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Role of prostaglandins in renin secretion

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The ability of the renal prostaglandin (PG) system to enhance renin secretion remains a subject of intense investigative interest and some controversy. Earlier studies had isolated several factors that could independently alter renin release: specifically, a decrease in renal perfusion pressure, the sympathetic nervous system, or alterations in sodium delivery to or transport at the macula densa were identified as important stimuli for renin release [1]. The subsequent demonstration that several PG's are capable of independently stimulating renin secretion has generated numerous recent investigations that probe the relative potency of the different PG's to stimulate renin release. Moreover, the importance of PG's for the function of other known renin secretion stimuli (such as the arterial baroreceptor) has also been examined.

This review highlights two distinct areas of the prostaglandin-renin interaction: *(1)* PG's as primary stimuli for renin release; and *(2)* PG's as integral cofactors for other stimuli to induce the juxtaglomerular cells to release renin. The relative potency of each of these stimuli will also be considered, and areas of the relationship between PG's and renin that particularly merit further clarification will be emphasized.

Prostaglandins as stimuli to renin secretion

The ability of the synthetic products of PG synthetase to stimulate renin release both in vivo and in vitro has been convincingly established over the past decade. The clearest results in these prior studies were obtained when stimulation of other known renin control factors (such as the renal arterial baroreceptor) was avoided. Thus, the intrarenal administration of arachidonic acid in nonhypotensive doses in the rat [2], rabbit [3], and dog [4] has been shown to increase renin release. Similarly, the in vitro incubation of either arachidonic acid or PGI_2 in renal cortical slices of the rabbit causes release of renin, which is inhibited by indomethacin, suggesting that PG's directly induce an increase in renin release [5, 6].

Further elucidation of the PG-renin relationship has been obtained from studies in which an inhibitor of the cyclooxygenase step of PG synthesis has been used. Yun et al demonstrated that the renal hemodynamic and renin-suppressing effects of indomethacin were reversed by an intrarenal infusion of PGE_2 or PGE_1 [7]. Prostaglandin synthesis inhibition has also been shown to inhibit the release of renin in the basal state [8, 9].

Some controversy exists regarding which of the renal PG's is most potent in stimulating renin release. Gerber et al recently reported that PGE_2 and PGI_2 were of equal potency in their capacity to release renin in the dog [10]. In contrast, Bolger et al found that an intrarenal infusion of PGI_2 failed to stimulate renin release [4]. A potential complicating feature of intrarenal PG infusions, however, is a significant natriuresis and thus an increase in sodium delivery to the macula densa [11, 12]. This effect might oppose any effect of PG's to directly stimulate renin via the juxtaglomerular cells [13]. Furthermore, the metabolism of PGE_2 and PGI_2 differs and could, theoretically, account for any observed differences in potency. To further clarify these issues, Gerber, Keller, and Nies recently infused several different PG compounds into the denervated, nonfiltering kidneys of dogs [14]. The use of this experimental model allows the dissociation of the stimulatory effects of PG's from any inhibitory effect of sodium delivery on the macula densa pathway to renin release and the input of the sympathetic nervous system to renin secretion. The

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results of these infusions showed that both PGI_2 and PGE_2 were capable of stimulating renin secretion in this nonfiltering model; PGI_2 was a slightly more potent stimulant for renin than PGE_2. Furthermore, additional studies with 13,14-dihydro-PGE_2 (a metabolite of PGE_2) demonstrated greater renin release potency than did PGI_2. The 13,14-dihydro-PGE_2 was included in these studies because it is a substrate that is poorly transported into cells, thus delaying its catabolism [14]. In summary, these results imply that the relative potency of a particular PG synthesis product may depend in part on the ability of the kidney to transport and catabolize the compound. Similar results with PGI_2 and PGD_2 infusions into canine denervated, nonfiltering kidneys have yielded significant increments in renin secretion [15]. It should be noted that although these studies in the denervated, nonfiltering kidney eliminate the macula densa and sympathetic nervous system as interfering stimuli to renin release, the renal baroreceptor mechanism remains functional in these kidneys. Thus, the PG infusions could alter renin secretion either indirectly via the baroreceptor or directly via the juxtaglomerular cells [14, 15].

To clearly isolate the direct effect of PG-induced renin secretion on the juxtaglomerular cells and to avoid the problem of rapid cellular uptake and catabolism, Franco-Saenz et al have recently developed a continuous superfusion system of rat renal cortical slices [16]. In this model, PGE_2 caused a dose-dependent stimulation of renin secretion at concentrations of 3×10^{-6} to 10^{-4} M that was not inhibited by propranolol. Dibutyryl cyclic AMP also caused a dose-dependent release of renin at concentrations of 10^{-5} to 5×10^{-3} M, but theophylline (at a dose of 4×10^{-3} M) had no effect on renin secretion. Interestingly, when theophylline was added to subthreshold doses of PGE_2 (10^{-6} M), renin release was significantly stimulated. Maximum stimulating doses of PGE_2 and dibutyryl cyclic AMP had no additive or synergistic effects. Taken together, these results in superfused kidney slices demonstrate that PGE_2 causes stimulation of renin release by a direct effect on the juxtaglomerular cell; this stimulation does not depend on the beta-adrenergic receptors but may be mediated in part by cyclic AMP. Recent observations by Campbell, Graham, and Jackson [17] differ with respect to the dependence of the renin-stimulating effects of PG's on cyclic AMP. Using a conscious rat model, these workers infused dibutyryl cyclic AMP into the renal artery (3 mg/kg/min) and noted a significant increase in serum renin activity, which was blocked by pretreatment with indomethacin (5 mg/kg). This result suggests that the renin stimulatory effect of PG's is distal to the stimulatory effect of cyclic AMP. This apparent discrepancy, however, may be resolved with future studies in the superfused renal cortical slice model testing the renin secretory effects of cyclic AMP with and without prostaglandin inhibition.

In summary, the recent series of investigations described above provide evidence that several PG's are capable of producing renin secretion. The in vivo experiments suggest renin stimulation is via direct effects on the juxtaglomerular cells of the kidney but do not exclude an effect on the intrarenal baroreceptor. In vitro data demonstrate a direct effect of several prostaglandins (for example, PGE_2 and PGI_2) on the juxtaglomerular cells directly to provoke a release of renin. The extent to which the stimulatory effects of these PG's depend on cyclic AMP must await further investigation.

Prostaglandins as necessary cofactors for other stimuli to renin secretion

Renal arterial baroreceptor. A decrease in renal perfusion pressure has been known for many years to result in a prompt and reproducible increase in renin secretion. But, the decrease in systemic pressure may potentially activate the juxtaglomerular cells via one of several pathways: *(1)* activation of an intrinsic baroreceptor sensitive to small changes in perfusion; *(2)* via efferent sympathetic nervous system reflexes activated by systemic baroreceptors; and *(3)* via a decrease in delivery of sodium to the macula densa.

The presence of an intravascular receptor sensitive to perfusion pressure changes and capable of stimulating renin secretion had been postulated for many years [18]. Later studies by Blaine and Davis [19] further clarified the mechanisms involved in renal baroreceptor function in studies in which the macula densa and sympathetic nervous system pathways were ablated by using a nonfiltering, denervated kidney model in the dog. These investigators also performed a bilateral adrenalectomy to reduce the influence of circulating catecholamines on renin secretion. In these experiments, hemorrhage (20 ml/kg) produced a significant increase in renin secretion. These authors subsequently observed an increase in renin secretion with graded decrements in perfusion pressure induced by a vascular clamp around the renal artery; the increase in renin secretion occurred even in the absence of a

decrease in renal blood flow (RBF) [19, 20]. Thus, this series of studies clearly documents the presence of an intrarenal, pressure-sensitive receptor that stimulates renin secretion when perfusion pressure falls. Moreover, the baroreceptor pathway is capable of producing large increments in renin release in the absence of other renin releasing factors such as the sympathetic nervous system or sodium delivery to the macula densa. Further evidence of the presence of the renal baroreceptor mechanism has been obtained in conscious sheep subjected to graded decreases in perfusion pressure [21]. In these studies, decreases in perfusion pressure in the autoregulatory range (13 and 21 mm Hg) resulted in prompt increases in renin secretion although RBF and GFR were not detectably decreased. These studies affirm the role of the intrarenal baroreceptor as a rapidly-acting defense against a decrease in systemic blood pressure via activation of the renin-angiotensin system.

Most of the known stimuli to renin release also result in an increase in renal PG synthesis and release. For example, renal hypoperfusion and renal nerve stimulation are known to induce the release of PG's in addition to renin [22, 23]. Several studies have recently assessed the relationship between and dependence of the renal baroreceptor mechanism on intact PG synthesis. In the first of these experiments, Data et al used the denervated, nonfiltering kidney model in adrenalectomized dogs receiving a continuous propranolol infusion [24]. This preparation obviated the complicating influences of the macula densa and sympathetic nervous system pathways. In the first series of studies, a vascular clamp was used to reduce renal perfusion pressure; RBF decreased 50% and renal venous renin activity increased from 3.1 to 13.1 ng AI/ml/hr ($P < 0.05$). When the clamping was repeated after pretreatment with indomethacin (8 mg/kg), renal venous renin did not increase. These studies therefore suggest that the integrity of the baroreceptor mechanism is PG dependent.

Similar results in the innervated filtering kidney have been observed by Berl et al [25] (Fig. 1). These investigators lowered renal perfusion pressure by aortic clamping (from 143 to 111 mm Hg) and noted a reversible increase in plasma renin activity from 6.3 to 11.2 ng AI/ml/hr ($P < 0.001$). When the clamping was repeated following pretreatment with indomethacin, plasma renin activity did not increase (4.5 to 4.0 ng AI/ml/hr [NS]). The RBF and the GFR were unchanged during both clamping procedures with this amount of perfusion pressure

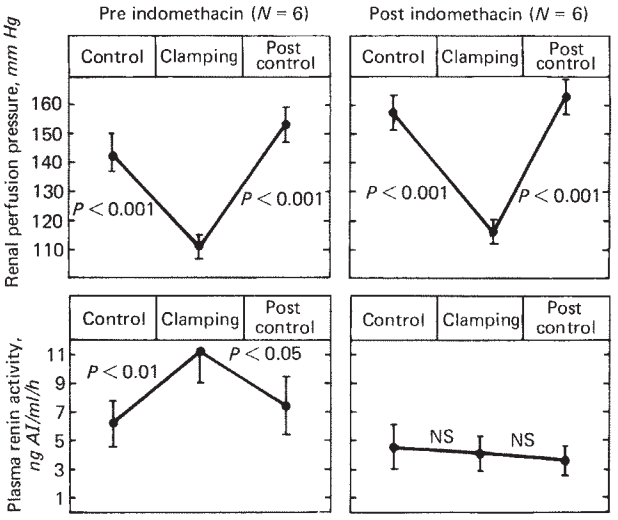

Fig. 1. *Effect of aortic clamping on renal perfusion pressure and plasma renin activity in prostaglandin-replete and -depleted dogs.* Plasma renin activity increased with clamping prior to indomethacin *(left panels)*, but failed to increase with repeated clamping after treatment with indomethacin *(right panels)*. (Adapted from Ref 25; reprinted with permission of *Am J Physiol*)

reduction; urinary sodium excretion declined significantly with clamping before indomethacin but was unchanged after indomethacin. These results provide support for the PG dependence of the baroreceptor within the autoregulatory range in the intact kidney; the data do not exclude a role for macula densa sodium delivery as important, however. Further studies using moderate hemorrhage (15 ml/kg) as the stimulus to renin secretion also identify baroreceptor integrity as PG dependent [26]. In these hemorrhage experiments, systemic blood pressure was reduced by 15% of control blood pressure via rapid arterial hemorrhage. β-Adrenergic blockade with propranolol was performed to block the sympathetic nervous system influence on renin secretion. When renal perfusion pressure was kept constant by means of a suprarenal aortic clamp during the hemorrhage, renin secretion did not increase during hemorrhage. Similarly, pretreatment with indomethacin (10 mg/kg) also prevented an increase in renin secretion when combined with β-adrenergic blockade with this amount of hemorrhage. These results were observed in the context of modest and insignificant decreases in both GFR and RBF. Thus, in summary, the results of these three experiments [24–26] demonstrate the renal arterial baroreceptor pathway to renin release to be PG dependent in the filtering kidney and nonfiltering kidney studied in vivo under conditions of both arterial clamping and hemorrhage.

These observations have been extended recently by Blackshear et al [27] by studies in which renal perfusion pressure was reduced by aortic clamping to levels below the autoregulatory range. In the first series of studies in intact canine kidneys, these investigators confirmed that with a decrease in renal perfusion pressure of 30 mm Hg (from 120 to 90 mm Hg), renin secretion increased significantly and could be attenuated by pretreatment with either indomethacin or meclofenemate. But, when perfusion pressure was further reduced to 60 mm Hg and RBF decreased significantly, the increase in renin secretion was not blunted by pretreatment with either of two PG synthesis inhibitors. These results argue that although the renal baroreceptor is PG dependent during reductions in perfusion pressure in the autoregulatory range (when RBF is well maintained), further reductions in perfusion pressure result in either the arterial baroreceptor becoming dissociated from PG dependence (via another efferent pathway to renin secretion) or the macula densa mechanism (or other tubular receptors) being sufficiently activated to independently provoke renin release. These results do not distinguish between these two possibilities. The data are consistent with the previous hypothesis proposed by Blaine, Davis, and Harris [28] that the arterial baroreceptor primarily controls renin release within the autoregulatory range of perfusion pressures and by the macula densa mechanism (or other tubular pathways) at perfusion pressures below this. The results of Blackshear et al [27] also provide evidence that PG's do not constitute a final common pathway to renin secretion because renin secretion dramatically increased when perfusion pressure was decreased below the autoregulatory range despite PG inhibition. Future investigations are needed to delineate the possibility of PG-inhibition "escape" of previously PG-dependent pathways from the activation of PG-independent pathways to renin release as responsible for these observations. Moreover, urinary or venous PG measurements should be made in future studies in order to exclude the real possibility that PG synthesis inhibition is not overcome by the stimulus to renin release being used.

Sympathetic nervous system. The adrenergic nervous system is a well-known stimulus to renin release under a variety of conditions. Electrical stimulation of the brain stem [29, 30], of the renal nerves [31, 32], as well as i.v. catecholamine infusions [33] are known to result in increased renin secretion. Furthermore, electron microscopy and histochemical fluorescence studies have shown that the juxtaglomerular cells of both rat and dog are supplied with adrenergic nerve endings [34].

Recent studies have clarified several aspects of the relationship between the adrenergic nervous system and renin. The stimulation of renal sympathetic nerves with a low dose of electricity (10 V; frequency, 0.33 Hz; duration, 0.5 msec) was demonstrated to provoke renin secretion (401 to 1255 U/min) but did not affect GFR, RBF, renal vascular resistance, systemic blood pressure, or urinary sodium excretion [35]. When the stimulation was repeated after the infusion of propranolol, however, the increase in renin secretion was abolished. These results supported a schema in which renal nerves stimulated the juxtaglomerular cells directly, and this effect was mediated through β-adrenergic receptors. Furthermore, subsequent pharmacologic investigations have established the β-1-adrenergic receptor as responsible for renin release [36, 37]. But, β-adrenergic blockade with propranolol does not affect the ability of PG's to induce renin release [16]. This finding implies that PG's have a renin stimulatory effect either separate from or distal to the β-adrenergic stimulatory effect.

In the recent investigation by Berl et al [25], the precise relationship of the β-adrenergic receptors and their dependence on PG's was examined in detail in dogs. In the first group of studies, an i.v. isoproterenol solution was found to stimulate an increase in plasma renin activity (from 3.2 to 15.6 ng AI/ml/hr, $P < 0.001$); this increase was not blunted by prior indomethacin administration (4.8 to 14.2 ng AI/ml/hr). But, the systemic isoproterenol infusion also caused a decrease in renal perfusion pressure, which could have accounted for this increase in plasma renin independently of the β-adrenergic stimulation. The studies were therefore repeated with renal perfusion maintained constant (Fig. 2) during isoproterenol infusion by means of a suprarenal aortic clamp. In this series of experiments, an increase in plasma renin was again observed after isoproterenol in both PG-synthesis-intact (11.7 to 23.8 ng AI/ml/hr, $P < 0.001$) and PG-synthesis-inhibited (8.6 to 18.9 ng AI/ml/hr, $P < 0.05$) conditions. These results in the dog strongly suggest that a PG-synthesis-independent pathway for renin release due to β-adrenergic stimulation exists and are in agreement with recent studies in man [38].

A similar finding was documented by Seymour and Zehr [39] in which i.v. isoproterenol (0.02 μg/kg/min) was used to provoke renin secretion in the presence and absence of an intrarenal infusion

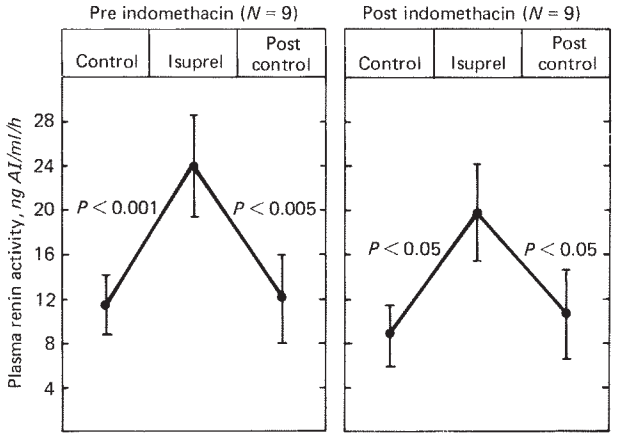

Fig. 2. *Effect of isoproterenol on plasma activity in prostaglandin-replete and -depleted dogs with controlled renal perfusion pressure.* Plasma renin activity increased significantly in both prostaglandin-intact *(left panel)* and prostaglandin-inhibited *(right panel)* groups. (Adapted from Ref. 25; reprinted with permission of *Am J Physiol*)

of indomethacin (0.1 mg/kg/min) in dogs. In the control studies, isoproterenol produced a significant increase in plasma renin activity (from 2.54 to 8.79 ng AI/ml/hr, $P < 0.05$). Despite the simultaneous intrarenal infusion of indomethacin in a dose documented to inhibit PG synthesis, isoproterenol again induced an increase in plasma renin activity (from 1.11 to 3.23 ng AI/ml/hr, $P < 0.05$). The baseline plasma renin activity was lower in the animals receiving the indomethacin, but the magnitude of the increase in plasma renin activity (approximately threefold) was similar for both groups of animals. Thus, these findings and those of Berl et al [25] provide evidence in the dog of a PG-independent pathway to renin release when a β-adrenergic agonist infusion is performed.

A similar conclusion is forthcoming from the study by Henrich, Schrier, and Berl [26] in which endogenous β-adrenergic stimulation induced by hemorrhage (15 ml/kg) was the stimulus to renin release. In these experiments, the increase in renin secretion observed with hemorrhage could not be blocked with constant renal perfusion pressure, propranolol, or indomethacin when used as solitary blocking maneuvers. Thus, a multifactorial mechanism seemed most likely to provoke renin release in this model of moderate hemorrhage in the dog. When renal perfusion control was combined with β-adrenergic blockade, renin secretion was blunted. This result suggested that the arterial baroreceptor and the β-adrenergic nervous system constituted the primary pathways to renin release. Because the arterial baroreceptor was observed to be PG-dependent in the earlier clamping experiments [24, 25], PG synthesis inhibition in combination with β-adrenergic blockade would be expected to also block renin secretion in this model. This, in fact, was the observation in the next group of dogs hemorrhaged with indomethacin and propranolol pretreatment, lending further support to the PG-dependent baroreceptor theory developed in the earlier clamping studies. Finally, the combination of PG synthesis inhibition and renal perfusion pressure control would not have been expected to attenuate renin secretion in the final group of animals unless the β-adrenergic nervous system was also PG-dependent. Renin secretion was observed to increase significantly in this final group of animals, supporting the earlier conclusion by Berl et al [25] and Seymour and Zehr [39] that the β-adrenergic nervous system pathway to renin secretion is PG independent, at least in the dog.

Anderson et al [40] have further probed the relationship of the endogenously stimulated β-adrenergic receptor and renin release in a series of experiments in which hypercapnic acidosis was induced in dogs. These workers demonstrated that hypercapnic acidosis (P_{CO_2} to 77 mm Hg; pH, 7.04) resulted in an increase in plasma renin activity and renin secretion in innervated kidneys. Renal denervation or β-adrenergic blockade with propranolol ablated these increases in renin secretion and plasma renin activity. This result would suggest that this stimulus to renin release is mediated primarily via the β-adrenergic component of renal nerves, although the contribution of circulating catecholamines to the increase in renin in this model is unknown. Pretreatment of the animals with indomethacin (5–10 mg/kg) did not, however, blunt the increase in plasma renin activity (1.5 to 5.1 ng AI/ml/hr, $P < 0.001$) or renin secretion rate in innervated kidneys (124 to 293 U/min, $P < 0.05$) in response to hypercapnic acidosis. This finding is most compatible with a β-adrenergic-mediated renin response induced via renal nerves and independent of the renal PG's system. Moreover, the results of these studies with hypercapnic acidosis are in agreement with the data derived in dogs undergoing hemorrhage [26] or isoproterenol infusions [25, 39]. In agreement with these studies is a recent preliminary report by Kopp et al [41] in which low level electrical renal nerve stimulation in the dog induced renin secretion in the presence of PG synthesis inhibition. This finding further implies a PG-independent pathway to renin release for the β-adrenergic nervous system.

The possibility that the integrity of the β-adrenergic pathway to renin release is modified by the absence of intact PG synthesis has been suggested by recent studies by Campbell, Graham, and Jackson [17]. The ability of the β-adrenergic agonists isoproterenol and a selective β-1 agonist (H133/22) to stimulate renin secretion was investigated with and without PG synthesis inhibition. In these studies in the rat, intrarenal isoproterenol caused a fourfold increase in serum renin activity. But, isoproterenol infusion in the presence of indomethacin (5 mg/kg) also caused renin to increase, but the magnitude of the increase (about 2.6-fold) was significantly less than the PG-synthesis-intact rats. Two doses of the selective β-1 agonist H133/22 (0.3 and 1.0 mg/kg, respectively) produced stepwise increments in serum renin activity that were statistically significant: 3.1 (control) to 10.4 (0.3-mg dose) to 25.0 ng AI/ml/hour (1-mg/kg dose). Although the increases in serum renin were significant in rats pretreated with indomethacin receiving the same doses of the β-1 agonist, the magnitude of the increases were again significantly less in these animals. Neither of these drugs detectably reduced blood pressure although effects on renal function were not measured. These investigators also infused dibutyryl cyclic AMP into the renal arteries of rats and noted an increase in serum renin activity; the magnitude of the increase was again diminished by indomethacin. The authors therefore postulate that PG's stimulate renin release at a site distal to the β-adrenergic receptor and cyclic AMP in the rat. More recent studies using an intrarenal dose of indomethacin (250 μg/kg/min) in the cat have also been demonstrated to blunt renin release stimulated by a β-adrenergic infusion [42].

Certainly these discrepancies in the β-adrenergic data in the dog [25, 26, 39–41] and man [38] versus the rat [17] and cat [42] may in part be related to species variation. Further, the nature and intensity of the β-adrenergic stimuli may be different in these series of studies: in the dog, *endogenous* renal nerve stimulation and catecholamine release after hemorrhage [26], hypercapnic acidosis [40], or isoproterenol systemically (0.018 μg/kg/min) [25, 39]. In the rat and cat studies, isoproterenol infusion into the renal artery in higher doses of 100 μg/kg/min [17] and 0.1 μg/kg/min [42], respectively, were used as stimuli. It is also conceivable that these higher β-adrenergic doses stimulate other pathways to renin release [43]. Moreover, the canine studies in which the β-adrenergic system appeared to be PG independent were not accompanied by simultaneous measurements of PG excretion. Therefore, it is possible that only partial cyclooxygenase inhibition may have been achieved with some stimuli and that this accounts for the failure to blunt renin secretion. Clearly, however, results in the dog [25–27] suggest that during PG synthesis inhibition some pathways to renin release are unblocked or, alternatively, a pathway may be only partially inhibited and is capable of "escape" during maximum stimulation. But, the data of Campbell et al [17] and Feurstein and Feurstein [42] do imply a modulating influence of PG synthesis inhibition of renin release in some species, and further suggest a series of studies to probe this question directly. These issues could be greatly clarified by the use of low level direct nerve stimulation studies (without alteration of renal hemodynamics) with and without PG synthesis inhibition and with measurements of renal venous and/or urinary PG levels. Moreover, experiments in which both rat and dog renal cortical slices are incubated with isoproterenol and dibutyryl cyclic AMP in the presence and absence of cyclooxygenase inhibition would serve to significantly clarify the apparent discrepancies in the results.

Macula densa. The relationship between the renal PG system and the macula densa pathway to renin release has been relatively unstudied. In fact, the relative importance of the macula densa to alter renin release is presently unclarified. Earlier studies by Vander and Miller [13] and later Vander and Carlson [44] suggested that decreased sodium delivery to the distal nephron enhanced renin secretion. In these experiments, renal artery clamping produced an increase in renin release and a decrease in sodium excretion. Subsequent administration of hydrochlorothiazide or production of an osmotic diuresis blunted the increases in renin when clamping was repeated. Later studies have implicated sodium transport at the macula densa as important for stimulation of the renin-angiotensin system [45, 46].

The ability of PG's to influence tubular fluid sodium delivery and thereby affect renin release is incompletely resolved at present. Prostaglandin infusions into the renal artery of dog [47, 48] and man [49, 50] have been shown to induce a natriuresis, thus potentially influencing renin release via the macula densa. Moreover, these agents induce marked changes in RBF, further obscuring an independent effect on distal tubular sodium composition. Tannenbaum et al [11] were able to induce an ipsilateral natriuresis with arachidonate infusion in

a dose (<3 μg/kg/min) that avoided alterations in GFR or RBF. This natriuresis was ablated by administration of an inhibitor of PG synthesis. These results suggest that products of PG synthetase are natriuretic, independently of recognized hemodynamic alterations.

In the experiments described earlier by Henrich et al [26], the relationship between PG synthesis and the macula densa was indirectly addressed. In one group of animals subjected to hemorrhage which received propranolol and indomethacin prior to hemorrhage, renin secretion was inhibited, and the usual increase in plasma renin activity was blunted. This inhibition of renin secretion occurred despite a significant fall in urinary sodium excretion. Although urinary sodium excretion may not precisely reflect sodium delivery to the macula densa, the likelihood of a decrease in distal tubular sodium delivery is high. These findings in this group of dogs suggests that the macula densa stimulus with this amount of hemorrhage is of secondary importance in renin secretion. Alternatively, one could argue that the macula densa stimulus was dependent on intact PG synthesis or intact β-adrenergic receptors. In the clamping studies by Blackshear et al [27], however, renin secretion was intact at low renal perfusion pressures (53 to 60 mm Hg) despite PG synthesis inhibition. This observation would support the view that the macula densa pathway operates independently of the PG system; as noted earlier, the results, however, are also consistent with the possibility that a previously inhibited process at higher renal perfusion pressures becomes sufficiently intense to escape from inhibition. The most direct study on the macula densa and renin-PG interaction is a recent series of experiments by Olson et al [51]. These investigators reduced distal sodium delivery with a clamp in a kidney maximally vasodilated and undergoing β-blockade. In these studies, PG synthesis inhibition blocked the expected increase in plasma renin activity. This suggests the macula densa mechanism is PG dependent. A similar preliminary result is forthcoming in data obtained in the rat [52].

Summary. Figure 3 schematically depicts a representation of the relationships that exist between the renal PG system and renin release. Prostaglandins may stimulate renin release directly [6, 10, 14, 16], and clearly appear to be an intermediary step in the function of the baroreceptor but not the β-adrenergic pathway for renin release in the dog [25, 26, 39, 40] and man [38]. Studies performed in the rat [17] and cat [42] suggest, however, PG modulation of

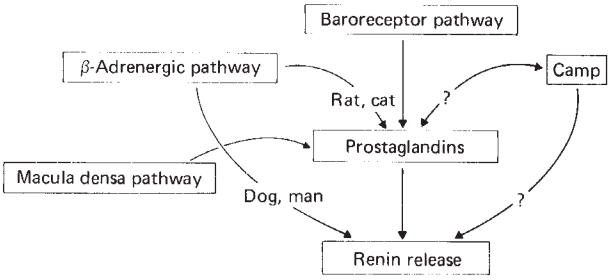

Fig. 3. *Schematic depiction of the prostaglandin-renin relationship.* See summary for detailed explanation.

the β-adrenergic pathway to renin release. Finally, although the macula densa pathway for renin release may be of relatively less importance at renal perfusion pressures in the autoregulatory range [26, 27], recent evidence points to the likely PG dependence of this pathway [51, 52]. The precise location of cyclic AMP in the PG-renin schema is presently unclear [16, 17].

Future investigations using superfusions of cortical slices and isolated renin releasing cells will be necessary to clarify the already complicated relationship between renin secretion and PG's. Such studies are particularly needed to answer the questions raised regarding species differences in renin release. Similarly, in vivo experiments with low-dose electrical nerve stimulation and specific β-agonist infusions in the presence and absence of cyclooxygenase inhibition with documented inhibition of PG's are also of critical importance if a clearer understanding of this fascinating aspect of renal physiology is to be realized.

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