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# Formation and metabolism of prostaglandins in the kidney

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*Diet, essential fatty acids, and the eicosanoid system*

In recent years, additional compounds have been demonstrated to originate from arachidonic acid. Apart from the classical prostaglandins (PG's) that have a prostanoic acid skeleton, novel compounds such as the thromboxanes, prostacyclin, and the leukotrienes have been discovered. The name eicosanoids has therefore been suggested for compounds originating from the unsaturated $C_{20}$ acids, eicosa-8,11,14-trienoic acid (bishomo-γ-linolenic acid), eicosa-5,8,11,14-tetraenoic acid (arachidonic acid), and eicosa-5,8,11,14,17–pentaenoic acid. The relationship between the dietary fatty acids, linoleic acid (18:2ω6) and linolenic acid (18:3ω3) and long-chain unsaturated fatty acid found in tissue lipids is shown in Fig. 1 [1, 2].

The amount of the different essential fatty acids incorporated into phospholipids, triglycerides, and cholesterol esters is dependent on dietary intake, on their respective specificity for incorporation into different lipids, on their degradation, as well as on the balance between chain elongation and desaturation versus retroconversion [1, 2]. These metabolic balances may differ from one tissue to another. Certain fatty acids are found in relatively higher amounts in some tissue, in a region of an organ, or even in some special lipids within a tissue. Thus, 22:4ω6 is abundant in rabbit kidney papilla, 22:5ω6 in the testes, and 20:3ω6 in the vesicular gland. Within the ω6-family, arachidonic acid (20:4ω6) is generally the most abundant. Within the ω3-family, 22:6ω3 seems to be the dominant. But, the total amount in the tissues of the fatty acids from the ω6 and ω3 families, respectively, is dependent on the dietary supply, because the mammalian organism is unable to produce fatty acids having ω6 and ω3 double bonds.

The polyunsaturated fatty acids have important roles maintaining cell membrane structure and fluidity, which in turn influences membrane functions. The 20:3ω6, 20:4ω6, and 20:5ω3 acids also serve as precursors for the biologically active eicosanoids. (For reviews see Refs. 3–9). In the kidney, arachidonic acid is the most abundant eicosanoid precursor. It is esterified to membrane phospholipids in the 2-position.

Following the appropriate physiologic stimulus, arachidonic acid is released and rapidly converted into PG endoperoxides, which in turn are metabolized to the classical PG's $PGE_2$, $PGD_2$ and $PGF_{2\alpha}$, as well as thromboxane $A_2$ and prostacyclin. This concerted series of reactions have been called the "prostaglandin cascade." The pathways and structures of the major eicosanoids derived from arachidonic acid are shown in Fig. 2.

Prostaglandin and thromboxane synthesis can also be modified by the diet. Essential fatty acid deficiency leads to a decrease in tissue levels of PG. Supplementation of the diet with 18:2ω6 leads to an increased PG biosynthesis [3, 7].

The physiologic control of the PG cascade is exerted by a postulated phospholipase $A_2$, probably situated in the cell membrane close to the stores of esterified precursor acids. In the kidney, a variety of factors have been shown to activate this mechanism and lead to intrarenal PG release. These include peptides such as bradykinin and angiotensin II (AII), catecholamines, as well as changes in perfusion pressure and intrarenal pressure. These aspects will be discussed elsewhere during this conference.

In the eicosanoic system, two major pathways are discerned, *the prostaglandin endoperoxide-*

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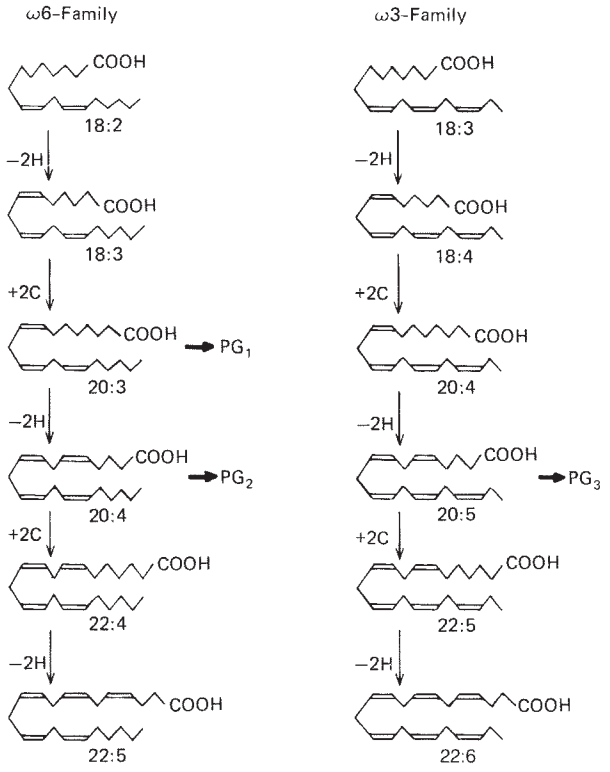


**Fig. 1.** *Metabolism of linoleic and linolenic acid.*

*synthase* (EC 1.14.99.1) pathway yielding prostanoids and thromboxanes and *the lipoxygenase* pathway yielding hydroperoxy and hydroxy unsaturated fatty acids [8–12].

Of particular interest are the newly discovered leukotrienes [13]. Leukotriene C has been suggested to be identical with the well-known slow reacting substance of anaphylaxis (SRS-A), a potent bronchoconstrictor released from the anaphylactically challenged lung. The leukotrienes may occur in the kidney [12, 14], but as yet have not been convincingly demonstrated in renal tissue.

The PG endoperoxide synthase probably consists of a cyclooxygenase and a lipoxygenase (for reviews, see Refs. 12–18). It is a multienzyme complex, located in the cell membranes concentrated in the microsomal fraction following differential centrifugation. In a concerted reaction, a hydrogen at $C_{13}$ is removed with hydroperoxidation at $C_{11}$, followed by cyclization. A lipoxygenase introduces a hydroperoxy group at $C_{15}$ to give the endoperoxides $PGG_2$ and $PGH_2$. The endoperoxides possess considerable biological activity. They contract smooth muscle, cause platelet aggregation, and serve as intermediates for the synthesis of other PG's. They are unstable in aqueous media and decompose spontaneously (t½, 4 to 6 min) to a mixture of $PGE_2$ and $PGD_2$. In the tissues, the endoperoxides are further metabolized by enzymes to a variety of PG's (Fig. 2). Each tissue may possess different enzymes using the endoperoxide as substrate and, therefore, produce different amounts and types of PG [8–10, 15–17]. Thus, in the rat brain, $PGG_2$ is converted by an isomerase to $PGD_2$ [15]. In the blood platelets, $PGG_2$ is metabolized to thromboxane $A_2$ [8]. In the arterial blood vessels, $PGG_2$ is preferentially converted to $PGI_2$ [19, 20]. The prostanoids have different biological properties. Thus, in response to an activation of the eicosanoid system, different profiles of PG's are formed, and different biological effects can be elicited in different organs and tissues. Conversely, inhibition of PG biosynthesis by nonsteroidal antiinflammatory drugs will give different results in different tissues, depending partly on the degree of activation of the eicosanoid system in the tissue and on the profile of compounds being generated.

A difficult question, as yet unsettled, is the relative contribution of the endoperoxides and their metabolites to the physiologic effects of the PG system. $PGG_2$ was earlier shown to be released from anaphylactically challenged guinea pig lungs [19]. Its release could also be demonstrated following mechanical stimulation, challenge with bradykinin, and arachidonic acid. If it is released, albeit hardly under physiologic conditions, it is difficult not to imagine that it contributes to the physiologic response, because it has such potent action on, for example, smooth muscle. In some tissues, for example, the platelets, it is likely that it contributes to the aggregatory effects of its metabolite thromboxane $A_2$. In other tissues, like the blood vessels, the net effect of activation of endogenous PG biosynthesis is release of $PGI_2$ and vasodilatation. Because $PGG_2$ has vasoconstrictor properties, it is likely that it is very rapidly metabolized to $PGI_2$ in vivo.

### *Formation of prostaglandins in the kidney*

Soon after the structure of the first PG's had been determined and after these compounds were shown to have a ubiquitous distribution in the mammalian body (for early review see Ref. 21), it became apparent that several previously undefined factors could be related to the PG's. One of these was "medullin," discovered by Lee, to occur in the renal medulla [21]. Medullin was then found to consist of a mixture of three prostaglandins, namely

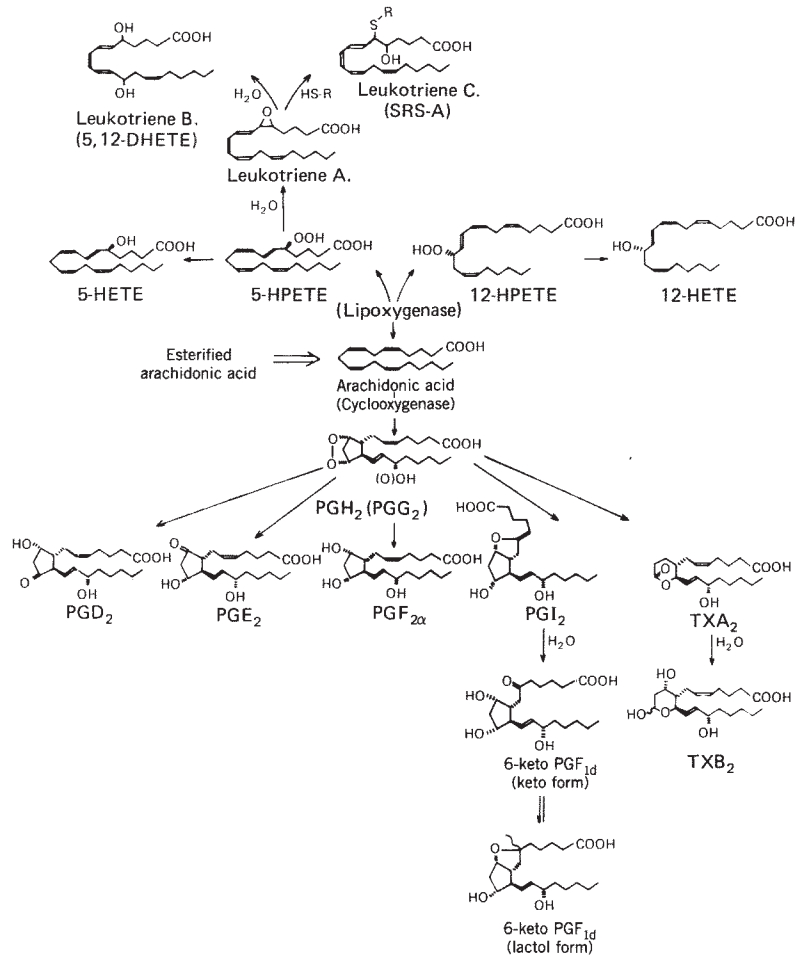


**Fig. 2.** *Scheme of biologically active compounds derived from arachidonic acid.*

$PGE_2$, $PGA_2$, and $PGF_{2\alpha}$ [22]. Later work has confirmed the presence of high levels of $PGE_2$ and $PGF_{2\alpha}$ in the renal medulla [24–27]. But, careful investigations have failed to demonstrate the presence of $PGA_2$ in the kidney and in circulating human plasma [27, 28]. The previously identified $PGA_2$ may therefore be artifactually formed from $PGE_2$ during the isolation procedure. $PGE_2$ readily dehydrates to $PGA_2$ under the acidic conditions used during extraction. In fact PGA was called A because it was formed under *acidic* conditions.

In the last years, additional eicosanoids have been discovered in the kidney. $PGD_2$ has been demonstrated to occur in the kidney in minor amounts [29]. The thromboxane pathway, which ordinarily seems to be of little significance in the kidney, is enhanced in the rabbit kidney, made hydronephrotic by ureteral obstruction [30, 31]. This metabolic switch from vasodilator to vasoconstrictor eicosanoids may be the body's way of shutting off blood flow to a nonfunctioning organ [32]. Prostacyclin ($PGI_2$) biosynthesis has been demonstrated in the rat, rabbit, pig, and human kidney by the isolation and determination of 6-keto-$PGF_{1\alpha}$, a stable degradation product of $PGI_2$ (Fig. 2) [33–37].

### *Regional and cellular localization*

In the kidney anatomy, the circulationary space is interphased with excretory space in a highly efficient system for filtration, diffusion, and active transport from the blood and into the urine. Apart from the vascular system and the glomerulus, the kidney has several other structures serving what appear to be special functions. The juxtaglomerular apparatus in the renal cortex responds to changes in intrarenal arterial pressure (baroceptor), in sodium concentration, and to β-receptor activation by release of renin. The interstitial cells in the renal medulla have been the subject of detailed investiga-

tions. Interestingly, changes in lipid granules occur during water loading, increased salt intake, and hydronephrosis [38–44]. The interstitial cells produce PG's [45–47]. They have also been suggested to be the chief source of the antihypertensive lipid, investigated by Muirhead et al [48]. These workers found that implantation of renal medullary interstitial tissue or cells from culture reduced the blood pressure of dogs, rats, and rabbits with diverse types of hypertension [48].

Early studies on the regional distribution of PG's in the kidney showed the occurrence of high $PGE_2$ and $PGF_{2\alpha}$ synthetic capacity in the medulla [21–27]. When the medulla was divided into inner and outer medulla (papilla), somewhat higher levels were found in the papilla [49–53]. Lower levels of $PGE_2$ were found in the cortex [49]. In recent years, $PGI_2$ has been demonstrated to be the quantitatively most important PG in the renal cortex [36]. The levels found in postmortem tissue are artificially elevated and represent a crude balance of biosynthetic and metabolic processes and can therefore only give limited information. Moreover, highly active local sites can be diluted by a larger mass of inactive cells. Histochemical studies can now provide a more accurate picture of the sites of PG formation in the kidney.

The specific cellular sites of synthesis have been studied using either histochemistry or immunohistochemistry. These methods demonstrate activity or presence of PG endoperoxide synthese and thus give no information of what the endoperoxide metabolites are in the particular cell. Janzen and Nugteren demonstrated high activity in the collecting ducts [54, 55]. This was confirmed by Smith and Wilkin [56], who in addition found lower concentrations of the enzyme in medullary interstitial cells. The presence of PG's in these cell types has also been demonstrated in isolated collecting duct cells [57, 58] and cultured medullary interstitial cells [45–47] and glomeruli [114]. In the cortex, Smith and Bell [59] reported most PG endoperoxide synthetase activity associated with endothelial cells lining arteries, arterioles, and in cortical collecting ducts. The activity in the cortical collecting ducts was somewhat weaker than that observed in the same structures in the medulla. In rabbits, the enzyme was also detected in epithelial cells of Bowman's capsule. No measurable activity was found in the glomeruli, vasa recta, renal veins, Henle's loop, macula densa, or the adjoining juxtaglomerular cells [59]. Thus, if these cells synthetize PG's, it must be in amounts much lower than those of the endothelial cells and those of the collecting ducts.

It seems likely that the high PG endoperoxide synthase activity in the arterial endothelium could be associated with $PGI_2$ synthase and possibly $PGE_2$ synthesis. Both compounds are active vasodilators, and are produced in the renal cortex and can be formed by isolated vascular endothelial cells [19].

Thus, the combination of the biochemical and histochemical studies has supported several possible roles for the renal PG's on physiology (Ref. 60, 61): *(1) Prostaglandins and renal blood flow.* $PGI_2$ and $PGE_2$, produced locally in the renal cortical afferent and efferent arterioles [19, 59], may attenuate vascular responses to vasoconstrictors such as catecholamines and AII [62]. *(2) Prostaglandins and release of renin.* Considerable evidence implicates PG's, particularly $PGI_2$, in renin release. (For review see Refs. 63, 64). But, no PG synthesis has been demonstrated in the juxtaglomerular apparatus [59]. It therefore seems possible that $PGI_2$ released from the adjoining arterial endothelium could trigger renin release. *(3) Prostaglandins and the antidiuretic hormone.* The heavy localization of PG synthesis, particularly $PGE_2$, to both cortical and medullary collecting ducts and the demonstration of the antagonism between the antidiuretic hormone and $PGE_2$ both in vitro and in vivo makes $PGE_2$ an attractive candidate as a local modulator of ADH [60, 61].

The role of PG's formed in the renal interstitial cells remain unclear at present but may be related to the suggested endocrine role of the kidney.

### *Prostaglandin metabolism*

The action of locally generated PG's is terminated either by transport into the blood or urine, by metabolism, or by both.

Relatively little work has been done in the field of renal disposition of PG's. Bito et al have shown that labeled PG's are accumulated in cortical but not in medullary slices of rabbit kidney [65–67]. Prostaglandins present in the arterial blood stream are subject both to filtration in the glomerulus and to probenecid-sensitive secretion by the tubuli [68]. Microinjection studies have shown that $PGE_2$ can be reabsorbed during passage through the loop of Henle and also to some extent in the proximal tubule. Prostaglandins released within the kidney can thus be recovered intact either in the venous blood or in the urine or as metabolites in the same fluids. The proportion of PG's release to blood and to urine probably varies between different sites of synthesis and to the stimuli causing PG release [69].

Five major metabolic transformations have been shown to occur in the kidney. These are: *(1)* oxidation of the 15-hydroxy group to ketone, *(2)* reduction of the $\Delta_{13}$ double bond, *(3)* β-oxidation, *(4)* reduction of the 9-keto group to a 9α-hydroxy group, and *(5)* omega-hydroxylation.

*(1) Dehydrogenation of 15-hydroxyl group.* The dehydrogenation at carbon 15 is the initial step in the metabolism of the PG's [70, 71]. It results in biological inactivation. The reaction can be catalyzed by at least three 15-hydroxy PG dehydrogenases (PGDH) (for review, see Refs. 72–74). PGDH type 1 (11α15-dehydroxy-9-keto-prost-13-enoate $NAD^+$-, 15 oxide reductase, E.C.1.1.1.1..4.) was first discovered in lung tissue [75]. It uses $NAD^+$ as cofactor. It is probably the most common of the different PGDH. In the kidney, it is concentrated to the cortex [50, 76]. Its preferred substrates are PGE, PGA, and PGF [78]. $PGI_2$ and thromboxane $A_2$ are probably substrates, because both 15-keto-$TXB_2$ and 13,14-dihydro-15-keto-$TXB_2$, as well as 6,15-diketo-13,14-dihydro-$PGF_{1\alpha}$ ($PGI_2$-metabolite), have been isolated under physiologic conditions. 6-Eto-$PGF_{1\alpha}$ and $TXB_2$ are relatively poor substrates [79].

As the enzyme catalyzing the initial step in the metabolism of the PG's resulting in their biological inactivation, PGDH could have a regulatory function in controlling the duration or degree of PG action. Thus, several studies have been concerned with levels of PGDH in tissues in relation to age, diet, exogenous factors, hormonal status, and effect of disease (for review see Refs. 72–74). The specific activity of the PGDH increases 59 times in the rat kidney of the first 19 days of life [81, 82]. Decreased levels of PGDH have been reported in spontaneously hypertensive rats, and in essential fatty acid deficient rats [83]. It is difficult to assess the physiologic importance of these changes because most of them have been performed on enzymes assayed in vitro. Future studies should be directed toward the determination of PGDH in vivo either by dynamic methods [79] or by following patterns of urinary PG metabolites.

PGDH type II uses $NADP^+$ as cofactor [84, 85]. This enzyme, in contrast to type I, occurs in 10 times higher levels in the medulla as compared with the cortex [86]. It is tempting to speculate that this may be a dehydrogenase specific for $PGI_2$, because $PGI_2$ metabolism is much higher in the medulla as compared with the cortex [79].

It was initially found that PGDH had a distribution in heavily vascularized tissue such as lung, renal cortex, and placenta [76, 87]. High levels of both PGDH type 1 and II have been found in blood vessels [88]. By a combination of active uptake from circulation and metabolism into biologically inactive PG metabolites, the PGDH may serve to protect intracellular PG receptor from being pertubed by circulatory PG's. Even $PGI_2$, which is formed in the arteries, is metabolized by PGDH in the blood vessels [84]. Veins are more active than arteries in metabolizing PG's [79].

PGDH type II has been partly purified. When the reversed action is run using 15-keto-PGE as substrate and NADPH as cofactor, reduction of both the 9- and 15-keto groups has been demonstrated [72–74]. There is thus the possibility of an association between PGDH type II and NADPH-dependent 9-keto reductase.

The physiologic importance of the type II PGDH is difficult to assess at this time. The cytoplasmatic concentration of $NAD^+$ is normally much higher than that of $NADP^+$, so this reaction may have a minor role in vivo.

*(2) Saturation of the $\Delta_{13}$ double bond.* The saturation of the double bond at carbon 13 is the second step in the metabolism of the PG's. It is catalyzed by 15-keto-prostaglandin $\Delta_{13}$-reductase. It has a widespread distribution in mammalian tissues [76]. A close association with the PGDH seems likely because the unsaturated 15-ketone can rarely be isolated except as a product from purified enzyme preparations of PGDH. Several forms of the enzyme have been purified from chicken heart [90] and human placenta [87]. The enzyme from chicken heart uses $NADP^+$, and that from placenta uses $NAD^+$. The enzymes are not capable of catalyzing reverse reactions. Together, the PGDH and the 15-keto-$\Delta_{13}$-reductase seem to have important physiologic functions in securing the irreversible biological inactivation of PG's.

*(3) β-oxidation.* β-oxidation is a major metabolic pathway for the PG's, because studies on in vivo metabolism of $PGE_2$, $PGD_2$, $PGF_{2\alpha}$, $PGI_2$, and $TXB_2$ have demonstrated that most metabolites have undergone one and in most cases two steps of β-oxidation before excretion (for review, see Refs. 91–94). It has been shown to occur in the mitochondrial fraction of rat liver, lung, and kidney. The renal cortex has a very active β-oxidation system. Labeled $PGI_2$ infused into the rabbit kidney is recovered partly as dinor metabolite [79, 95].

*(4) Reduction of the 9-keto group.* The reduction of the 9-keto group in $PGE_2$ to a 9α-hydroxy group ($PGF_{2\alpha}$) is an example of the transformation of one biologically active PG to another. At least two types of 9-keto reductase have been found in the kidney,

one requiring NADH and the other NADPH as cofactor [97–100]. Both enzymes have been found in the kidney from several mammals including rat and swine. The NADH-dependent enzyme may be identical with the 9-hydroxy PG dehydrogenase shown to catalyze the reverse reaction, namely oxidation of a 9α-hydroxy group to a ketone [100].

In the preparations studied so far, the $NADP^+$-dependent enzyme has been associated with a 15-hydroxy prostaglandin dehydrogenase. The existence of multiple enzyme forms and the lack of pure and well-characterized enzyme preparations make this area of PG metabolism difficult to survey at this time. Although the enzymologic details of the oxidation-reduction reaction at carbon 9 appear to be obscure at present, several investigators have studied the physiologic aspects of its regulation by endogenous activators and inhibitors, by diet and by the salt intake. In the latter study, Weber et al observed an increased 9-keto-reductase activity in rabbit kidney after chronic sodium loading, with concomitant decreases in the ratio of urinary $PGE_2/PGF_{2\alpha}$ [101]. PG-9-keto-reductase from rabbit and chicken kidney has been shown to be inhibited by indomethacin, furosemide, and ethacrynic acid. The significance of these studies for the inhibition of the enzyme in vivo is not yet known.

*(5) Omega-hydroxylation.* Since the discovery of the omega-hydroxylated PG's in the seminal fluid of men over 15 years of age, omega-hydroxylation has proved to be a major metabolic pathway for the PG's. The hydroxylation can occur both at carbon 19 and 20. Further oxidation may lead to formation of dicarboxylic acids, usually with 16 and 18 carbon atoms. Thus, the major urinary metabolite of $PGE_2$ in man is 5,11-diketo-7α-hydroxy-tetranor prostadioic acid. Several studies indicate that exogenous PG's are omega-hydroxylated in the kidney. Thus, Powell recently described the occurrence of PG omega-hydroxylase in renal tissue [110]. Furthermore, infusions of PG's into the renal artery have led to isolation of omega-hydroxylated urinary metabolites [111–112].

*Urinary prostaglandins.* When labeled $PGE_2$ and $PGF_{2\alpha}$ are injected i.v. into animals and humans, no parent compounds can be recovered in the urine [91–93]. Because $PGE_2$ and $PGF_{2\alpha}$ can be definitely isolated and quantitated in rat, rabbit, dog, and human urine, it seems likely that these PG's originate from the kidney [103]. The primary PG's in the urine thus become useful biochemical indicators of intrarenal PG biosynthesis although the site (or sites) of intrarenal synthesis is not definitely known. In both clinical and experimental situations, urine samples from females give the most reliable results [103, 104]. PG levels in males are spuriously high probably due to the contribution from secretions of the male accessory genital glands [105]. The possibilities of artefactual contributions from vaginal secretions and of PG productions in the ureters and urinary bladder also need to be considered. Stop-flow experiments in the dog indicated that the loop of Henle was the major tubular site of entry for PGE into the urine [103]. Stimulation of renal PG biosynthesis by infusion of AII also increased the $PGE_2$ outflow from this site.

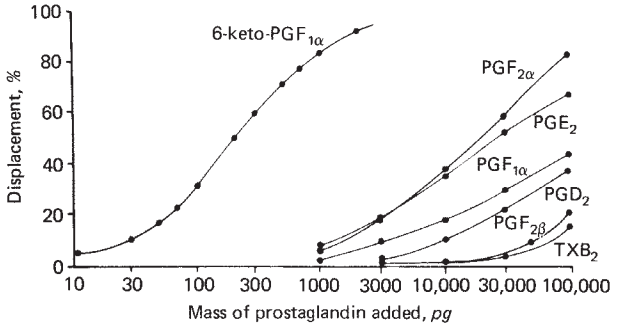


**Fig. 3.** *Crossreaction of 6-MeON-$PGF_{1\alpha}$ antiserum with some prostaglandins and $TXB_2$ under radioimmunoassay conditions involving methoxy amine HCl treatment.*

*$PGI_2$ metabolites in urine.* Relatively little is known of the fate of $PGI_2$ and $TXA_2$ in the kidney. Of these, $PGI_2$ is more interesting from a physiologic viewpoint because it is formed in the cortex and probably participates in the modulation of renal blood flow and of renin release. $PGI_2$ infused into the rabbit kidney led to the appearance of 6-keto-$PGF_{1\alpha}$, dinor 6-keto-$PGF_{1\alpha}$, and 13,14-dihydro-6,15-diketo dinor $PGF_{1\alpha}$ in the effluent [106]. The major urinary metabolites of 6-keto-$PGF_{1\alpha}$ in the rat were dinor-6-keto-$PGF_{1\alpha}$ and dinor-ω-1-hydroxy-6-keto-$PGF_{1\alpha}$ [108]. $TXA_2$ biosynthesis has been demonstrated only under pathologic conditions—hydronephrosis. In vivo studies of $PGI_2$ have shown that it follows the same metabolic pathways as the classical PG's [74]. A key question is whether a renal $PGI_2$ metabolite in urine is derived from 6-keto-$PGF_{1\alpha}$ or if $PGI_2$ is metabolized by adjacent cortical PGDH and $\Delta_{13}$-reductase enzymes prior to its excretion in urine. The 6-keto-$PGF_{1\alpha}$ in human urine is probably derived from the kidney, for the infusion of high amounts of $PGI_2$ to healthy volunteers failed to increase the urinary 6-keto-$PGF_{1\alpha}$ [64].

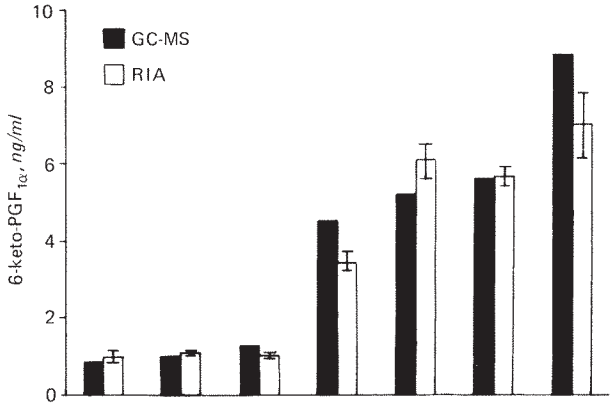


**Fig. 4.** *Validation of the 6-keto-$PGF_{1\alpha}$ by radioimmunoassay (RIA) in comparison with gas chromatography mass spectrometry (GC-MS) analysis of three cortical and four medullary samples.*

Because several laboratories report difficulties in raising a specific and sensitive immunoassay for 6-keto-$PGF_{1\alpha}$, we chose another approach. Antibodies were raised against 6-methoxime-$PGF_{1\alpha}$. Unlike 6-keto-$PGF_1$, this compound cannot form lactols. $PGI_2$ and 6-keto-$PGF_{1\alpha}$ in biological samples are converted to 6-MeON-$PGF_{1\alpha}$ and then assayed by the 6-MeON-$PGF_{1\alpha}$ antibodies. The crossreaction of the antibodies are shown in Fig. 3. Good agreement between this RIA and GC-MS was obtained in samples of rabbit renal cortex and medulla as shown in Fig. 4. The method has been found to be suitable both for analysis of 6-keto-$PGF_{1\alpha}$ in tissue [107] and in human urine.

### *Conclusions*

The renal PG story is still emerging. More detailed work is necessary regarding the localization of various biosynthetic pathways in different cells and structures in the kidney. The closer details of the control of arachidonic acid release in various sites need further studies, particularly in relation to renal physiology and pathology. The formation and action of products of the lipoxygenase pathway in the kidney are not known. The metabolism of extrarenal and intrarenal PG's in the kidney needs to be clarified. The fate of intrarenally released PG's at different sites, the enzymes participating in the metabolism, their localization, and how the metabolism is balanced by endogenous and exogenous factors are further questions remaining to be answered.

Last, investigators will have to pay particular attention to the numerous methodologic problems in the measurement of renal PG's and their metabolites [109]. Apart from the proper use of specific, sensitive, and properly validated methods, it must be realized that physiologic and pharmacologic interventions can change metabolic pathways of PG's without any overall change in PG synthesis. Thus, an inhibition of the dehydrogenase pathway could lead to a reduction of 15-keto metabolites, which could erroneously be interpreted as a decrease in the activity of the PG system. In the future, we expect that metabolic profiles of eicosanoids in tissue, urine, and other body fluids will provide a more complete picture of the participation of these compounds in physiologic and pathologic processes.

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