Activity Profiles of Prostaglandin 15- and 9-Hydroxydehydrogenase and 13-Reductase in the Developing Rat Kidney

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SUMMARY
Three prostaglandin \(\text{F}_{2\alpha}\)-catabolizing enzyme activities have been demonstrated in kidneys from adult rats. Activity of each of these enzymes varied with animal age. Whereas 15-hydroxydehydrogenase and \(\Delta 13\)-reductase appeared important to the early developing kidney (prior to 4 weeks of age), 9-hydroxydehydrogenase appeared to be characteristic of the adult kidney. Prostaglandin 15-hydroxydehydrogenase rose sharply after birth to a maximal value at 19 days (59-fold relative to the adult) decreasing to adult values by Day 40. Prostaglandin \(\Delta 13\)-reductase followed a similar pattern rising about 20-fold at Day 19. Prostaglandin 9-hydroxydehydrogenase, on the other hand, was undetectable up to Day 19, rising gradually to adult values by Day 50. Prostaglandin biosynthesis in whole kidney and renal papilla at the peak period of 15-hydroxydehydrogenase activity, i.e. 19, 22, and 24 days, did not vary significantly from adult values. The dramatic rise in 15-hydroxydehydrogenase activity, reflecting an important requirement for prostaglandin inactivation during the first 3 weeks after birth, appears to correlate well with the increase during this period in the number of glomeruli, cortical tubules, and redistribution of blood flow to the cortex. These results suggest for the first time an important relationship between prostaglandin catabolizing activities and nephrogenesis.

Little work has been reported on developmental changes in the prostaglandin system (biosynthesis and catabolism). Our first study with rat lung (15) showed interesting variations in product types and enzyme activities between rates of various ages from birth to the adult. High prostaglandin inactivation appears to be an important feature of the early developing tissue (15). Since the adult kidney has been reported to contain the highest 15-hydroxydehydrogenase activity of all tissues tested in this species (6), we decided to study next the kidney from developing rats in order to determine whether our findings of high prostaglandin inactivation during early development would also be applicable to this tissue, and to investigate whether a correlation might exist between changes in prostaglandin inactivation with nephrogenesis.

EXPERIMENTAL PROCEDURE

Materials
Prostaglandin standards were generously supplied by Dr. J. E. Pike and Dr. U. Aksen, The Upjohn Company, Kalamazoo. Tritiated prostaglandin metabolites were prepared by the methods described below using only tracer as substrate.

Animals—Pregnant rats (Wistar strain) were purchased from a local supplier and housed in our animal quarters. Birth time was approximated to within a few hours by checking the animals periodically. Male Wistar rats weighing 220 to 250 g are referred to as adult in the subsequent sections.

Reagents and Solvents—The following reagents were purchased as indicated: NAD\(^+\) (Sigma Chemical Co.); tritiated \(\text{PGF}_{2\alpha}\) \(\text{H}^{3}\)-labeled, specific activity = 162 Ci/mmol; \(\text{H}^{3}\)-labeled, specific activity = 9.26 Ci/mmol; \(\text{H}^{3}\)-labeled, specific activity = 93 Ci/mmol); and Aquasol (New England Nuclear); commercially precoated thin layer plates of Silica Gel G (Brinkmann); BioSil HA silica acid (Calbiochem); sodium borodeuteride (Merck, Sharpe and Dohme, Quebec). All solvents were reagent grade (Fisher Scientific), dried, and glass-distilled within 1 week before use. Chloroform was distilled from anhydrous calcium chloride (Fisher Scientific) and methanol and ethanol were reacted first with magnesium metal and iodine (Fisher Scientific) and then distilled. Diethyl ether was freshly distilled before use in a Buchler rotary evaporator. Water was deionized and then distilled.

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through glass (Corning). Diazo methane was generated by dropping small portions of N-methyl-N-nitro-N-nitosoguanidine (1 g) in a mixture of ice-cold KOH (10 g) in water (10 ml) and diethyl ether (10 ml). The ethereal diazonium was cubed quantitatively distilled.

**Methods**

**Enzyme Assays**

The right kidney from one adult was routinely used as control with every assay of renal catabolism in newborn rats. Usually four newborn rats were used except at the early ages (fetal, 1 and 6 days after birth) when the right kidneys from eight rats were pooled.

Each kidney was removed, cleaned from capsular tissue, opened, with 0.05 M KH_2PO_4-NaOH buffer, pH 7.4, and homogenized briefly (top speed, 10 s) in 20 volumes of buffer at 0° with a Polytron tissue homogenizer (Brinkmann).

15-Hydroxydehydrogenase and 15-Reductase Assays

Aliquots (0.5 ml) of homogenate were incubated for 10 min at 30° in a series of test tubes containing NAD⁺ (4 mM final concentration) and 2.2 × 10⁵ dpm [3H]15-KD-PGF_2α, or [3H]15-KD-PGF_2α diluted with 0, 1, 5, 10, 50, and 100 µg of unlabeled PGF_2α. In this way data were obtained to construct a saturation curve for each animal investigated (15).

9-Hydroxydehydrogenase Assay

Aliquots (0.5 ml) of the same homogenate were incubated for 2.5 min at 30° in duplicate tubes containing NAD⁺ (4 mM final concentration) and 0.5 × 10⁴ dpm [3H]15-KD-PGF_2α or [3H]15-KD-PGF_2α. Recovery of radioactivity in the residue was 98%. Radio thin layer chromatographic analysis showed two peaks of radioactivity, one migrating with K_β 0.40 as in the reference starting material, and a less polar product, R_β 0.45. Complete resolution of both products was achieved by silicic acid column chromatography (Bio-Sil HA-minus 325 mesh, Calbiochem). The mixture was introduced to a column (1 × 15 cm) of silicic acid in benzene and eluted with the following solvent mixture in benzene: 0:10, 2:8, 4:6, 6:4, and 10:0. The starting material (15KD-PGF_2α) was found in ethyl acetate-benzene 6:4 fraction and the metabolite (15KD-PGE_2) was obtained in the 4:6 fraction. Each product was over 90% pure as judged by radio thin layer chromatography. Further purification of the metabolite was required and was achieved by preparative thin layer chromatography as in previous section.

**Biosynthesis Experiments**

The conversion of tritiated arachidonic acid ([H] 20:4, 2.2 × 10⁴ dpm) into PGE_2 and PGF_2α was measured in homogenates of whole kidney from one adult and one 22-day-old rat and in homogenates of papilla from kidneys from adult, 19- and 24-day-old rats. Papilla from kidneys of three adult and seven newborn rats were removed, washed with cold 0.05 M KH_2PO_4-NaOH, pH 7.4, buffer, and homogenized in 20 volumes of buffer in a Polytron tissue homogenizer (10 s, top speed). Aliquots (0.5 ml) were incubated (10 min, 37°, O_2) in flasks (25 ml) containing tracer arachidonic acid. Reaction was terminated by the addition of water (5 ml), freshly distilled diethyl ether (10 ml), and enough 0.05 N HCl to bring the aqueous phase to pH 3.0. The aqueous phase was extracted twice with diethyl ether (300 ml) and the diethyl ether layers were washed to neutrality with several small portions of water (5 ml). The combined diethyl ether phases were taken to dryness in vacuo and analysed for distribution of radioactivity by radio thin layer chromatography (Table II).

**Sodium Borohydride and Borodeuteride Reduction**

The sample (20 to 50 µg) was dissolved in 2 ml of methanol and placed in a glass stoppered flask maintained at 0°. Twenty milli grams of NaBH₄ or NaBD₄ were added slowly to the stirred solution. After 30 min, the mixture was diluted with 10 ml of diethyl ether, 10 ml of water, and enough N HCl to bring the pH to 3. The contents were then transferred to a separatory funnel, diluted with diethyl ether and water, and extracted. The ether extract was subsequently washed to neutrality with water and evaporated to complete dryness. An aliquot was assayed for completion of reduction by radio thin layer chromatography and the sample was used without further purification for gas chromatography and mass spectrometry. Usually complete reduction was observed under these conditions.

**Derivatives for Gas Chromatography-Mass Spectrometry**

Samples (20 to 50 µg) were converted to methyl esters in 50-µl glass vials by the addition of 2 µl of methanol and 18 µl of freshly prepared and distilled solution of ethereal diazomethane. After 60 min at 23°, the solvent was blown off with a fine stream of nitrogen and the residue was converted to trimethylsilyl ethers by the addition of 20 µl of Tri Sil Z (Pierce Chemical Co.) and heating at 60° for 5 min. Gas chromatography retention data of the isolated metabolite prior to reduction with sodium borohydride was obtained on the methyl ester methoxime trimethylsilyl ether derivatives. The methyl esters were first converted to methoxime derivatives by reacting overnight (23°) in 15 µl of MOX reagent (Pierce Chemical Co.). The solvent was blown off with nitrogen and the residue converted to trimethylsilyl ethers as described above.

**Gas Chromatography and Mass Spectrometry**

Gas chromatograph retention data were obtained on methyl ester trimethylsilyl ether derivatives of the metabolites before
and after sodium borohydride or sodium borodeuteride reduction (Table 1) as well as on methyl ester methoxime trimethylsilyl ethers. Analyses were performed on a Hewlett-Packard model 5711 equipped with flame ionization detector (300°) and a stream splitter attached to a Packard model 892 radioactivity proportional counter. The heated inlet to the proportional counter was maintained at 300°. The gas chromatograph contained a glass column filled with 3% SE-30 on Gas Chrom Q (Applied Science) maintained at 250°. Mass spectra were recorded on a Varian MAT CH-5 mass spectrometer coupled to a gas chromatograph and computer (Varian PDP-8) assembly. The same column packing was used as in the gas chromatographic analyses and this column was maintained at 250°. The electron energy was 70 eV.

**Protein Measurement**

Protein in homogenates was assayed by the method of Lowry et al. (17).

**Method of Expression of Data**

Each assay for 15-hydroxydehydrogenase and Δ13-reductase activity was performed on a fixed quantity of tracer substrate (PGF2α) containing at least four different concentrations of unlabeled substrate. In this way, the amount of product formed could be determined by the percentage radioactivity in the various products since the specific activity of the precursor in each tube was known. This allowed construction of saturation curves for each homogenate (Fig. 4). Maximal activity was calculated from these curves and is expressed as picomoles/min/mg of protein. Since 15-hydroxydehydrogenase activity is the first step in the catalysis of PGF2α and the product, 15K-PGF2α, is further catalyzed by Δ13-reductase into 15K-PGF2α, which in turn is converted into 15K-PGE2 (16), total 15-hydroxydehydrogenase activity is represented by the sum of 15K-PGF2α, 15K-PGF2α, and 15K-PGE2 formed. Similarly Δ13-reductase activity is represented by the sum of 15K-PGE2 and 15K-PGF2α formed. 9-Hydroxydehydrogenase activity is expressed as per cent of activity observed in the adult using tracer 15K-PGF2α as substrate (16). An incubation period was chosen such that only 66% of substrate was converted by the adult.

**RESULTS**

Incubation of homogenates of adult rat kidney with tritium-labeled prostaglandin F2α gave three main metabolites (Fig. 1). Sufficient material for mass spectrometric characterization was obtained from large scale incubations. The thin layer chromatographic mobility of these compounds suggested that one or two keto groups had been introduced into PGF2α. Direct evidence for this was as well as the localization of the keto groups was obtained by sodium borodeuteride and sodium borohydride reduction of the metabolites with subsequent comparison of the mass spectra of these reduced derivatives with that of authentic PGF2α (18).

Sodium borohydride reduction of Metabolite I (Rf 0.32) gave two more polar radioactive products (Rf 0.22 and 0.15, Table 1, Fig. 2) whose mass spectra were identical with that of authentic PGF2α (18). The reduced double bond at Δ13. Reduction of Metabolite II with sodium borohydride gave a product with a molecular ion mass units higher than prostaglandin F2α, indicating that Metabolite II had only one double bond and one keto group. The location of the deuterium atom at position 15 was established in a similar way to Metabolite I. Metabolite II was therefore 15-keto-13,14-dihydroprostaglandin F2α, and the two isomers after chemical reduction had the same chromographic mobility.

Metabolite III (Rf 0.45) gave two radioactive products after sodium borohydride reduction (Rf 0.23, 0.15, Table 1, Fig. 2) as expected of 15-keto-13,14-dihydroprostaglandin F2α. Mass spectral analysis of the reduced compound showed a molecular ion mass units higher than PGF2α, with a pattern very similar to the reduced product of Metabolite II. Reduction of Metabolite III with sodium borodeuteride and subsequent mass spectral analysis showed a displacement of the molecular ion by two mass units from the sodium borohydride reduced product indicating that two deuterium atoms had been incorporated during chemical reduction. Comparison of the mass spectra of the deuterated and protonated reduced derivatives of Metabolite III and with PGF2α indicated that both fragments at m/e 173 and 217 in the

![Fig. 1. Radioactivity profile of an ethanol extract from incubation of [15H]PGF2α with a kidney homogenate from an adult rat. I, 15K-PGF2α; II, 15KD-PGF2α; III, 15KD-PGE2. The incubation system (final volume 0.5 ml) consisted of homogenate (0.5 ml, approximately 5 mg of protein), tritiated prostaglandin F2α (2.2 × 106 dpm), and NAD+ (4 μM final concentration). Incubation (10 min at 30°) was terminated with the addition of absolute ethanol (2.5 ml). The precipitate was centrifuged and the supernatant was transferred and evaporated to dryness in vacuo. The residue was resuspended in 300 μl of chloroform-methanol (2:1) and an aliquot (1/4) was spotted on thin layer plates (5 x 20 cm) and developed with chloroform-methanol-acetic acid-water (90:9:1:0.05, v/v/v). Standards (5 μg each) were spotted on the side and visualized after development by spraying with an ethanolic solution of phosphomolybdic acid (v/v, 1:10) and gentle heating. Radioactivity profile was obtained by scanning the plate with a Panax radiochromatogram scanner.](http://www.jbc.org/fig1.png)
TABLE I
Chromatographic properties of metabolites of PGF$\alpha$

| Metabolite | Before NaBH$_4$ | After NaBH$_4$ |
|------------|----------------|----------------|
|            | $R_F$ | Me-Me-C | $R_F$ | Me-Me-C |
| Metabolite I | 0.32 | 0.37-0.50$^d$ | 0.22; 0.15 |
| Metabolite II | 0.40 | 0.57 | 0.23 |
| Metabolite III | 0.45 | 0.64 | 0.23; 0.15 |
| Standard PGFa  | 0.15 | 0.32 | 0.23; 0.15 |
| Standard 15K-PGF$\alpha$ | 0.32 | 0.37-0.56$^d$ | 0.23; 0.15 |
| Standard 15KD-PGF$\alpha$ | 0.40 | 0.57 | 0.23; 0.15 |
| Standard 15KD-PGE$\alpha$ | 0.45 | 0.64 | 0.23; 0.15 |

*Chloroform-methanol-acetic acid-water 90:9:1:0.65 (v/v) 75 min at 23°. TLC, thin layer chromatography.
$^a$ Values were calculated from a semi-log plot of retention time versus chain length constructed from a standard mixture of saturated fatty acids. GLC, gas-liquid chromatography.
$^b$ Me, methyl ester; MesSi, trimethylsilyl ether; MO, methoxime.
$^c$ Multiple peaks were observed.

mass spectra of the protonated derivatives were shifted to $m/e$ 174 and $m/e$ 218 in the deuterated derivative. Since these fragments are derived from parts of the molecule containing carbon 15 and carbon 9, respectively, i.e. C$_5$H$_{11}$CD$_3$O-Si(CH$_3$)$_3$ and (CH$_3$)$_2$SiOCD-CH=CH-O-Si(CH$_3$)$_3$, then the deuterium atoms (and therefore the original keto groups) are located at the 9 and 15 positions. Metabolite III is therefore 15-keto-13,14-dihydro prostaglandin $\alpha_2$ and the two products obtained after chemical reduction constituted isomers about the 9 and 15 positions.

That the keto group was not at position 11 instead of position 9 was ruled out by a separate set of experiments in which prostaglandin $\alpha_2$ specifically labeled at the 9-0 position was incubated with adult kidney homogenates. The taurine-dependent elimination of tritium from the 9-0 position was shown in the preceding paper (16). No such loss of radioactivity would have occurred if the 11-hydroxyl group was oxidized to a keto group.

Prostaglandin 9- and 15-hydroxydehydrogenase and 13-reductase activities were linear up to 10 min at 30° (Fig. 3). The effect of increasing substrate concentration on prostaglandin 15-hydroxydehydrogenase and 13-reductase is shown in Fig. 4. $V_{max}$ for adult kidney was 6.1 ± 3.5 S.D. pmol/min/mg of protein for 15-hydroxydehydrogenase and 3.8 ± 1.6 S.D. pmol/min/mg of protein for 13-reductase, and varied significantly with the age of the animal.

Fig. 5 shows the activity profiles for the three enzymes measured as a function of increasing animal age. At gestational age 20 days, 15-hydroxydehydrogenase activity was 15-fold greater than the adult and rose linearly to a peak at 19 days postnatally, 59-fold higher than the adult, decreasing thereafter to adult levels by Day 40. A similar but less spectacular increase occurred with 13-reductase activity (6-fold higher than adult at gestational

![Fig. 2. Thin layer chromatogram of sodium borohydride reduced kidney metabolites (I to III) and authentic reference metabolites (A to C) treated in a similar way. A, 15K-PGF$\alpha$; B, 15KD-PGF$\alpha$; C, 15KD-PGE$\alpha$. Reference compounds are shown on the extreme left and right of the plate. Spots were visualized by spraying the plate with an ethanolic solution of phosphomolybdic acid (w/v 1:10) and gentle heating. Samples to be reduced (20 to 50 µg) were dissolved in 2 ml of distilled and dry methanol, and sodium borohydride (20 mg) was added slowly to the stirred solution maintained at 0°. After 30 min at 0°, the mixture was diluted with distilled diethyl ether (10 ml), water (5 ml), and enough $\mathrm{HCl}$ to adjust the pH to 3.0. The mixture was extracted in a separatory funnel and the diethyl ether phase was washed to neutrality with water. Evaporation of the diethyl ether phase to complete dryness in vacuo gave a residue which was analyzed by thin layer chromatography using the same developing system as in Fig. 1.](http://www.jbc.org/Downloadedfrom)
FIG. 3. Rate of conversion of [9-3H]PGF\(_2\alpha\) by 15-hydroxydehydrogenase (X—X), \(\Delta 13\)-reductase (●—●) and 9-hydroxydehydrogenase (■—■) present in adult rat kidney homogenates. The incubation system was the same as in Fig. 1 except that tracer [9-3H]PGF\(_2\alpha\) was used in 4 tubes incubated for different periods. The workup procedure was the same as in Fig. 1. 9-Hydroxydehydrogenase activity was ascertained by the loss of radioactivity calculated at the ethanol extract stage as described in the preceding paper (16).

Prostaglandin biosynthesis was measured at the peak points of prostaglandin catabolism (Days 19, 22, and 24) and was compared with that observed in the adult. The results are shown in Table II. Prostaglandin biosynthesis in the whole kidney and in the papilla appeared similar in both age groups suggesting that prostaglandin biosynthesis does not vary like prostaglandin catabolism, at least at these stages of animal development.

DISCUSSION

The activity of three enzymes involved in the conversion of PGF\(_2\alpha\) into 15KD-PGE\(_2\) have been measured in the rat kidney (Fig. 6) and found to vary with animal development. In an earlier study (15) we also observed that prostaglandin catabolism in developing rat lung varied with animal age. In that study it

TABLE II

|                | Papilla       | Whole kidney* |
|----------------|---------------|---------------|
|                | Newborn (19 days) | Adult | Newborn (24 days) | Adult | Newborn (22 days) | Adult |
| PGE\(_1\)      | 13.9          | 10.9         | 21.8          | 26.0           | 3.3              | 2.1              |
| PGE\(_{2\alpha}\) | 14.7          | 23.4         | 6.7           | 8.6            | 7.6              | 5.4              |

* Fifty micrograms of unlabeled PGE\(_1\) and PGE\(_{2\alpha}\) were added at the start of the incubation to minimize degradation of the tritiated prostaglandin formed during incubation.
was interesting to observe a dissociation between Δ13-reductase and 15-hydroxydehydrogenase catabolizing activities reaching maxima at different periods in postnatal lung development (Δ13-reductase at 1 day postnatally; 15-hydroxydehydrogenase at 19 days postnatally). In the present study, both enzymes reached maximal activity at the same stage in kidney development (19 days postnatally) although another enzyme, 9-hydroxydehydrogenase (16, 19), displayed a completely different activity profile. It was absent in kidney from prenatal and early postnatal rats, appeared around Day 19, and reached adult levels by Day 50.

The cortical region of the rat kidney is very immature at birth. Its morphology develops almost completely within a brief 3-week postnatal period. The main thrust of nephrogenesis and functional differentiation of tubules occurs within 4 weeks after birth. During this period the number of glomeruli increases almost 3-fold and a marked redistribution of blood flow to the cortex takes place (20-26).

Prostaglandin E₂ and F₂α are potent vasoconstrictors in the rat kidney (27). Although no studies are available describing the effects of these compounds on kidneys from newborn rats, this tissue probably behaves in a similar fashion to that from an adult rat although the extent of its sensitivity to prostaglandins might be different from that of the adult animal. Prostaglandins, unless eliminated, would therefore be expected to interfere with and likely inhibit blood flow to the cortex during this critical period (1 to 4 weeks). Our observations show that the developing kidney is capable of catabolizing prostaglandins more efficiently (59-fold greater than the adult) during the first 3 weeks after birth (Fig. 5).

The rapid postnatal rise in prostaglandin catabolism does not reflect an overall increase in the turnover of prostaglandins since prostaglandin biosynthesis in the whole kidney as well as in the papilla, the main site of the prostaglandin biosynthetic enzymes (12), does not vary appreciably between the peak period of prostaglandin catabolism (Day 19 to 24) and the adult (Table II). In fact, our observation of a higher catabolism in the newborn (59-fold) with similar biosynthetic activity relative to the adult suggests that during the first 4 weeks of postnatal development, the rat kidney is in a state of local prostaglandin deficiency. This may be an important requirement to permit the proper renal blood flow needed for cortical development. Interference with prostaglandin catabolism during this period may be expected to result in abnormal renal corticogenesis. Studies along these lines are presently in progress.

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Fig. 6. Metabolites of PGF₂α formed by the adult rat kidney.
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