STATE OF THE ART REVIEW

Interactions of prostaglandins with the kallikrein-kinin and renin-angiotensin systems

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Summary

1. Prostaglandins together with the kallikrein-kinin system comprise a major vasodepressor system.
2. Prostaglandins can antagonize the actions of pressor hormones and the adrenergic nervous system. They also contribute to the blood pressure-lowering effects of kinins by enhancing the vasodilator and diuretic-natriuretic actions of the peptide.
3. Deficiency of the vasodepressor system may lead to hypertension without any increase in the basal activity of the blood pressure-elevating system.
4. Increased activity of the renin-angiotensin and adrenergic nervous systems evoked by stress-ful stimuli enhances prostaglandin synthesis, which protects organ function from excessive effects of angiotensins and catecholamines.
5. Several findings preclude unqualified acceptance of prostacyclin as the only important vascular prostaglandin: first, in some blood vessels prostacyclin is not the principal product of enzymic transformation of the cyclic endoperoxides. Secondly, prostaglandin E₂, which is also synthesized in the vascular wall, may be the principal modulator prostaglandin. Lastly, prostacyclin may be transformed by some tissues to 6-keto-prostaglandin E₆, a more stable product having similar biological potency.
6. Synthesis of prostaglandins by the kidney is important to mechanisms which control renin release and renal vascular resistance.

Key words: angiotensins, blood vessels, hypertension, kidney, kinins, prostacyclin, prostaglandin E₂, prostaglandin F₂α.

Abbreviations: PG, prostaglandin.

Introduction

An antihypertensive mechanism operates through interactions of kinins and prostaglandins intrarenally and within the vasculature (McGiff, Terragno, Malik & Lonigro, 1972; Terragno, Crowshaw, Terragno & McGiff, 1975). Prostaglandins together with the kallikrein-kinin system comprise a major vasodepressor system opposing the pressor effects of the adrenergic nervous-renin-angiotensin-aldosterone system (McGiff & Nasjletti, 1973). Prostaglandins not only antagonize the actions of pressor hormones (McGiff, Crowshaw, Terragno & Lonigro, 1970a) and the adrenergic nervous system (Malik & McGiff, 1975) but also contribute to the blood pressure-lowering effects of kinins by enhancing their vasodilator and diuretic-natriuretic actions (McGiff, Itskovitz & Terragno, 1975; Blasingham & Nasjletti, 1979). The basal release of renal prostaglandins has been linked to the level of activity of the renal kallikrein-kinin system (Nasjletti, McGiff & Colina-Chourio, 1978). Thus, coupling of the kallikrein-kinin and prostaglandin systems was suggested from measuring changes in urinary excretion of PGE₂, and kallikrein, which were considered to reflect changes in the intrarenal activity of the prostaglandin and kallikrein-kinin systems respectively (Nasjletti et al., 1978). Either augmentation or depression of urinary kallikrein excretion evoked corresponding changes in prostaglandin excretion. If one assumes tonic activity of the opposing blood pressure-regulating systems, a deficiency of the vasodepressor system may lead to hypertension without any increase in the basal activity of the blood pressure-elevating system.

Altered activity of the kallikrein-kinin system is only one of several signals to which prostaglandins respond in the regulation of blood pressure. Increased activity of the renin-angiotensin and adrenergic nervous systems evoked by a variety of stressful stimuli enhances
prostaglandin synthesis (Terragno, Terragno & McGiff, 1977), which protects organ function from excessive effects of angiotensins and catecholamines (McGiff et al., 1970a). The importance of this defensive role of prostaglandins is particularly evident after inhibition of prostaglandin synthesis in the surgically stressed animal, an experimental condition characterized by high activity of the renin–angiotensin system. Under these conditions, administration of indomethacin causes a precipitous decline in renal blood flow associated with elevation of blood pressure (Lonigro, Itskovitz, Crowshaw & McGiff, 1973). A significant relationship between pressor and depressor factors was first established with the demonstration that one or more vasodepressor prostaglandins was released into renal venous blood during infusion of angiotensin II into the renal artery (McGiff, Crowshaw, Terragno & Lonigro, 1970b). Renal blood flow and urine flow were greatly decreased by angiotensin II, reflecting its vasoconstrictor and antidiuretic actions. However, within 2–5 min, both returned toward control levels despite continued infusion of angiotensin II. This recovery phase coincided with increased prostaglandin release. When this experiment was repeated after inhibition of prostaglandin synthesis, the vasoconstrictor and antidiuretic actions of angiotensin II were increased and a recovery phase did not occur (Aiken & Vane, 1973).

Mechanisms subserved by prostaglandins appear to maintain normotension; e.g., inhibition of prostaglandin synthesis with non-steroidal anti-inflammatory drugs can cause hypertension in animals when these drugs are administered either acutely (Lonigro et al., 1973) or for periods of several weeks (Colina-Chourio, McGiff & Nasjletti, 1979). Administration of indomethacin has also been shown to increase blood pressure in normotensive man (Wennmalm, 1978); long-term administration of indomethacin increased the severity of hypertension in man (Ylitalo, Pitkäjärvi, Metsä-Ketelä & Vapaatalo, 1978). These studies, when considered together with evidence of prostaglandin deficiency in hypertensive man (Abe, Yasujima, Chiba, Irokawa, Ito, Yoshinaga & Saito, 1977; Tan, Sweet & Mulrow, 1978), support the proposal that diminished production of prostaglandins may contribute to blood pressure elevation in all species studied thus far except the rat.

Blood pressure control may involve primarily prostaglandin mechanisms, which: (1) regulate the renal circulation and extracellular fluid volume; (2) operate within the vascular wall, affecting the integrity of endothelial surfaces and the response of smooth muscle to pressor stimuli; (3) cause vasodilation. This review will address, then, the kidney and the renal and systemic vasculatures, primarily in terms of the interactions of kinins and angiotensins with prostaglandins. The autonomic nervous system receives scant attention, as does the neurohypophysis; each may interact importantly with prostaglandins and each deserves separate consideration and ultimate integration within the framework of hypertension as a disorder of regulatory systems.

Release of prostaglandins from tissues in response to kinins and angiotensins, as well as other stimuli, denotes increased prostaglandin synthesis within that tissue. This results in the immediate entry of the newly synthesized prostaglandin into the extracellular compartment. Kinins and angiotensins increase prostaglandin synthesis primarily by enhancing delivery of substrate, arachidonic acid, to the prostaglandin-synthesizing complex (Damas & Bourdon, 1974). Thus the arachidonic acid cascade is initiated by its release from storage in a bound form, chiefly as phospholipids, through activation of acylhydrolases, such as phospholipase A₂ and tri-glyceride lipase (Fig. 1). As the tissue phospholipids are the richest source of arachidonic acid, the intrinsic phospholipases of the cell have been assumed to be essential parts of the sequence of events involved in prostaglandin biosynthesis. However, in a number of tissues, arachidonate was shown to be released by the actions of enzymes other than phospholipase A₂. For example, the mechanism releasing arachidonate from thrombin-stimulated platelets may involve two enzymes: a phosphatidylinositol-specific phospholipase C and a diglyceride lipase, which hydrolyses arachidonate esterified to the C-2 position of the diglyceride (Bell, Kennerly, Stanford & Majerus, 1979).

Activation of tissue acylhydrolases (Danon, Chang, Sweetman, Nies & Oates, 1975) by kinins and angiotensins can result in changes in the intensity and range of their activities as the released prostaglandins can inhibit or augment the action of the polypeptide; that is, prostaglandins modulate the activity of kinins and angiotensins (McGiff, Malik & Terragno, 1976). This modulator action of prostaglandins is the basis for their antihypertensive effect, namely inhibition of pressor hormones and augmentation of depressor hormones. However, the possibility should be considered that, under some conditions such as high salt intake, PGF₂α, and possibly thromboxane A₂, may contribute to the elevation...
of blood pressure and indeed may reinforce the vasoconstrictor action of angiotensin. Because of the importance of renal and vascular mechanisms to the regulation of blood pressure, interactions of prostaglandins with the kallikrein–kinin and renin–angiotensin systems will be explored in detail in the kidney and in blood vessels.

Vascular prostaglandins and antihypertensive mechanisms

The first biochemical study to demonstrate synthesis of prostaglandins by blood vessels was reported by Terragno et al. in 1975. Arachidonic acid was shown to be transformed into prostaglandins by bovine mesenteric blood vessels. Further, bradykinin increased the release of prostaglandins from these blood vessels, i.e., enhanced release of PGE, from arteries and PGF, from veins. This finding provided an explanation for the variable effects of bradykinin on blood vessels, e.g., bradykinin dilates arteries and constricts veins (Bobbin & Guth, 1968). In those organs in which bradykinin increases synthesis of PGE, e.g. kidney (McGiff et al., 1972), uterus (Terragno, Terragno, Pacholczyk & McGiff, 1974) and skeletal muscle (Messina, Weiner & Kaley, 1975), the released PGE, can reinforce the vasodilator action of the kinin. Moreover, the vasoconstrictor action of bradykinin may depend on the capacity of the vein to increase synthesis of PGF, a known vasoconstrictor (Ducharme, Weeks & Montgomery, 1968), in response to the kinin. In keeping with this interpretation, contraction of the bovine mesenteric vein evoked by bradykinin was selectively abolished by indomethacin (Wong, Terragno, Terragno & McGiff, 1977a). However, the release of PGF, from veins by bradykinin cannot be simply due to enhanced delivery of substrate to the cyclo-oxygenase, consequent to activation of an acylhydrolase (Needleman, Minkes & Raz, 1976), for such activity should not change the ratio PGE, /PGF, in the released prostaglandins. That bradykinin altered the ratio in a widely different manner in veins (0.3/1) and arteries (5.7/1), although the ratios were similar (2/1) before addition of bradykinin, also argues against an effect of the kinin on the primary degradative enzyme, prostaglandin 15-hydroxydehydrogenase, as the K values of PGE, and PGF, with respect to this enzyme are similar (Nakano, Ånggard & Samuelsson, 1969). Therefore an additional action of bradykinin was sought, i.e. one which might be exerted through a mechanism that affects the ratio of PGE, to PGF, released by a tissue. Leslie & Levine (1973) have described stereospecific reduction of the 9-keto group of PGE, by PGE-9-ketoreductase, thereby generating PGF,. High-speed supernates of bovine mesenteric blood vessels contain PGE-9-ketoreductase. Incubation of radioactive PGE, with this fraction at 37°C in the presence of an NADPH-generating system resulted in time-dependent conversion of PGE, into PGF, (Wong et al., 1977a). Bradykinin (0.01 mmol/l) increased the activity of PGE-9-ketoreductase by two- to three-fold as measured by conversion of PGE, into PGF, in the cytoplasmic fraction obtained from veins (Fig. 2), whereas the kinin had little effect on the enzymic activity of cytoplasmic fractions of mesenteric arteries. However, after inhibition of kinin catabolism with the angiotensin converting enzyme inhibitor, teprotide (SQ 20 881), brady-
FIG. 2. Time course study of PGE-9-ketoreductase activity in bovine mesenteric veins with (A) and without (△) bradykinin.

Bradykinin increased PGE-9-ketoreductase activity of arteries and veins to the same degree, suggesting that the effect on arteries was prevented by destruction of bradykinin and could be demonstrated after inhibiting the kinin-catabolizing enzyme, which is found in abundance in arteries. Angiotensin I and II are also able to increase the activity of PGE-9-ketoreductase of vascular tissues.

There is an additional consideration, however, which raises the question whether the PGE-9-ketoreductase can be directly affected by vasoactive hormones. Thus, an intermediate step through which bradykinin stimulates PGE-9-ketoreductase is probable in view of three considerations: (1) PGE-9-ketoreductase activity is associated with the cytosol and, therefore, would not be likely to be accessible to the direct action of agents which penetrate the cell poorly; (2) bradykinin, a nonapeptide, has limited access to intracellular sites (Barabé, Park & Regoli, 1975); (3) bradykinin-induced contractions of blood vessels are related to increased levels of cyclic GMP (Clyman, Sandler, Manganiello & Vaughn, 1975a). Changes in the levels of cyclic GMP have been suggested to serve as a common mechanism to elevate vascular tone in response to diverse stimuli (Dunham, Haddox & Goldberg, 1974; Amer, Gomoll, Perhach, Ferguson & McKinney, 1974). Wong, McGiff & Terragno (1977) have obtained evidence that those vascular actions of bradykinin mediated by PGF$_{2α}$ may occur through a mechanism involving cyclic GMP. Cyclic GMP mimicked the effect of bradykinin on PGE-9-ketoreductase activity; i.e., each affected the conversion of PGE$_2$ into PGF$_{2α}$ by increasing the rate ($V_{\text{max}}$) of PGE$_2$ reduction by PGE-9-ketoreductase without affecting the apparent $K_m$ of the enzyme. Cyclic AMP (1 μmol/l) did not affect PGE-9-ketoreductase activity.

The functional significance of the finding that cyclic GMP affects the activity of PGE-9-ketoreductase is that it may represent an intermediate in some of the vascular actions of kinins and angiotensins. Clyman, Blacksin, Manganiello & Vaughn (1975b) showed that bradykinin increased the accumulation of cyclic GMP in human umbilical arteries, without affecting the level of cyclic AMP. The venoconstrictor action of the kinin was also associated with increased levels of cyclic GMP (Dunham et al., 1974). Bradykinin-induced constriction of isolated bovine mesenteric veins, therefore, may be mediated through accumulation of cyclic GMP, the latter increasing the activity of PGE-9-ketoreductase, which promotes formation of PGF$_{2α}$. Whether bradykinin has a direct effect on guanylate cyclase or cyclic GMP-specific phosphodiesterase, either of which may be responsible for the accumulation of cyclic GMP, remains to be established. Expression of prostaglandin activity through determining the ratio of PGE$_2$ to PGF$_{2α}$, therefore, may be effected by a cyclic GMP-dependent system. This mechanism, by determining the ratio of PGE$_2$ to PGF$_{2α}$ within the vascular wall, could contribute to the regulation of blood pressure; e.g., increased formation of PGF$_{2α}$ would facilitate, whereas elevated levels of PGE$_2$ would inhibit hormonally and neurally induced vasoconstriction (McGiff et al., 1976). This hypothesis embodies two earlier proposals: (1) that increased levels of cyclic GMP can be associated with constriction of blood vessels (Dunham et al., 1974) and (2) that the biological activities of prostaglandins of the F series are related to the guanylate cyclase system as those of the E series are related to the adenylate cyclase system (Kuehl, Circilo, Ham & Humes, 1973).

**Prostacyclin**

Since the discovery of prostacyclin in blood vessels (Moncada, Gryglewski, Bunting & Vane, 1976), it has been assumed to be the principal
product of enzymic transformation of the cyclic endoperoxides, PG\textsubscript{G2} and PGH\textsubscript{1}, in all vascular elements. In addition to its potent anti-aggregatory properties, prostacyclin causes vasodilatation and may contribute importantly to vasodilator mechanisms of blood vessels (Dusting, Moncada & Vane, 1978). Terragno, McGiff, Smigiel & Terragno (1978a) have shown that foetal vascular tissues have the largest capacity to generate prostacyclin, a property presumably related to the low peripheral vascular resistance that characterizes the foetal circulation. In addition (Fenwick, Jones, Naylor, Poyser & Wilson, 1977), prostacyclin is a major product of the utero–placental complex; it may contribute to the ameliorating effect of pregnancy on both experimental hypertension and human essential hypertension. A deficiency in prostaglandin production could contribute to the initiation and evolution of toxaemia of pregnancy. The possible participation of prostaglandins in toxaemia of pregnancy has been studied with umbilical blood vessels obtained from pre-eclamptic women (Terragno, Terragno & McGiff, 1980). A significant decrease in prostaglandin release from these umbilical blood vessels has been shown. As one of the earliest findings in women who develop pregnancy-induced hypertension is progressive sensitivity to the pressor effects of angiotensin II (Grant, Daley, Chand, Whalley & MacDonald, 1973), a deficiency of one or more factors which modulate pressor hormones is probable.

However, several findings preclude the unqualified acceptance of prostacyclin as the only important vascular prostaglandin: (1) in some blood vessels there is evidence that prostacyclin is not the principal product of enzymic transformation of the cyclic endoperoxides [Terragno & Terragno (1979) have shown that PGE\textsubscript{2}, as identified by mass spectrometry, is the principal product of enzymic transformation of cyclic endoperoxides in umbilical blood vessels]; (2) PGE\textsubscript{2}, which is also synthesized in the vascular wall (Terragno et al., 1978a), may be the principal modulator prostaglandin, affecting the vascular actions of vasoactive polypeptides and autonomic nervous activity (McGiff et al., 1976) [in contrast to PGE\textsubscript{2}, PGF\textsubscript{1} does not inhibit the effects of angiotensin on the microcirculation (Messina & Kaley, 1980); this finding challenges a proposed modulator role for PGF\textsubscript{1}]; moreover PGF\textsubscript{1}, unlike PGE\textsubscript{2}, has little effect on the release of noradrenaline from the adrenergic nerve endings (Hedqvist, 1979) and (3) prostacyclin may be transformed by some tissues into a more stable product, 6-keto-PGE\textsubscript{1a}, having similar biological potency (Wong, Malik, Desiderio, McGiff & Sun, 1980). In addition, rapid termination of the action of prostacyclin may occur as it is avidly metabolized by prostaglandin 15-hydroxydehydrogenase. This enzyme, abundantly present in blood vessels, inactivates PGF\textsubscript{1} by transforming it into 6,15-diketo-PGF\textsubscript{1a} (Wong, Sun & McGiff, 1978a).

After generation within the vascular wall, that prostacyclin which escapes local destruction may enter the blood stream, where it may function as a circulating hormone (Gryglewski, Korbut & Ocetkiewicz, 1978; Moncada, Korbut, Bunting & Vane, 1978). Less than 15% of prostacyclin was shown to be metabolized during one passage across the lung (Wong, McGiff, Sun & Malik, 1978b), probably due to the low affinity of PGF\textsubscript{1} for the transport system of the lung, as it is rapidly metabolized by the major pulmonary degradative enzyme, prostaglandin 15-hydroxydehydrogenase, when tested in a cell-free preparation. The first study which suggested that a prostaglandin could function as a circulating hormone was published more than 10 years ago; PGA\textsubscript{1} was shown to pass through the lung without loss of activity (McGiff, Terragno, Strand, Lee, Lonigro & Ng, 1969). However, PGA\textsubscript{1} almost certainly does not occur naturally; it arises from PGE\textsubscript{2} during extraction and purification of blood (Frölich, Sweetman, Carr & Oates, 1975a).

**Renal prostaglandins and antihypertensive mechanisms**

Antihypertensive mechanisms centred in the kidney are pivotal to the regulation of blood pressure. For example, an increase in renal vascular resistance has been considered to be an initiating factor in the pathogenesis of hypertension (Tobian, 1974). Prostaglandins have been shown to have major effects on vascular resistance of the kidney (Lonigro et al., 1973), particularly during stress or in disease; inhibition of their synthesis under these conditions can result in a precipitous elevation of renal vascular resistance (Terragno et al., 1977).

The renin–angiotensin and the kallikrein–kinin systems of the kidney participate in the control of blood pressure through their effects on the renal circulation and extracellular fluid volume. They have important interactions with prostaglandins intrarenally, an interaction which is related to their effects on blood pressure. Thus intrarenal release of the enzymes, renin and kallikrein, is under the partial control of prostaglandin mechanisms (Larsson, Weber & Ånggärd, 1974; Olsen, 1977). The actions of the
effector hormones of each system, angiotensin II and kinins, are themselves modified by their capacity to release prostaglandins. The release of prostaglandins by kinins and angiotensins can result in major modifications of the effects of these hormonal systems on renal hemodynamics and excretion of salt and water, attenuation of the vasoconstrictor-antidiuretic action of angiotensin and enhancement of the vasodilator-diuretic action of kinins (McGiff et al., 1970a, 1975).

Zonal stratification within the kidney of the enzymes renin (Thurau, 1964) and kallikrein (Carretero & Scicli, 1976) are similar; the concentration is highest in the outer cortex and diminishes progressively towards the corticomedullary junction. Despite similar renal cortical gradients for kallikrein and renin, there are important differences in their primary functional localization within the kidney; namely, the renin-angiotensin system is located in the vasculature and the kallikrein-kinin system in the tubules (McGiff & Wong, 1979). These differences have important implications for the regulation of the renal circulation and salt water excretion; e.g. kinins generated in the distal tubular fluid can affect prostaglandin synthesis by the cells lining the collecting ducts (Fig. 3), a site of heavy concentration of cyclo-oxygenase (Smith & Wilkin, 1977). Changes in the activity of the renal kallikrein-kinin and renin-angiotensin systems have been determined by measuring changes in the activity of kallikrein and renin in the urine and plasma respectively. However, urinary kallikrein excretion may not be a reliable predictor of changes in the activity of the renal kallikrein-kinin system. Dissociations between excretion of kallikrein and kinins have been reported in Bartter’s syndrome (Vinci, Gill, Bowden, Pisano, Izzo, Radfar, Taylor, Zusman, Bartter & Keiser, 1978) and after administration of a converting enzyme inhibitor (Vinci, Horwitz, Zusman, Pisano, Catt & Keiser, 1979a). In Bartter’s syndrome (McGiff, 1977) elevated excretion of kallikrein and decreased excretion of kinins occur; indomethacin treatment depresses the former and elevates the latter (Vinci et al., 1978). Moreover, Vinci, Zusman, Izzo, Bowden, Horwitz, Pisano & Keiser (1979b) have shown that urinary kallikrein excretion can be affected over a 50-fold range by alteration in the intake of either mineralocorticoids or potassium, whereas excretion of urinary kinins is unchanged.

Prostaglandins formed within the kidney exit in both urinary (Fröhlich, Wilson, Sweetman, Smigel, Nies, Carr, Watson & Oates, 1975b) and venous effluents (McGiff, Crowshaw & Itskovitz, 1974). Changes in the activity of the renal prostaglandin system, such as those produced by close-arterial infusion of vasoactive substances, are reflected in increased efflux of prostaglandins into urine and renal venous blood. Thus
PGE₂ and renin activity in renal venous blood are correlated positively over a wide range of experimental conditions (Terragno et al., 1977), as are urinary excretion of PGE₂ and kallikrein (Nasjletti et al., 1978). Infusion of angiotensin II into the renal artery released prostacyclin from the kidney (Shebuski & Aiken, 1980). The released prostaglandin may act as a circulating hormone (Gryglewski et al., 1978; Moncada et al., 1978) and can affect aggregation and deposition of platelets at remote sites such as within the coronary blood vessels (Shebuski & Aiken, 1980). Bradykinin, like angiotensin II, released PGE₂ from the rabbit isolated kidney (Colina-Chourio, McGiff, Miller & Nasjletti, 1976), whereas arachidonic acid released prostacyclin, suggesting that the mechanism which regulates PG₁₂ synthesis is unresponsive to kinins. The possibility should be considered, however, that under these experimental conditions bradykinin may be unable to release prostacyclin from the kidney because of destruction of the kinin by the kininases of blood vessels, which restrict its access to sites of prostacyclin synthesis in the renal vasculature. The study of Mullane, Moncada & Vane (1979) supports this explanation; they showed that after inhibition of kininase II with an angiotensin converting enzyme inhibitor, bradykinin-induced release of prostacyclin-like material into renal venous blood was enhanced. In contrast, angiotensin II apparently is not denied access to the sites of prostacyclin generation in the vasculature by degradative enzymes.

Renal prostaglandin–kinin interactions

The renal kallikrein–kinin system has been suggested to be a major determinant of the activity of renal prostaglandins under basal conditions because induced changes in kallikrein excretion produced corresponding changes in PGE₂ excretion. Nasjletti et al. (1978) measured changes in urinary prostaglandins and kallikrein simultaneously in long-term studies in the rat. Wide variations in urinary kallikrein excretion, induced by activation and inhibition of the renal kallikrein system, were accompanied by corresponding alterations in excretion of PGE₂. It is possible to increase kallikrein excretion by giving mineralocorticoids (Margolius, Horwitz, Pisano & Keiser, 1976); this effect of mineralocorticoids requires large doses for its demonstration. When high doses of either aldosterone or deoxycorticosterone (DOC) were given to rats, the excretion of kallikrein and PGE₂ increased by two- to four-fold for as long as the mineralocorticoid was administered, 1–2 weeks in this study (Nasjletti et al., 1978). Injections of a kallikrein inhibitor, aprotinin (Trasylo), decreased excretion of bio-assayable kallikrein and secondarily reduced PGE₂ excretion. Thus enhanced excretion of prostaglandins induced by mineralocorticoids is a consequence of activation of the renal kallikrein–kinin system. However, when the animal is stressed the renin–angiotensin system may supersede the renal kallikrein–kinin system in regulating prostaglandin synthesis within the kidney (Terragno et al., 1977).

The contributions of prostaglandins to the renal action of kinins are uncertain. In the canine isolated blood-perfused kidney, a significant, albeit small, component of the renal vasodilator action of bradykinin was related to a prostaglandin mechanism (McGiff et al., 1975). However, the vasodilator response to bradykinin for the kidney in situ was considered to be independent of a prostaglandin mechanism (Longo, Hagemann, Stephenson & Fry, 1978) although demonstration of a prostaglandin component in bradykinin-induced renal vasodilation may be critically dependent on electrolyte balance, as well as on the manner in which the kinin is administered, by bolus or by infusion. Thus the prostaglandin component in the renal vasodilatation induced by infused bradykinin may become evident only after the first 2 min, becoming increasingly more important as the infusion is continued. A prostaglandin contribution to the effects of kinins on salt and water excretion is probable; a renal prostaglandin, presumably PGE₂, may mediate the effects of bradykinin on free water excretion and excretion of sodium chloride (McGiff et al., 1975; Blasingham & Nasjletti, 1979).

Assignment of the primary renal activity of the kallikrein–kinin system to the tubular compartment and of the renin–angiotensin system to the vascular compartment may be useful conceptually. It should not, however, prevent recognition that kinins affect the renal circulation and angiotensins influence tubular reabsorption of salt and water. Thus inhibition of the principal kinin-degradative enzyme of the kidney, kininase II, by use of a converting enzyme inhibitor, resulted in elevated renal blood flow, accompanied by a tenfold increase in excretion of kinins and a twofold increase in the concentration of kinins in renal venous blood (Nasjletti, Colina-Chourio & McGiff, 1975). These findings were extended by Olsen & Arrigoni-Martelli (1979) to include observations on the excretion of prostaglandins as a result of increased generation of kinins intrarenally caused by inhibition of angio-
tensin converting enzyme. Despite increased excretion of kinins of greater than tenfold, prostaglandin excretion was not affected whereas kallikrein excretion was decreased. This study suggests that the sphere of activity of kinins generated intrarenally after inhibition of kininase II is separated from sites of prostaglandin synthesis; otherwise prostaglandin excretion should have increased. In contrast, when bradykinin was infused, excretion and renal venous levels of prostaglandins increased (Dunn, Liard & Dray, 1978). However, kininogen, the inactive precursor of kinins, when infused into the rabbit isolated kidney, released prostaglandins, an effect which indicates that generation of kinins intrarenally, at least in this experimental preparation, occurred at a site accessible to induction of prostaglandin synthesis (Colina-Chourio et al., 1976).

Renal prostaglandin–angiotensin interactions

The microcirculation of the kidney, particularly the glomerular capillaries, has been the subject of intensive investigation since the classical study of Richards & Schmidt (1924). Many studies have been directed towards examination of the role of the renin–angiotensin system in regulating glomerular capillary flow and filtration rate (GFR) by affecting the tone of the pre- and post-glomerular arterioles. The regulation of GFR at the level of the individual nephron may be mediated by a prostaglandin mechanism which responds to a signal arising in the distal nephron, such as delivery or re-absorption of sodium chloride at the macula densa (Schnermann, Schubert, Hermle, Herbst, Stowe, Yarimizu & Weber, 1979). This in turn influences the filtration rate of the nephron, i.e., subserves the mechanism relating tubular events to glomerular capillary filtration, commonly referred to as tubuloglomerular feedback. In support of this hypothesis Schnermann et al. (1979) have demonstrated reduced tubuloglomerular feedback responses during inhibition of prostaglandin synthesis.

Activation of the renin–angiotensin system is a major determinant of renal perfusion pressure and, thereby, GFR when renal blood flow is compromised by local factors such as lesions of the renal artery or systemic factors such as diminished extracellular fluid volume. These conditions evoke a prostaglandin mechanism which contributes to the maintenance of the renal circulation (Terragno et al., 1977; Vatner, 1974) and GFR during stress.

Regional variation in prostaglandin synthesis within the kidney

Zones and structures within the kidney vary quantitatively and qualitatively in their capacity to form prostaglandins. Renal prostaglandins have been assumed to be formed only within the medulla as the renal cortex has been reported to be unable to metabolize arachidonic acid (Crowshaw, 1971). Further, the highest activity of the major prostaglandin degradative enzyme, prostaglandin 15-hydroxydehydrogenase, is found in the cortex (Ånggard, Larsson & Samuelsson, 1971); a rapid destruction of prostaglandins either synthesized in the cortex or present in the arterial blood perfusing the cortex is assumed. However, large amounts of prostaglandins are synthesized by renal cortical blood vessels after their removal from the cortical matrix (Terragno, Terragno, Early, Roberts & McGiff, 1978b). Arteriolar elements thus far examined include the main renal artery and lobar, lobular and interlobular arteries, the last-named with attached afferent arterioles; all demonstrate similar capacities to convert arachidonic acid into prostaglandins, chiefly prostacyclin. Isolated glomeruli can also synthesize prostaglandins (Hassid, Konieczkowski & Dunn, 1979). In contrast, isolated convoluted tubules show a low capacity to generate prostaglandins; this residual prostaglandin synthesis may be related to adherent vascular elements, a possibility which cannot be excluded (Terragno et al., 1978b). The difficulty in demonstrating renal cortical prostaglandin synthesis by slices or homogenates of kidney may be due to an inhibitor of cyclo-oxygenase (Terragno et al., 1978b). If an inhibitor can be shown in the renal cortex, it could serve as a target for hormones or drugs; repression or stimulation of the inhibitor should then result in changes in renal vascular resistance because tissue levels of vasodilator prostaglandins, PGE₂, and PGI₂, will be affected within the vascular wall.

Synthesis of prostaglandins by the renal cortex has important implications, particularly for the regulation of renin release and vascular resistance within the kidney. Evidence for a major effect of prostaglandins on cortical vascular resistance was obtained by Gerber, Data & Nies (1978). They infused arachidonic acid, the precursor of bisenoic prostaglandins, into the renal artery of the dog; a possible medullary component of the prostaglandin-mediated renal vascular response was abolished in this preparation, the non-filtering kidney. Arachidonic
Acid caused renal vasodilatation, which could be prevented by inhibiting prostaglandin synthesis. As the contribution of the renal medulla to this effect should have been eliminated in the non-filtering kidney, the action of arachidonic acid on renal vascular resistance must arise from its conversion into prostaglandins by the renal cortex. It is within the cortex that drug-related effects may be expressed through major changes in renal vascular resistance. For example, the antihypertensive vasodilator agent, hydralazine, operates within the wall of the afferent arteriole to regulate vascular resistance a similar mechanism operates within the cortical blood vessels to control renin release (Whorton, Misono, Hollifield, Frolich, 1977, Inagami, Quilley, 1980). Three doses of hydralazine, selected for their different effects on renal blood flow, were infused into the renal artery of the chloralose-anaesthetized dog, causing decreased renal blood flow, a marked reduction in renal vascular resistance and changes in mean aortic blood pressure, renal blood flow and concentrations of PGE-like material in renal venous blood were measured (Table 1). As this study was completed before the discovery of prostacyclin, it is important to recognize that 6-keto-PGF₁₀₋, the hydrolysis product of PGI₂, would have been measured as PGE-like material as it co-migrates with PGE₁ in the solvent system used for separation of prostaglandins on thin-layer plates before their assay. Given this qualification, namely, that the renal venous concentration of PGE-like material may receive a contribution from one or more products of prostacyclin, this study shows a remarkable correlation between the concentration of PGE-like material in renal venous blood, as well as its rate of efflux from the kidney and the renal vasodilator response to hydralazine. Moreover, when high concentrations of hydralazine were infused, causing decreased renal blood flow, a marked reduction in the concentration and efflux of PGE-like material occurred. Spokas & Wang (1980) have reported that treatment of dogs with indomethacin prevents the renal action of hydralazine but not its dilator effects in other regional vascular beds. These findings mandate that the mechanism of action of vasodilator antihypertensive agents be re-evaluated in terms of a possible prostaglandin mechanism.

In addition to a prostaglandin mechanism operating within the cortical blood vessels to regulate vascular resistance a similar mechanism operates within the wall of the afferent arteriole to regulate renin release (Larsson et al., 1974; Data, Gerber, Crump, Fröhlich, Hollifield & Nies, 1978). Prostacyclin and its active metabolite 6-keto-PGE₁ are prime candidates to mediate the prostaglandin mechanism which controls renin release (Whorton, Misono, Hollifield, Fröhlich, Inagami & Oates, 1977; Wong et al., 1980). Renin release and subsequent generation of angiotensin II can in turn affect prostaglandin synthesis at vascular sites distal to the afferent arteriole, as well as those cellular elements in contact with the vasculature such as the interstitial cells which synthesize prostaglandins (Muirhead, Germain, Leach, Pitcock, Stephenson, Brooks, Brosius, Daniels & Hinman, 1972). Renin passes into the interstitial space (Morgan & Davis, 1975), as does kallikrein (Mills, McFarlane, Ward & Obika, 1976). Prostaglandins released from these several sites, both within the vascular and interstitial spaces, can in turn terminate the action of angiotensin (Olsen, Magnussen & Eilertsen, 1976; Romero & Strong, 1977). The latter probably occurs only in the face of excessive levels of angiotensin II, concentrations which are likely to cause rapid deterioration of renal function if unopposed.

These interactions of the renal prostaglandin and renin–angiotensin systems occur in the vascular and interstitial compartments of the kidney and are important to the regulation of the renal circulation, particularly during stress or in disease. Therefore prostaglandins have been proposed to serve a primary defensive role; i.e., when organ function is threatened, a prostaglandin mechanism is evoked which sustains

| TABLE 1. Effects of hydralazine intrarenally on renal blood flow in the chloralose-anaesthetized dog |
| Mean results ± SEM are shown. | Hydralazine |
| Arterial blood pressure (mmHg) | Control | 3·12 × 10⁻⁴ mmol/min | 3·12 × 10⁻³ mmol/min | 3·12 × 10⁻² mmol/min |
| 95 ± 3 | 93 ± 3 | 88 ± 5 | 94 ± 4 |
| Renal blood flow (ml/min) | 313 ± 24 | 379 ± 22 | 298 ± 24 | 228 ± 31 |
| Renal vein resistance (mmHg min⁻¹ ml⁻¹) | 10⁻¹ × PGE efflux (mmol/min) | 10−² × PGE concn. (mmol/ml) | 0·312 ± 0·085 | 0·540 ± 0·170 | 0·483 ± 0·114 | 0·114 ± 0·085 |
| 0·31 ± 0·03 | 0·25 ± 0·01 | 0·30 ± 0·02 | 0·44 ± 0·05 |
| 102 ± 31·2 | 170 ± 45·4 | 131 ± 25·6 | 25·6 ± 14·0 |
| 0·312 ± 0·085 | 0·540 ± 0·170 | 0·483 ± 0·114 | 0·114 ± 0·085 |
function in the face of the noxious stimulus, such as elevation of blood pressure (Terragno et al., 1977). For example, activation of the renin–angiotensin system, by either hypovolaemia or laparotomy, resulted in increased synthesis of renal prostaglandins, as indicated by enhanced renal venous efflux of PGE₂; concentrations of PGE₂ in renal venous blood increased by as much as 15-fold (Terragno et al., 1977). As indicated, changes in renal venous PGE₂ concentrations were highly correlated with the level of plasma renin activity. The contribution of prostaglandins to the support of the renal circulation in acutely stressed animals can be uncovered by administration of indomethacin (Terragno et al., 1977). A large reduction in renal blood flow occurred rapidly in response to indomethacin, despite an attendant increase in systemic blood pressure. There was a simultaneous decline in renal efflux of PGE₂ which was proportional to the reduction of renal blood flow. Romero & Strong (1977) have shown that administration of indomethacin to the rabbit, after constricting a single renal artery, can precipitate malignant hypertension associated with rapid deterioration in renal function.

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