Role of Renal Prostaglandins in the Control of Renin Release

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CONTROL of renin release is multifactorial and complex. Stimuli for renin release act through three groups of mechanisms which include: two intrarenal receptors, the renal vascular baroreceptor in the afferent arterioles and the macula densa in the distal nephron; the renal sympathetic nerves and a renal \( \beta \)-adrenergic receptor; and a group of humoral agents (Davis and Freeman, 1976; Keeton and Campbell, 1980). During the past decade, attention has focused increasingly on the potential role of the renal prostaglandin system in renin release, both as an independent mechanism and as an essential component in stimulus-secretion coupling for the other major mechanisms that control renin release (Hench, 1981; Oates et al., 1979). The purpose of this communication is to review this evidence and to analyze the possible mechanisms through which the renal prostaglandins exert their actions on the renin secretory process.

The prostaglandins are not stored in the tissues, but, rather, are synthesized and released on demand. Hassid and Dunn (1980) have reported that microsomes prepared from the medulla and cortex of human kidneys convert precursor arachidonic acid to PGE\(_2\), PGD\(_2\), 6-keto-PGF\(_{1\alpha}\), and thromboxane B\(_2\); the relative amounts of these generated prostaglandins were found to be similar in both regions. However, the quantitative capacity of the renal medulla to synthesize prostaglandins is clearly 5- to 10-fold greater than the capacity of the cortex (Larsson and Anggard, 1973). Immunochemistry studies have localized renal cyclooxygenase activity principally to the vascular endothelial cells of the renal arteries and arterioles, the collecting duct cells, and the medullary interstitial cells in several species. Cyclooxygenase activity was also identified in epithelial cells of Bowman’s capsule in the rabbit and in mesangial cells of bovine and ovine glomeruli, but the enzyme was not found in the area of the macula densa or in the juxtaglomerular (JG) cells of any animal species (Smith and Bell, 1978; Smith and Wilken, 1977). Biochemical studies have identified PGE\(_2\) as a major synthetic product of arachidonic acid metabolism in the medullary interstitial cells (Dunn et al., 1976; Zusman and Keiser, 1977) and the papillary collecting tubules (Bohman, 1977). Isolated glomeruli synthesize large amounts of PGF\(_{2\alpha}\) and PGE\(_2\) and smaller quantities of 6-keto-PGF\(_{1\alpha}\), the stable aqueous breakdown product of prostacyclin (Folkert and Schlondorff, 1977; Hassid et al., 1979). Prostacyclin appears to be the principal end product of arachidonic acid metabolism within the renal arteries and arterioles, but both PGE\(_2\) and PGF\(_{2\alpha}\) are synthesized also (Terragno et al., 1978). It has been suggested (McGiff and Wong, 1979) that the compartmentalization of prostacyclin biosynthesis within the renal vascular compartment has potential functional significance for the regulation of renin release and renal vascular resistance.

Available data show, therefore, that at least three renal tissues contain cyclooxygenase and are capable of prostaglandin biosynthesis: (1) the vascular compartment which includes the glomerulus and renal arterioles, (2) the collecting duct cells, and (3) the medullary interstitial cells. These tissues metabolize arachidonic acid to a number of different prostaglandins, but the major end product may differ at the various anatomical sites. Cyclooxygenase is not found within the juxtaglomerular cell, and this is inconsistent with the concept that intracellular prostaglandin biosynthesis functions in stimulus-secretion coupling for renin release. However, it is clear that prostaglandins are synthesized at strategically located renal sites within the vascular, urinary, and interstitial spaces wherefrom they may gain access to the juxtaglomerular apparatus to exert their influence on renin release.

Prostaglandin Stimulation of Renin Release

Eicosatetraenoic (arachidonic) acid, precursor of the diene series of prostaglandins, is a potent stimulus for renin release. The intrarenal infusion of
nonhypotensive doses of arachidonic acid demonstrated produces a consistent increase in renin release in several animal models (Bolger et al., 1976; Larsson et al., 1974; Weber et al., 1975), including the dog with a single denervated nonfiltering kidney to eliminate the potential complicating influence of the macula densa and the renal nerves (Data et al., 1978; Seymour and Zehr, 1979). Arachidonic acid also stimulates renin release in vitro when added to isolated rat glomeruli (Beierwaltes et al., 1980, 1982) or to renal cortical slices (Lin et al., 1981; Weber et al., 1976; Whorton et al., 1977, 1980). Indomethacin blocks this increased renin response produced by the administration of arachidonic acid, suggesting that arachidonic acid stimulates renin release after its enzymatic conversion to one or more of its synthetic products, presumably the prostaglandins (Bolger et al., 1976; Data et al., 1978; Lin et al., 1981; Seymour and Zehr, 1979; Weber et al., 1976). Several prostaglandins derived from arachidonic acid metabolism also stimulate renin release when infused into animals (Bolger et al., 1977, 1978; Echtenkamp et al., 1982; Gerber et al., 1978, 1979; Seymour et al., 1979; Yun et al., 1977) or when added to in vitro systems (Franco-Saenz et al., 1980; Lin et al., 1981; Whorton et al., 1977, 1980) and these include PGD₂, PGI₂, PGE₂, and 13,14-dihydro PGE₂. These findings are consistent with a direct stimulatory action on the JG cells of one or more prostaglandins derived from precursor arachidonic acid. However, these findings do not preclude the possibility that end products of arachidonic acid metabolism also act indirectly in the intact animal to amplify or attenuate the signal for other renin release mechanisms, e.g., arachidonic acid can alter both fluid and electrolyte excretion and renal arteriolar tone (Bolger et al., 1976; Tannenbaum et al., 1975) and, thus, might influence indirectly the macula densa and the renal vascular baroreceptor, respectively (Davis and Freeman, 1976; Keeton and Campbell, 1980).

Since arachidonic acid is converted within the kidney to a number of prostaglandins, there remains the question of which of these end products mediates the renin response elicited by arachidonic acid administration. There is no clear answer to this question, but a great deal of interest has focused on PGI₂ and PGE₂ as potential candidates for this function. Because PGE₂ was discovered, isolated, and synthesized prior to PGI₂, the effects of PGE₂ on renin release were examined first, but more recent studies have focused on PGI₂ stimulation of renin release. Also, as noted earlier, both PGI₂ and PGE₂ are synthesized in the wall of the renal arterioles in close proximity to the granular JG cells, but PGI₂ apparently is the predominant synthetic end product (Terragno et al., 1978; McGiff and Wong, 1979).

Evidence for a direct action of PGI₂ on renin release has been provided by Whorton et al. (1977), who reported that PGI₂ stimulated renin release in a dose-dependent manner when added to an in vitro system of rabbit renal cortical slices; addition of 6-keto-PGF₁ₐ, the aqueous breakdown product of PGI₂, failed to stimulate renin release. Prostacyclin also strongly stimulated renin release from slices of mouse renal cortex, and this stimulation was dose-dependent (Lin et al., 1981). Subsequently, Whorton et al. (1980) reported that selective inhibition of PGI₂ synthesis with 9,11-azoprosta-5,13-dienoic acid decreased basal and arachidonic acid-stimulated renin release from rabbit cortical slices by 22% and 60%, respectively; synthesis of PGI₂ was inhibited by 68% but synthesis of PGE₂ and PGE₂ₖ, remained intact. In more recent studies, Beierwaltes et al. (1982) also reported selective inhibition of arachidonic acid-stimulated renin release and prostacyclin biosynthesis from isolated rat glomeruli with 9,11-azoprosta-5,13-dienoic acid at a dose which did not attenuate the PGE₂ response to arachidonic acid administration. These results are consistent with the concept that PGI₂ acts directly on the JG cells to stimulate renin release (Lin et al., 1981; Whorton et al., 1977) and, therefore, might be the selective mediator of arachidonic acid-induced renin release (Beierwaltes et al., 1982; Whorton et al., 1980). Recent observations (Jackson et al., 1981a; Spokas et al., 1982) suggest that the renin response to PGI₂ might be mediated partially by a stable metabolite of prostacyclin, 6-keto-PGE₁ₕ.

To summarize this section, it is clear that arachidonic acid stimulates renin release in several animal species via its conversion to one or more of the prostaglandins. Stimulation of renin release with these compounds is observed in the intact animal and in several in vitro systems. The results are consistent with the concept that the prostaglandins increase renin release by a direct action on the JG cells and, perhaps, also by an indirect action to influence other renin release mechanisms in the intact animal. Current evidence suggests a selective role for PGI₂ in renin secretion for several reasons: (1) it is the predominant synthetic product of arachidonic acid metabolism in the renal arterioles; (2) selective inhibition of prostacyclin synthesis blocks the increased renin response to administration of arachidonic acid; and (3) PGI₂ consistently appears to be more potent than PGE₂ in stimulating the release of renin. Finally, a stable active metabolite of PGI₂, 6-keto-PGE₁ₕ, may partially mediate this renin response.

Prostaglandins As Possible Mediators in Stimulus-Secretion Coupling for Other Renin Release Mechanisms

In the early 1970's it was realized that the non-steroidal anti-inflammatory drugs such as aspirin and indomethacin suppressed endogeneous synthesis of the prostaglandins (Vane, 1971). Subsequently, numerous investigators have used these inhibitors to evaluate the renal prostaglandin system in the control of renin release (Keeton and Campbell,
Evidence has been provided to suggest an important contribution of the prostaglandins in the hyperreninemia of patients with Bartter's syndrome (Gill et al., 1976) and in several chronic animal models with hyperreninemia, including chronic sodium depletion (DeForrest et al., 1980; Frolich et al., 1979; Suzuki et al., 1981b), chronic constriction of the thoracic inferior vena cava in the dog (Echtenkamp et al., 1981), and experimental hypertension in several species (Dietz et al., 1981; Jackson et al., 1981b; Romero and Strong, 1977). However, these studies indicate also that inhibition of prostaglandin biosynthesis attenuates but rarely obliterates completely the hyperreninemia (DeForrest et al., 1980; Dietz et al., 1981; Echtenkamp et al., 1981; Jackson et al., 1981b; Suzuki et al., 1981b). Indeed, following administration of indomethacin to conscious animals, the plasma renin activity remained elevated 10- and 17-fold, respectively, in one-kidney Goldblatt hypertensive dogs and in dogs with chronic sodium depletion, and it was concluded that the basic mechanisms for stimulation of renin secretion remained intact after inhibition of prostaglandin synthesis (DeForrest et al., 1980; Dietz et al., 1981). Although these and similar observations make it unlikely that the renal prostaglandin system functions as the final common pathway for renin release, it has been suggested that the prostaglandins function as essential mediators for one or more of the major mechanisms for renin release (Henrich, 1981; Oates et al., 1978). Let us now consider the evidence for and against this hypothesis for each of the three major receptor mechanisms that control renin release.

Renal Vascular Baroreceptor Mechanism

According to current theory (Davis and Freeman, 1976), the renal vascular baroreceptor includes the JG cells and adjacent renal afferent arteriole, and this receptor senses alterations in afferent arteriolar wall tension or stretch and releases renin when renal perfusion pressure is decreased. In addition, an acute reduction in renal perfusion pressure also increases the release of renal prostaglandins (McGiff et al., 1970; Herbaczynska-Cedo and Vane, 1973; Jackson et al., 1982a), which can stimulate renin release by a direct action on the JG cell. These observations raise the question of the possibility that the prostaglandins mediate or modulate intrarenal baroreceptor-stimulation of renin release (Jackson et al., 1982a). Indeed, the fundamental importance of the autonomous renal vascular baroreceptor mechanism for renin release led to early studies evaluating its dependency on the renal prostaglandin system, and one of the first suggestions that prostaglandins function as mediators for secretion-coupling was for the renal vascular baroreceptor (Data et al., 1978).

In 1979, Seymour and Zehr reported that indomethacin failed to attenuate increased renin release in response to a reduction in perfusion pressure below the renal hemodynamic autoregulatory range in the anesthetized dog with a filtering kidney in which the renal vascular baroreceptor and macula densa both were present. In the same year, Blackshear and coworkers (1979) evaluated the renin response to decreased renal perfusion pressure within and below the autoregulatory range for renal blood flow in anesthetized dogs with filtering kidneys. In this study (Blackshear et al., 1979), neither indomethacin nor meclofenamate prevented the stimulation of renin secretion when renal perfusion pressure was reduced below the autoregulatory level to 53-60 mm Hg. However, both inhibitors of prostaglandin synthesis blunted the stimulation of renin secretion when perfusion pressure was reduced within the autoregulatory range to only 83-90 mm Hg. Berl et al. (1979) also reported that indomethacin blocked the renin response to decrease in renal perfusion pressure within the renal hemodynamic autoregulatory range in the anesthetized dog. These results (Berl et al., 1979; Blackshear et al., 1979) indicate that decreases in renal perfusion pressure to levels within the autoregulatory range stimulated renin release from intact filtering kidneys via a prostaglandin-dependent mechanism. However, further decreases in renal perfusion pressure to levels below the autoregulatory range clearly stimulated renin release via mechanisms independent of renal prostaglandin biosynthesis (Blackshear et al., 1979; Seymour and Zehr, 1979). It is emphasized that the macula densa was potentially functional and, very likely, was activated in all of these studies and, therefore, it is difficult to reach any specific conclusions concerning stimulus-secretion coupling for the vascular baroreceptor mechanism per se. It is concluded that the findings in these experiments are consistent with the interpretation that in the filtering kidney at least three potentially independent mechanisms for renin release are activated by decreases in renal perfusion pressure: the intrarenal vascular baroreceptor, the macula densa, and increased prostaglandin biosynthesis. There is little information concerning the relative importance of these three mechanisms at different levels of perfusion pressure within and below the autoregulatory range, and the concept that the renal prostaglandins function as a final common pathway for renin release seems unlikely (Blackshear et al., 1979; Seymour and Zehr, 1979).

With the realization that the intact-filtering kidney preparation presented some difficult problems of interpretation, Data et al. (1978) decided to evaluate the renin response to decreased renal perfusion pressure in the adrenalectomized dog with a single denervated nonfiltering kidney before and after indomethacin administration. In this experimental model, the renal vascular baroreceptor mechanism for renin release functions autonomously without support from the macula densa and the β-adrenergic receptor mechanisms (Blaine et al., 1970, 1971).
changes in plasma renin activity were evaluated in response to suprarenal aortic constriction before and after meclofenamate administration in anesthetized rats with a single denervated nonfiltering kidney. In all groups, suprarenal aortic constriction was adjusted to decrease perfusion pressure by about 50% to a level below the autoregulatory pressure for renal blood flow. In the control group of rats with a single denervated nonfiltering kidney, 15 minutes of suprarenal aortic constriction significantly increased plasma renin activity 3-fold. Administration of meclofenamate (10 mg/kg, iv) failed to block or attenuate this response in a separate group of rats. Meclofenamate also failed to attenuate the renin response to aortic constriction in another group of rats with a single denervated nonfiltering kidney and with bilateral adrenalectomy, to exclude any possible influence of the adrenal catecholamines on renin release. These results (Freeman et al., 1982; Villarreal et al., 1983) in the dog and the rat models with a single denervated nonfiltering kidney demonstrate that the renal prostaglandin system is not essential for the full renin release response to activation of the isolated renal vascular baroreceptor mechanism.

To summarize this section, pharmacological inhibition of endogenous prostaglandin biosynthesis has provided evidence for both prostaglandin-dependent and prostaglandin-independent mechanisms of renin release in response to decreased perfusion pressure in the anesthetized animal with intact filtering kidneys. The prostaglandin-dependent mechanism was reported following reductions in perfusion pressure within the autoregulatory range of filtering kidneys, and may reflect a direct action of endogenous prostaglandins on the JG cells. An alternative interpretation is that the prostaglandins partially mediate baroreceptor and/or macula densa-stimulated renin release in the filtering kidney preparation, but renin release becomes prostaglandin independent with greater reductions in perfusion pressure that, presumably, fully activate all three potential mechanisms. Finally, the results from studies with the denervated nonfiltering kidney in the dog and rat models suggest that the renal prostaglandins do not function as essential mediators in stimulus-secretion coupling for the isolated renal vascular baroreceptor mechanism in control of renin release below the autoregulatory range of renal blood flow. It should be appreciated, however, that the relationship between the prostaglandins and renin release may not be entirely normal in the nonfiltering kidney preparation. Additional studies are needed to evaluate the role of the prostaglandin system in the stimulation of renin release from the isolated renal vascular baroreceptor under more physiological conditions when perfusion pressure is reduced within the autoregulatory range for renal blood flow; there are no published data on this important point.
Macula Densa Mechanism

The importance of the macula densa region of the distal nephron as a sensor for renin secretion in various experimental and clinical situations remains poorly defined, as does the nature of the signal perceived by the macula densa (Davis and Freeman, 1976; Keeton and Campbell, 1980). Current evidence suggests that renin release is related inversely to chloride delivery and/or transport into or across the macula densa cells (Kirchner et al., 1978; Kotchen et al., 1976). The relationship between the renal prostaglandin system and the macula densa mechanism for renin release is unclear. As pointed out earlier in this review, however, it is important to remember that cyclooxygenase is not found in the area of the macula densa cells (Smith and Bell, 1978; Smith and Wilkins, 1977). In a recent study (Gerber et al., 1981), changes in plasma renin activity were evaluated in response to suprarenal aortic constriction in anesthetized dogs undergoing intrarenal infusions of the vasodilator papaverine in an attempt to block the renal vascular baroreceptor mechanism and with renal denervation and propranolol administration to block adrenergic pathways for renin release. In this experimental model, a 50% reduction in renal perfusion pressure from approximately 130 to 61–69 mm Hg decreased renal blood flow and urinary sodium excretion, while plasma renin activity increased 2- to 3-fold after 10 and 25 minutes of aortic constriction. In these studies, inhibition of prostaglandin biosynthesis with indomethacin or meclofenamate prevented this increase in plasma renin activity. It was concluded that macula densa stimulation of renin release is mediated by the renal prostaglandin system (Gerber et al., 1981).

Francisco et al. (1982) examined the role of the prostaglandin system in the hyperreninemia of chronic sodium depletion in anesthetized rats prepared for micropuncture studies; also, acute bilateral denervation was performed by cutting the renal nerve bundles, stripping the renal arteries of their adventitia, and painting the vessels with 10% phenol. Compared with rats fed a normal sodium diet, both vehicle-and indomethacin-pretreated sodium-depleted rats had reduced rates of early distal tubular fluid sodium delivery. The control sodium-depleted rats pretreated with vehicle only had an elevated plasma renin level, and this elevation in renin was not observed in the indomethacin-pretreated sodium-depleted group. Indomethacin-pretreatment failed to alter mean arterial pressure or renal hemodynamic function in rats fed either normal or low sodium diets. It was concluded that the increase in plasma renin activity during chronic sodium deprivation in rats is dependent on intact prostaglandin synthesis and, possibly, results from stimulation of the macula densa. Again, it is important to recall that anesthesia and acute laparotomy stimulate basal levels of renin and prostaglandin release (Davis and Freeman, 1976; Terragno et al., 1977). Two separate studies in the conscious sodium-deplete rat reported only partial (Suzuki et al., 1981b) or no attenuation (Campbell et al., 1979b) of the hyperreninemia after indomethacin administration.

A different approach to studying the interaction between the prostaglandins and the macula densa mechanism for renin release was taken by Villarreal et al. (1982). Intrarenal infusion of prostacyclin at nonhypotensive doses significantly increased renin secretion 3-fold in anesthetized dogs with a single filtering kidney; renal blood flow also increased markedly, but creatinine clearance did not change during PGI2 infusions. Superimposition of intrarenal hypertonic sodium chloride during PGI2 infusion increased the renal venous plasma sodium concentration, the tubular load of sodium chloride, and urinary sodium excretion, while renin secretion was inhibited and decreased to a level not different from the control level obtained before PGI2 infusion. Prostacyclin also was infused intrarenally into anesthetized dogs with a single denervated nonfiltering kidney and, again, renin secretion significantly increased, 3- to 4-fold, while renal blood flow increased markedly. In striking contrast to the filtering kidney series, however, the superimposition of intrarenal hypertonic sodium chloride during PGI2 infusion now failed to attenuate renin secretion in these dogs without a functional macula densa receptor; renin secretion remained significantly elevated 3-fold, and this was not different from the renin secretion rate obtained during PGI2 infusion alone. Intrarenal hypertonic sodium chloride infusion did not attenuate PGI2-mediated renal blood flow increments in either the filtering or nonfiltering kidney series, again suggesting that hypertonic sodium chloride suppressed renin secretion in the filtering kidneys by a tubular mechanism in the absence of an associated change in renal hemodynamic function. Thus, a well-defined signal to the macula densa, increased delivery of sodium chloride, specifically inhibited renin secretion when renin stimulating levels of PGI2 were maintained constant by exogenous infusion. This finding is consistent with the suggestion that the mechanism for inhibition of renin release via the macula densa receptor functions independent of the mechanism for PGI2-stimulated renin release.

To summarize this section, there is a paucity of information on the renal prostaglandin system in stimulus-secretion coupling for the macula densa mechanism in control of renin release. Additional observations are needed to help clarify this controversial and important problem, but the necessary methodology required to isolate and stimulate selectively the macula densa has not been developed at this time.
Renal Adrenergic Mechanisms

Renal nerve stimulation and infusion of norepinephrine and epinephrine not only increase renin secretion (Vander, 1965), but also increase the production and release of renal prostaglandins (Dunham and Zimmerman, 1970; Needleman et al., 1974). The increase in renin secretion produced by low intensity renal nerve stimulation is mediated by a β-adrenergic receptor mechanism (Taher et al., 1976; Kopp et al., 1980). Catecholamine-induced prostaglandin release appears to be mediated by α-adrenergic receptor stimulation, since isoproterenol does not cause prostaglandin release and β-adrenergic receptor blockade with propranolol does not attenuate epinephrine-induced prostaglandin release (Needleman, et al., 1974). α-Adrenergic receptor blockade with phenoxybenzamine inhibits both prostaglandin release and renal vasoconstriction in response to epinephrine infusion and to renal nerve stimulation (Needleman et al., 1974). It is unclear whether renin release and prostaglandin release occur in series and are causally related, or occur in parallel and represent two separate and independent responses to adrenergic stimulation. It is possible that the renin response to adrenergic stimulation might involve both prostaglandin-dependent and prostaglandin-independent mechanisms.

One approach to this problem has been to compare adrenergic stimulation of renin release before and after the inhibition of prostaglandin synthesis with cyclooxygenase inhibitors. In the anesthetized dog, intravenous infusions of isoproterenol stimulated renin release, both before and after administration of indomethacin, to inhibit renal prostaglandin synthesis (Berl et al., 1979; Seymour and Zehr, 1979). In the experiments by Seymour and Zehr (1979), isoproterenol infusion (0.02 μg/kg per min, iv) significantly increased plasma renin activity approximately 3-fold in control dogs and in dogs pretreated with indomethacin; renal venous efflux of prostaglandin was decreased by approximately 90% in the indomethacin-treated dogs. Similarly, Berl and coworkers (1979) reported that isoproterenol infusions (0.018 μg/kg per min, iv) stimulated plasma renin activity 3- to 5-fold both before and after indomethacin administration in anesthetized dogs. In both of these experiments (Berl et al., 1979; Seymour and Zehr, 1979), the intravenous infusion of isoproterenol to stimulate renin release also produced increases in heart rate and decreased mean arterial pressure. However, when isoproterenol infusion was repeated in dogs with a suprarenal aortic clamp to control renal perfusion pressure, again no attenuation of the plasma renin response was observed during indomethacin inhibition of prostaglandin synthesis (Berl et al., 1979). Indomethacin administration also failed to attenuate the renin secretory response to the intravenous infusion of isoproterenol in the conscious dog (Seymour et al., 1981). These results in the dog are in agreement with recent studies in humans (Frolich et al., 1979), and suggest that β-adrenergic stimulation of renin release with isoproterenol occurs via a prostaglandin-independent mechanism.

Additional support for the concept that renal β-adrenergically mediated renin release occurs independently of the renal prostaglandin system is provided from studies in the anesthetized dog with renal nerve stimulation before and after blockade of prostaglandin synthesis with indomethacin (Jackson et al., 1982b). In phentolamine-treated dogs, renal nerve stimulation produced a frequency-related (0.5-5.0 Hz) increase in renin secretion without a significant change in renal blood flow. Propranolol administration markedly attenuated (73-86%) this increased renin response to renal nerve stimulation in these phentolamine-treated dogs. In contrast to these results obtained with propanolol, however, indomethacin failed to attenuate the renin secretory response at any frequency of nerve stimulation in the phentolamine-treated animal. Adequacy of cyclooxygenase blockade was demonstrated by an approximately 80% decrease in urinary excretion rate of dinor-6-keto-PGF₁α, a metabolite of PG₁. In agreement with these results, Kopp et al. (1981) also reported that the inhibition of prostaglandin synthesis with indomethacin or diclofenac sodium failed to attenuate the increase in renin secretion in response to low-intensity renal nerve stimulation in the anesthetized dog. In both of these studies (Jackson et al., 1982b; Kopp et al., 1981) it was concluded that the renal prostaglandin system does not mediate β-adrenergic stimulation of renin release in the dog.

Another approach in evaluating the participation of the renal prostaglandins in β-adrenergic receptor-mediated renin release has been the use of in vitro preparations. In studies with superfused isolated rat glomeruli, Beierwaltes et al. (1980) reported that isoproterenol increased renin release without increasing PGE₂ release; isoproterenol stimulation of renin release was blocked by addition of propranolol but not by meclofenamate. Conversely, addition of arachidonic acid to the isolated glomeruli increased both PGE₂ and renin release, and meclofenamate blocked both responses. Propranolol had no effect on either the renin or the PGE₂ response to arachidonic acid stimulation. Indomethacin also failed to attenuate isoproterenol stimulation of renin secretion from the isolated perfused rabbit kidney, although urinary excretion of 6-keto-PGF₁α was suppressed by more than 90% (Vandongen et al., 1981). In both studies (Beierwaltes et al., 1980; Vandongen et al., 1981), it was concluded that the β-adrenergic pathway for renin release operates independently of the renal prostaglandin system.

In contrast to these results, it has been reported (Campbell et al., 1979a; Suzuki et al., 1981b) that isoproterenol stimulation of renin release in the conscious rat is attenuated markedly by pretreatment
with indomethacin to suppress prostaglandin synthesis. Additionally, Suzuki et al. (1981a) reported that isoproterenol stimulated both renin release and prostaglandin E₂ release when added to rat renal cortical slices, and meclofenamate and indomethacin blocked both the renin and the PGE₂ responses to isoproterenol. Dibutyryl cAMP also stimulated renin release from rat cortical slices, but this response was not blocked by indomethacin; moreover, dibutyryl cAMP stimulation of renin release was not accompanied by stimulation of PGE₂ (Suzuki et al., 1981a).

In direct contrast to these in vitro observations, is the fact that the increase in serum renin activity produced by dibutyryl cAMP in the conscious rat was completely abolished by indomethacin administration (Campbell et al., 1979a). It was concluded (Campbell et al., 1979a; Suzuki et al., 1981a, 1981b) that the renal prostaglandin system plays an important role in mediating adrenergic stimulation of renin release.

In conclusion, the bulk of the current evidence fails to support the concept that β-adrenergic stimulation of renin release is mediated by the renal prostaglandin system. This conclusion is reached with the knowledge that there are data from studies in the cat (Feuerstein and Feuerstein, 1980) and in the rat (Campbell et al., 1979a; Suzuki et al., 1981a, 1981b) which imply a modulating influence of prostaglandin biosynthesis in β-adrenergically mediated renin release. However, a very significant component of the renin response to isoproterenol stimulation in the rat is not blocked by indomethacin (Campbell et al., 1979a; Seymour et al., 1981; Suzuki et al., 1981b), and this suggests that β-adrenergic stimulation of renin release in this species also can occur without support of intact prostaglandin biosynthesis.

Conclusions

It is clear that the renal prostaglandins stimulate renin release by a direct action on the JG cells and, possibly, also, by an indirect action to amplify or attenuate the signals for other receptor mechanisms, i.e., prostaglandins alter both urinary electrolyte excretion and renal arteriolar tone and thus might indirectly influence the macula densa and the renal vascular baroreceptor, respectively. A number of prostaglandins can stimulate renin release, but prostacyclin has received the most consideration as the likely endogenous mediator. The use of indomethacin and other nonsteroidal anti-inflammatory drugs to inhibit endogenous prostaglandin biosynthesis has demonstrated an important prostaglandin-dependent component of renin release in patients with Bartter's syndrome and in several chronic animal models with hyperreninemia including sodium depletion, experimental renovascular hypertension, and the low cardiac output state of chronic thoracic caval constriction. Thus, the important influence of the renal prostaglandins in renin release is firmly established. There is, however, little direct support for the hypothesis that the renal prostaglandin system functions as an essential intermediary step in stimulus-secretion coupling for the renal vascular baroreceptor, the macula densa, and the renal β-adrenergic receptor mechanisms. Rather, the collective evidence suggests that the renal prostaglandin system functions to modulate the rate of renin secretion which is controlled by these other receptor mechanisms in a variety of experimental and clinical situations.

References


Bohman SO (1977) Demonstration of prostaglandin synthesis in collecting duct cells and other types of the rabbit renal medulla. Prostaglandins 14: 729–744


Dunham EW, Zimmerman BG (1970) Release of prostaglandin...


Folkow B, Schlondorff D (1979) Prostaglandin synthesis in isolated glomeruli. Prostaglandins 17: 79–86


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