems: *(a)* Prostaglandins antagonize the constrictor effects of the renin-angiotensin system within the kidney. They are partly responsible for renin release and their synthesis is in turn augmented by angiotensin. *(b)* Prostaglandins antagonize the intrarenal constrictor effects of the catecholamine-sympathetic nervous system. *(c)* Prostaglandins may potentiate the effects of the dilator bradykinin and mediate some of its actions. *(6)* Prostaglandins are required

for tubuloglomerular feedback control of GFR and thus participate in protection of extracellular volume against excessive salt loss. *(7)* Prostaglandins interact with other intrarenal hormone systems at the level of both afferent and efferent arterioles.

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References

1. LARSSON C, ÄNGGARD E: Regional differences in the formation and metabolism of prostaglandins in the rabbit kidney. *Eur J Pharmacol* 21:30–36, 1973
2. PONG SS, LEVINE L: Biosynthesis of prostaglandins in rabbit renal cortex. *Res Comm Chem Pathol Pharmacol* 13:115–123, 1976
3. STAHL RAK, ATTALLAH AA, BLOCH DL, LEE JB: Stimulation of rabbit renal PGE_2 biosynthesis by dietary sodium restriction. *Am J Physiol* 237:F344–F349, 1979
4. WHORTON AR, SMIGEL M, OATES JA, FRÖLICH JC: Regional differences in prostaglandin formation by the kidney: Prostacyclin is a major prostaglandin of renal cortex. *Biochem Biophys Acta* 529:176–180, 1978
5. OLIW E, LUNDEN I, SJÖQUIST B, ÄNGGARD E: Determination of 6-keto-prostaglandin $F_{1\alpha}$ in rabbit kidney and urine and its relation to sodium balance. *Acta Physiol Scand* 105:359–366, 1979
6. SMITH WL, BELL TG: Immunohistochemical localization of the prostaglandin-forming cyclooxygenase in renal cortex. *Am J Physiol* 235:F451–F457, 1978
7. TERRAGNO NA, TERRAGNO A, EARLY JA, ROBERTS MA, MCGIFF JC: Endogenous prostaglandin synthesis inhibitor in the renal cortex: Effects on production of prostacyclin by renal blood vessels. *Clin Sci Mol Med* 55:199s–202s, 1978
8. FOLKERT VW, SCHLÖNDORFF D: Prostaglandin synthesis in isolated glomeruli. *Prostaglandins* 17:79–86, 1979
9. HASSID A, KONIECZKOWSKI M, DUNN MJ: Prostaglandin synthesis in isolated rat kidney glomeruli. *Proc Natl Acad Sci USA* 76:1155–1159, 1979
10. HASSID A, DUNN MJ: In vitro prostaglandin biosynthesis by human kidney. *Kidney Int* 16:819, 1979
11. GRENIER FC, SMITH WL: Formation of 6-Keto-$PGF_{1\alpha}$ by collecting tubule cells isolated from rabbit renal papillae. *Prostaglandins* 16:759–772, 1978
12. TERRAGNO NA, TERRAGNO DA, MCGIFF JC: Contribution of prostaglandins to the renal circulation in conscious, anesthetized, and laparotomized dogs. *Circ Res* 40:590–595, 1977
13. SCHERER B, SCHNERMANN J, SOFRONIEV M, WEBER PC: Prostaglandin (PG) analysis in urine of humans and rats by different radioimmunoassays: Effect on PG-excretion by PG-synthetase inhibitors, laparotomy and furosemide. *Prostaglandins* 15:255–266, 1978
14. VATNER SF: Effects of hemorrhage on regional blood flow distribution in dogs and primates. *J Clin Invest* 54:225–235, 1974
15. SWAIN JA, HENDRIX GR, BOETTCHER DH, VATNER SF: Prostaglandin control of renal circulation in the unanesthetized dog and baboon. *Am J Physiol* 229:826–830, 1975
16. ZINS GR: Renal prostaglandins. *Am J Med* 58:14–24, 1975
17. DÜSING R, MELDER B, KRAMER HJ: Prostaglandins and renal function in acute extracellular volume expansion. *Prostaglandins* 12:3–10, 1976
18. KIRSCHENBAUM MA, STEIN JH: Effect of inhibition of prostaglandin synthesis on urinary sodium excretion in conscious dog. *J Clin Invest* 57:517–521, 1976
19. FEJES-TOTH G, MAGYAR A, WALTER J: Renal response to vasopressin after inhibition of prostaglandin synthesis. *Am J Physiol* 232:F416–F423, 1977
20. ZIMMERMANN BG: Effect of meclofenamate on renal vascular resistance in early Goldblatt hypertension in conscious and anesthetized dog. *Prostaglandins* 15:1027–1034, 1978
21. ZAMBRASKI EJ, DUNN MJ: Renal prostaglandin E_2 secretion and excretion in conscious dogs. *Am J Physiol* 236:F552–F558, 1979
22. HAYLOR J, LOTE CJ: Renal function in conscious rats after indomethacin: Evidence for a tubular action of endogeneous prostaglandins. *J Physiol* 298:371–380, 1980
23. BEILIN LJ, BHATTACHARYA J: The effect of prostaglandin synthesis inhibitors on renal blood flow distribution in conscious rabbits. *J Physiol* 269:395–405, 1977
24. EPSTEIN M, LIFSCHITZ MD, HOFFMAN DS, STEIN JH: Relationship between renal prostaglandin E and renal sodium handling during water immersion in normal man. *Circ Res* 45:71–80, 1979
25. ATTALLAH A, STAHL R: Inhibition of renal PGE_2 biosynthesis in vivo: Regional differences. *Prostaglandins* 19:649–650, 1980
26. MCGIFF JC, CROWSHAW K, TERRAGNO NA, LONIGRO AJ, STRAND JC, WILLIAMSON MA, LEE JB, NG KFK: Prostaglandin-like substances appearing in canine renal venous blood during renal ischemia: Their partial characterization by pharmacologic and chromatographic procedures. *Circ Res* 27:765–782, 1970
27. HERBACZYNSKA-CEDRO K, VANE JR: Contribution of intrarenal generation of prostaglandin to autoregulation of renal blood flow in the dog. *Circ Res* 33:428–436, 1973
28. SATOH S, ZIMMERMAN BG: Influence of renin-angiotensin system on the effect of prostaglandin synthesis inhibitors in the renal vasculature. *Circ Res* 36 (suppl. 1):189–196, 1975
29. DUNN MJ, LIARD JF, DRAY F: Basal and stimulated rates of renal secretion and excretion of prostaglandins E_2, F and 13,14-dihydro-15-keto F_α in the dog. *Kidney Int* 13:136–143, 1978
30. COLLIER JG, HERMAN AG, VANE JR: Appearance of prostaglandins in the renal venous blood of dogs in response to acute systemic hypotension produced by bleeding or endotoxin. *J Physiol* 230:19P–20P, 1973
31. HENRICH WL, ANDERSON RJ, BERNS AS, MCDONALD KM, PAULSEN PJ, BERL T, SCHRIER RW: Role of renal nerves and prostaglandins in control of renal hemodynamics and plasma renin activity during hypotensive hemorrhage in dog. *J Clin Invest* 61:744–750, 1978
32. TOBIAN L, O'DONNELL M, SMITH P: Intrarenal prostaglandin levels during normal and high sodium intake. *Circ Res* 34, 35 (suppl. 1):183–186, 1974
33. WEBER PC, LARSSON C, SCHERER B: Prostaglandin E_2-9-ketoductase as a mediator of salt intake-related prostaglandin-renin interaction. *Nature* 266:65–66, 1977
34. DAVILA D, DAVILA T, OLIW E, ÄNGGARD E: Influence of dietary sodium on urinary prostaglandin excretion. *Acta Physiol Scand* 103:100–106, 1978

35. TORRES VE, ROMERO JC, STRONG CG, WILSON DM, WALKER ER: Renal prostaglandins E during acute renal failure. *Prostaglandins* 8:353–360, 1974
36. KESSLER E, HUGHES RC, BENNETT EN, NADELA SY: Evidence for the presence of prostaglandin like material in the plasma of dogs with endotoxic shock. *J Lab Clin Med* 81:85–94, 1973
37. OLSEN UB, MAGNUSSEN MP, EILERTSEN E: Prostaglandins, a link between renal hydro- and hemodynamic in dogs. *Acta Physiol Scand* 97:369–376, 1976
38. NISHIKAWA K, MORRISON A, NEEDLEMAN P: Exaggerated prostaglandin biosynthesis and its influence on renal resistance in isolated hydronephrotic rabbit kidney. *J Clin Invest* 59:1143–1150, 1977
39. LONIGRO J, ITSKOVITZ D, CROWSHAW K, MCGIFF C: Dependency of renal blood flow on prostaglandin synthesis in the dog. *Circ Res* 32:712–717, 1973
40. SOLEZ K, FOX JA, MILLER M, HEPTINSTALL RH: Effects of indomethacin on renal inner medullary plasma flow. *Prostaglandins* 7:91–98, 1974
41. KIRSCHENBAUM MA, WHITE N, STEIN JH, FERRIS TF: Redistribution of renal cortical blood flow during inhibition of prostaglandin synthesis. *Am J Physiol* 227:801–805, 1974
42. LEYSSAC PP, CHRISTENSEN P, HILL R, SKINNER SL: Indomethacin blockade of renal PGE-synthesis: Effect on total renal and tubular function and plasma renin concentration in hydropenic rats and on their response to isotonic saline. *Acta Physiol Scand* 94:484–496, 1975
43. OWEN TL, EHRHART IC, WEIDNER WJ, SCOTT JB, HADDY FJ: Effects of indomethacin on local blood flow regulation in canine heart and kidney. *Proc Soc Exp Biol Med* 149:871, 1975
44. SEYMOUR AA, ZEHR JE: Influence of renal prostaglandin synthesis on renin control mechanisms in the dog. *Circ Res* 45:13–25, 1979
45. HENRICH WL, BERL T, MCDONALD KM, ANDERSON RJ, SCHRIER RW: Angiotensin II, renal nerves and prostaglandins in renal hemodynamics during hemorrhage. *Am J Physiol* 235:F46–F51, 1978
46. YUN J, KELLY G, BARTTER FC, SMITH HJ: Role of prostaglandins in the control of renin secretion in the dog. *Circ Res* 40:459–464, 1977
47. TORRES VE, STRONG CG, ROMERO JC, WILSON DM: Indomethacin enhancement of glycerol-induced acute renal failure in rabbits. *Kidney Int* 7:170–178, 1975
48. MILLARD RW, BAIG H, VATNER SF: Prostaglandin control of the renal circulation in response to hypoxemia in the fetal lamb in utero. *Circ Res* 45:172–179, 1979
49. ICHIKAWA I, BRENNER BM: Local intrarenal vasoconstriction-vasodilator interactions in mild partial ureteral obstruction. *Am J Physiol* 236:F131–F140, 1979
50. BAYLIS C, BRENNER BM: Modulation by prostaglandin synthesis inhibitors of the action of exogenous angiotensin II on glomerular ultrafiltration in the rat. *Circ Res* 43:889–898, 1978
51. ANDERSON RJ, TAHER MS, CRONIN RE, MCDONALD KM, SCHRIER RW: Effect of β-adrenergic blockade and inhibitors of angiotensin II and prostaglandin on renal autoregulation. *Am J Physiol* 229:731–736, 1975
52. VENUTO RC, O'DORISIO T, FERRIS TF, STEIN JH: Prostaglandins and renal function II. The effect of prostaglandin inhibition on autoregulation of blood flow in the intact kidney of the dog. *Prostaglandins* 9:817–828, 1975
53. FINN WF, ARENDSHORST WJ: Effect of prostaglandin synthetase inhibitors on renal blood flow in the rat. *Am J Physiol* 231:1541–1545, 1976
54. KALOYANIDES GJ, AHRENS RE, SHEPHERD JA, DIBONA GF: Inhibition of prostaglandin E_2 secretion: Failure to abolish autoregulation in the isolated dog kidney. *Circ Res* 38:67–73, 1976
55. BEILIN LJ, BHATTACHARYA J: The effect of indomethacin on autoregulation of renal blood flow in the anaesthetized dog. *J Physiol* 271:625–639, 1977
56. FLYNN JT, LEFER AM: Beneficial effects of arachidonic acid during hemorrhagic shock in the dog. *Circ Res* 40:422–428, 1977
57. JOHNSTON HH, HERZOG JP, LAULER DP: Effect of prostaglandin E_1 on renal hemodynamics, sodium and water excretion. *Am J Physiol* 213:939–946, 1967
58. VANDER AJ: Direct effect of prostaglandins on renal functions and renin release. *Am J Physiol* 214:218–221, 1968
59. MARTINEZ-MALDONADO M, TSAPARAS N, EKNOYAN G, SUKI WN: Renal actions of prostaglandins: comparison with acetylcholine and volume expansion. *Am J Physiol* 222:1147–1152, 1972
60. BAER G, NAVAR L: Renal vasodilation and uncoupling of blood flow and filtration rate autoregulation. *Kidney Int* 4:12–21, 1973
61. GROSS JB, BARTTER FC: Effects of prostaglandins E_1, A_1 and F_2 on renal handling of salt and water. *Am J Physiol* 225:218–224, 1973
62. ARENDSHORST WJ, JOHNSTON PJ, SELKURT EE: Effect of prostaglandin E_1 on renal hemodynamics in nondiuretic and volume-expanded dogs. *Am J Physiol* 226:218–225, 1974
63. FÜLGRAFF G, BRANDENBUSCH G, HEINTZE K: Dose response relation of the renal effects of PGA_1, PGE_2 and $PGF_{2\alpha}$ in dogs. *Prostaglandins* 8:21–30, 1974
64. ITSKORITZ HD, TERRAGNO NA, MCGIFF JC: Effect of a renal prostaglandin on distribution of blood flow in the isolated canine kidney. *Circ Res* 34:770–776, 1974
65. BOLGER PM, EISNER GM, RAMWELL PW, SLOTKOFF LM, COREY EJ: Renal actions of prostacyclin. *Nature* 271:467–469, 1978
66. TANNENBAUM J, SPLAWINSKI JA, OATES JA, NIES AS: Enhanced renal prostaglandin production in the dog: I. Effects on renal function. *Circ Res* 36:197–203, 1975
67. CHANG LCT, SPLAWINSKI JA, OATES JA, NIES AS: Enhanced renal prostaglandin production in the dog: II. Effects on intrarenal hemodynamics. *Circ Res* 36:204–207, 1975
68. LARSSON C, ÄNGGARD E: Increased juxtamedullary blood flow on stimulation of intrarenal prostaglandin biosynthesis. *Eur J Pharmacol* 25:326–334, 1974
69. MALIK KU, MCGIFF JC: Modulation by prostaglandins of adrenergic transmission in the isolated perfused rabbit and rat kidney. *Circ Res* 36:599–609, 1975
70. ARMSTRONG JM, BLACKWELL GJ, FLOWER RJ, MCGIFF JC, MULLANE KM, VANE JR: Genetic hypertension in rats is accompanied by a defect in renal prostaglandin metabolism. *Nature* 260:582–586, 1976
71. GERBER JG, NIES S: The hemodynamic effects of prostaglandins in the rat: evidence for important species variation in renovascular responses. *Circ Res* 44:406–410, 1979
72. BAYLIS C, DEEN WM, MYERS BD, BRENNER BM: Effects of some vasodilator drugs on transcapillary fluid exchanges in renal cortex. *Am J Physiol* 230:1148–1158, 1976

73. GERBER JG, NIES AS, FRIESINGER GC, GERKENS JF, BRANCH RA, OATES JA: Effect of PGI_2 on canine renal function and hemodynamics. *Prostaglandins* 16:519–528, 1978
74. HILL TWK, MONCADA S: The renal hemodynamic and excretory actions of prostacyclin and 6-oxo-PGF_1 in anaesthetized dogs. *Prostaglandins* 17:87–98, 1979
75. GERBER JG, ELLIS E, HOLLIFIED J, NIES AS: Effect of prostaglandin endoperoxide analogue on canine renal function, hemodynamics and renin release. *Eur J Pharmacol* 53:239–246, 1979
76. MORRISON AR, NISHIKAWA K, NEEDLEMAN P: Unmasking of thromboxane A_2 synthesis by ureteral obstruction in the rabbit kidney. *Nature* 267:259–260, 1977
77. YARGER WE, SCHOCKEN DD, HARRIS RH: Obstructive nephropathy in the rat: Possible roles for the renin-angiotensin system, prostaglandins, and thromboxanes in postobstructive renal function. *J Clin Invest* 65:400–412, 1980
78. BENABE JE, KLAHR S, HOFFMAN MK, MORRISON AR: Production of thromboxane A_2 by the kidney in glycerol-induced acute renal failure. *Prostaglandins* 19:333–347, 1980
79. AIKEN JW, VANE JR: Intrarenal prostaglandin release attenuates the renal vasoconstrictor activity of angiotensin. *J Pharmacol Ther* 184:678–687, 1973
80. CHAPNICK BM, PAUSTIAN PW, FEIGEN LP, JOINER PD, HYMAN AL, KADOWITZ PJ: Influence of inhibitors of prostaglandin synthesis on renal vascular resistance and on renal vascular responses to vasopressor and vasodilator agents in the cat. *Circ Res* 40:348–354, 1977
81. YABEK SM, AVNER BP: Effects of prostacyclin (PGI_2) and indomethacin on neonatal lamb mesenteric and renal artery responses to electrical stimulation and norepinephrine. *Prostaglandins* 19:23–30, 1980
82. NEEDLEMAN P, MARSHALL GR, JOHNSON EM: Determinants and modification of adrenergic and vascular resistance in the kidney. *Am J Physiol* 227:665–669, 1974
83. FREEMAN RH, DAVIS JO, VITALE SJ, JOHNSON JA: Intrarenal role of angiotensin II: Homeostatic regulation of renal blood flow in the dog. *Circ Res* 32:692–698, 1973
84. SATOH S, ZIMMERMAN BG: Effect of (Sar^1, Ala^8) angiotensin II on renal vascular resistance. *Am J Physiol* 229:640–645, 1975
85. ARENDSHORST WJ, FINN WF: Renal hemodynamics in the rat before and during inhibition of angiotensin II. *Am J Physiol* 233:F290–F297, 1977
86. KIMBROUGH HM, VAUGHAN ED, CAREY RM, AYERS CR: Effect of intrarenal angiotensin II blockade on renal function in conscious dogs. *Circ Res* 40:174–178, 1977
87. SCHOR N, ICHIKAWA I, TROY JL, BRENNER BM: Effects of prostacyclin (PGI_2) on glomerular hemodynamics. *Kidney Int* 16:835, 1979
88. WERNING C, VETTER W, WEIDMANN P, SCHWEIKERT HV, STIEL D, SIEGENTHALER W: Effect of prostaglandin E_1 on renin in the dog. *Am J Physiol* 220:852–856, 1976
89. LARSSON C, WEBER P, ÄNGGARD E: Arachidonic acid increases and indomethacin decreases plasma renin activity in the rabbit. *Eur J Pharmacol* 28:391–394, 1974
90. WEBER P, HOLZGREVE H, STEPHAN R, HERBST R: Plasma renin activity and renal sodium and water excretion following infusion of arachidonic acid in rats. *Eur J Pharmacol* 34:299–304, 1975
91. BOLGER PM, EISNER GM, RAMWELL PW, SLOTKOFF LM: Effect of prostaglandin synthesis on renal function in the dog. *Nature* 259:244–245, 1976
92. WEBER PC, LARSSON C, ÄNGGARD E, HAMBERG M, COREY EJ, NICOLAOU KC, SAMUELSSON B: Stimulation of renin release from rabbit renal cortex by arachidonic acid and prostaglandin endoperoxides. *Circ Res* 39:868–874, 1976
93. SEYMOUR AA, DAVIS JO, FREEMAN RH, DEFORREST JM, ROWE BP, WILLIAMS GM: Renin release from filtering and nonfiltering kidneys stimulated by PGI_2 and PGD_2. *Am J Physiol* 237:F285–F290, 1979
94. WHORTON AR, MISONO K, HOLLIFIELD J, FRÖLICH JC, INAGAMI T, OATES JA: Prostaglandins and renin release: I. Stimulation of renin release from rabbit renal cortical slices by PGI_2. *Prostaglandins* 14:1095–1104, 1977
95. GERBER JG, BRANCH RA, NIES AS, GERKENS JG, SHAND DG, HOLLIFIELD J, OATES JA: Prostaglandins and renin release: II. Assessment of renin secretion following infusion of PGI_2, E_2 and D_2 into the renal artery of anesthetized dogs. *Prostaglandins* 15:81–88, 1978
96. WEEKS JR, COMPTON LD: The cardiovascular pharmacology of prostacyclin (PGI_2) in the rat. *Prostaglandins* 17:501–513, 1979
97. MCGIFF JC, CROWSHAW K, TERRAGNO NA, LONIGRO AJ: Release of a prostaglandin-like substance into renal venous blood in response to angiotensin II. *Circ Res* 27 (suppl. 1):I-121–I-130, 1970
98. DANON A, CHANG LCT, SWEETMAN BJ, NIES AS, OATES JA: Synthesis of prostaglandins by the rat renal papilla in vitro. Mechanism of stimulation by angiotensin II. *Biochem Biophys Acta* 388:71–83, 1975
99. ZUSMAN RM, KEISER HR: Regulation of prostaglandin E_2 synthesis by angiotensin II, potassium, osmolarity and dexamethasone. *Kidney Int* 17:277–283, 1980
100. FRÖLICH JC, WILSON TW, SWEETMAN BJ, SMIGEL M, NIES AS, CARR K, WATSON JT, OATES JA: Urinary prostaglandins: Identification and origin. *J Clin Invest* 55:763–770, 1975
101. GERBER JG, HUBBARD WC, NIES AS: Role of renal metabolism of PGE_2 in determining its activity as a renal vasodilator in the dog. *Prostaglandins* 17:323–336, 1979
102. DUNHAM EW, ZIMMERMAN BG: Release of prostaglandin-like material from dog kidney during nerve stimulation. *Am J Physiol* 219:1279–1285, 1970
103. DAVIS HA, HORTON EW: Output of prostaglandins from the rabbit kidney, its increase on renal nerve stimulation and its inhibition by indomethacin. *Br J Pharmacol* 46:658–675, 1972
104. MCGIFF JC, CROWSHAW K, TERRAGNO NA, MALIK KU, LONIGRO AJ: Differential effect of noradrenaline and renal nerve stimulation on vascular resistance in the dog kidney and the release of a prostaglandin E-like substance. *Clin Sci* 42:223–233, 1972
105. NEEDLEMAN P, DOUGLAS JR, JAKSCHIK B, STOECKLEIN PB, JOHNSON EM: Release of renal prostaglandin by catecholamines: Relationship to renal endocrine function. *J Pharm Exp Ther* 188:453–460, 1974
106. HEDQUIST P: Control by prostaglandin E_2 of sympathetic neuro-transmission in the spleen. *Life Sci* 9:269–278, 1970
107. SAMUELSSON B, WENNMALM A: Increased nerve stimulation induced release of noradrenaline from the rabbit heart after inhibition of prostaglandin synthesis. *Acta Physiol Scand* 83:163–168, 1971
108. VANDER AJ: Effect of catecholamines and the renal nerves

on renin secretion in anesthetized dogs. *Am J Physiol* 209:659–662, 1965
109. Bunag RD, Page IH, McCubbin JR: Neural stimulation of renin release. *Circ Res* 19:851–858, 1966
110. Johnson JA, Davis JO, Witty RT: Effects of catecholamines and renal nerve stimulation on renin release in the nonfiltering kidney. *Circ Res* 29:646–653, 1971
111. Coote JH, Johns EJ, Macleod VH, Singer B: Effect of renal nerve stimulation, renal blood flow and adrenergic blockade on plasma renin activity in the cat. *J Physiol* 226:15–36, 1972
112. Winer N, Chokshi DS, Walkenhorst WG: Effects of cyclic AMP, sympathomimetic amines and adrenergic receptor antagonists on renin secretion. *Circ Res* 29:239–248, 1971
113. Assaykeen TA, Tanigawa H, Allison DJ: Effect of adrenoceptor-blocking agents on the renin response to isoproterenol in dogs. *Eur J Pharmacol* 26:285–297, 1974
114. Henrich WL, Schrier RW, Berl T: Mechanisms of renin secretion during hemorrhage in the dog. *J Clin Invest* 64:1–7, 1979
115. Nasjletti A, Malik KU: Relationships between the kallikrein-kinin and prostaglandin system. *Life Sci* 25:99–110, 1979
116. Okiba LFO, Mills IH: Effect of arterial infusion of prostaglandin E on the release of renal kallikrein. *J Endocrinol* 69:45P–46P, 1979
117. McGiff JC, Terragno NA, Malik KU, Lonigro AJ: Release of a prostaglandin E-like substance from canine kidney by bradykinin: comparison with eledoisin. *Circ Res* 31:36–43, 1972
118. Cholina-Chourio J, McGiff JC, Miller MP, Nasjletti A: Possible influence of intrarenal generation of kinins on prostaglandin release from the rabbit perfused kidney. *Br J Pharmacol* 58:165–172, 1976
119. Lonigro AJ, Hagemann MH, Stephenson AH, Fry CL: Inhibition of prostaglandin synthesis by indomethacin augments the renal vasodilator response to bradykinin in the anesthetized dog. *Circ Res* 43:447–455, 1978
120. Flamenbaum W, Gagnon J, Ramwell P: Bradykinin-induced renal hemodynamic alterations: renin and prostaglandin relationship. *Am J Physiol* 237:F433–F440, 1980
121. Juan H: Mechanism of action of bradykinin-induced release of prostaglandin E. *Naunyn-Schmiedebergs Arch Pharmacol* 300:77–85, 1977
122. Nasjletti A, McGiff JC, Colina-Chourio J: Interrelations of the renal kallikrein-kinin system and renal prostaglandins in the conscious rat: Influence of mineralocorticoids. *Circ Res* 43:799–807, 1978
123. MacFarlane NAA, Adetuyibi A, Mills IH: Changes in kallikrein excretion during arterial infusion of angiotensin. *J Endocrinol* 61:72P, 1974
124. Wong PY, Talamo RC, Williams GH, Colman RW: Response of the kallikrein-kinin and renin-angiotensin systems to saline infusion and upright posture. *J Clin Invest* 55:691–698, 1975
125. Margolius HS, Horwitz D, Geller RG, Alexander RW, Gill JR, Pisano JJ, Keiser HR: Urinary kallikrein excretion in normal man: relationship to sodium intake and sodium-retaining steriods. *Circ Res* 35:812–819, 1974
126. Schnermann J, Schubert G, Hermle M, Herbst R, Stowe NT, Yarimizu S, Weber PC: The effect of inhibition of prostaglandin synthesis on tubuloglomerular feedback in the rat kidney. *Pfluegers Arch* 379:269–279, 1979
127. Schnermann J, Weber PC: A role of renal cortical prostaglandins in the control of glomerular filtration rate in rat kidneys. *Adv Prostaglandin Thromboxane Res* 7:1047–1052, 1980
128. Schnermann J, Wright FS, Davis JM, v. Stackelberg W, Grill G: Regulation of superficial nephron filtration rate by tubulo-glomerular feedback. *Pfluegers Arch* 318:147–175, 1970
129. Burke TJ, Navar LG, Clapp JR, Robinson RR: Response of single nephron glomerular filtration rate to distal nephron microperfusion. *Kidney Int* 6:230–240, 1974
130. Hierholzer K, Müller-Suur R, Gutsche HU, Butz M, Lichtenstein I: Filtration in surface glomeruli as regulated by flow rate through the loop of Henle. *Pfluegers Arch* 352:315–337, 1974
131. Briggs JP, Wright FS: Feedback control of glomerular filtration rate: site of the effector mechanism. *Am J Physiol* 236:F40–F47, 1979
132. Schnermann J, Briggs J, Kriz W, Moore L, Wright FS: Control of glomerular vascular resistance by the tubulogomerular feedback mechanism, in *Renal Pathophysiology Recent Advances*, edited by Leaf A, Giebisch G, Bolis L, Gorini S, New York, Raven Press, 1980, pp. 165–182
133. Bailie MD, Barbour JA, Hook JB: Effects of indomethacin on furosemide-induced changes in renal blood flow. *Proc Soc Exp Biol Med* 148:1173–1176, 1975
134. Data JL, Rane A, Gerkens JF, Wilkinson GR, Nies AS, Branch RA: The influence of indomethacin on the pharmacokinetics, diuretic response and hemodynamics of furosemide in the dog. *J Pharmacol Exp Ther* 206:431–438, 1978
135. Briggs J, Schnermann J: Suppression of GFR during acute hypernatremia. *Kidney Int* 16:808, 1979
136. Gerber JG, Branch RA, Nies AS, Hollified JW, Gerkens JF: Influence of hypertonic saline on canine renal blood flow and renin release. *Am J Physiol* 237:F441–446, 1979
137. Schnermann J, Davis JM, Wunderlich P, Levine DZ, Horster M: Technical problems in the micropuncture determination of nephron filtration rate and their functional implications. *Pfluegers Arch* 329:307–320, 1971
138. Schnermann J, Persson E, Agerup B: Tubulo-glomerular feedback. Nonlinear relation between glomerular hydrostatic pressure and loop of Henle perfusion rate. *J Clin Invest* 52:862–869, 1973
139. Dev B, Drescher C, Schnermann J: Resetting of tubuloglomerular feedback sensitivity by dietary salt intake. *Pfluegers Arch* 346:263–277, 1974
140. Källskog O, Lindbom LO, Ulfendahl HR, Wolgast M: Hydrostatic pressures within the vascular structures of the rat kidney. *Pfluegers Arch* 363:205–210, 1976
141. Steven K, Strobaek S: Renal corpuscular hydrodynamics: digital computer simulation. *Pfluegers Arch* 348:317–331, 1974
142. Huss RE, Marsh DJ, Kalaba RE: Two models of glomerular filtration rate and renal blood flow in the rat. *Ann Biomed Eng* 3:72–99, 1975
143. Brenner B, Deen WM, Robertson CR: Glomerular filtration, in *The Kidney*, edited by Brenner B, Rector FC, Saunders, Philadelphia, 1976, pp. 251–269

144. NAVAR LG: The regulation of glomerular filtration rate in mammalian kidneys, in *Physiology of Membrane Disorders,* edited by ANDREOLI TE, HOFFMAN JF, FANESTIL DD, New York, Plenum Publishing Corp, 1978, pp. 593–627
145. SCHOR N, ICHIKAWA I, BRENNER BM: Glomerular adaptations to chronic dietary salt restriction or excess. *Am J Physiol* 238:F428–F436, 1980
146. DAVALOS M, FREGA NS, SAKER B, LEAF A: Effect of exogenous angiotensi II in the isolated perfused rat kidney. *Am J Physiol* 235:F605–F610, 1978
147. MYERS BD, DEEN WM, BRENNER BM: Effects of norepinephrine and angiotensin II on determinants of glomerular ultrafiltration and proximal tubule fluid reabsorption in rat. *Circ Res* 37:101–110, 1975
148. BLANTZ RC, KONNEN KS, TUCKER BJ: Angiotensin II effects upon glomerular microcirculation and ultrafiltration coefficient of rat. *J Clin Invest* 57:419–434, 1976
149. HORNYCH H, BEAUFILS M, RICHET G: The effect of exogenous angiotensin on superficial and deep glomeruli in the rat kidney. *Kidney* 2:336–343, 1972
150. AUSIELLO DA, KREISBERG JI, ROY C, KARNOVSKY MJ: Contraction of cultured rat glomerular cells of apparent mesangial origin after stimulation with angiotensin-II and arginine vasopressin. *J Clin Invest* 65:754–760, 1980