To study survival through the lungs, prostacyclin was infused alternately through two catheters whose tips were located in the right atrium and in the ascending aorta or left ventricle. Intraaortic or intravenous infusions of prostacyclin (0.1–0.5 μg kg^{-1}-min^{-1}) for 10–15 min induced similar hypotensive effects and similar steady-state relaxations of the BCA. In the same dogs more than 90% of PGE_2 (0.05–0.5 μg $kg^{-1}min^{-1}$), assayed by contraction of RSS, was removed through the lungs.

The disappearance of prostacyclin in the hindquarters and liver was studied by infusions (0.2–1.0 μg $kg^{-1}min^{-1}$) through catheters inserted into the abdominal aorta (just above the iliac bifurcation) and the portal vein respectively. By comparing relaxation of BCA during infusion into the right atrium with infusions through these catheters it was estimated that the hind quarters removed 48 ± 4% (4 dogs) of prostacyclin in one passage and the liver removed 73% and 75% (2 dogs).

Thus, in contrast to PGE_2 and $PGF_{2\alpha}$ the activity of prostacyclin does not disappear after passage through the lungs. However, prostacyclin is inactivated to about the same extent as PGE_2 and $PGF_{2\alpha}$ in the hind quarters and the liver (Ferreira & Vane, 1967).

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Enzyme in rabbit kidney converts prostaglandin $F_{2\alpha}$ directly to prostaglandin E_2 *in vitro*

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Classical prostaglandins (PG) such as PGE_2 and $PGF_{2\alpha}$ are metabolised in most tissues by the sequential action of prostaglandin 15-hydroxydehydrogenase and prostaglandin Δ–13 reductase, yielding biologically inactive 13,14-dihydro-15-keto prostaglandins. We have recently demonstrated such pathways of $PGF_{2\alpha}$ breakdown in the kidneys of several species and observed in rabbit kidney a novel enzyme which converts $PGF_{2\alpha}$ directly to PGE_2 (Hoult & Moore, 1977).

Highspeed (100,000 *g*) supernatants obtained from homogenized kidneys of adult male animals were incubated at 37°C with 5 mM NAD^+ and PGE_2 or $PGF_{2\alpha}$ (10 μg/ml) containing 0.05 μCi [$^3H_7$]-PGE_2 or [$^3H_1$-9β]-$PGF_{2\alpha}$. Samples removed at timed intervals were either assayed directly on up to four rat fundus strips, or acidified, extracted and evaporated prior to scintillation counting and either bioassay or thin layer radiochromatography in solvent F6 (Andersen, 1969).

Guinea pig, rat and rabbit kidneys (in descending order of activity) metabolised PGE_2 exponentially and more rapidly than $PGF_{2\alpha}$: $T_{\frac{1}{2}}$ measured by bioassay were 3.0 ± 0.3, 15.5 ± 1.4, 49.8 ± 3.9 min for PGE_2, and 7.9 ± 0.9, 36.6 ± 2.8, 132.0 ± 4.5 min for $PGF_{2\alpha}$ (n = 6). The bioassay and radio-t.l.c. results agreed closely except for $PGF_{2\alpha}$ metabolism by rabbit kidney; in 8 experiments the biological activity of the incubation increased to 207.9 ± 16.6%, peaking at 10–20 min, and thereafter declined as the active material was itself metabolised. Simultaneous radiochemical experiments showed a progressive loss of the 9β-tritium label consistent with oxidation of the secondary alcohol at C-9 to a ketone. Generation of biologically active material was prevented reversibly at 4°C and inhibited irreversibly by preincubation for 15 min at 50°C or 1 min at 100°C. Thin layer chromatography in five solvents of material derived from large scale incubations extracted at the peak of biological activity showed that >80% of the bioassayable material recovered was located in the 'PGE_2 zone'. It possessed properties similar to PGE_2 in several biological assays, and could be converted to $PGF_{2\alpha}$ by sodium borohydride reduction.

This enzyme is located exclusively in the rabbit kidney cortex: using a radiochemical method and highspeed supernatants containing approximately equal amounts of soluble protein, 68.9 ± 2.3% $PGF_{2\alpha}$ was converted to E-type derivatives in 240 min by cortex, but only 8.2 ± 1.8% by medulla (n = 5). Conversion of $PGF_{2\alpha}$ to PGE_2 was observed biologically at a wide range of substrate concentrations (100 μg/ml down to 0.5 μg/ml). There was no evidence from either bioassay or radiochemical methods for conversion of $PGF_{2\beta}$ (10 μg/ml) to PGE_2

or any PGE metabolite. However, $PGF_{2\beta}$ was metabolized at the same rate as $PGF_{2\alpha}$ by the conventional two step pathway to a compound provisionally identified as 13,14-dihydro-15-keto $PGF_{2\beta}$.

These results show that the rabbit renal cortex contains an enzyme capable of converting $PGF_{2\alpha}$ directly to PGE_2. Pace-Asciak (1975) has described a similar enzyme in rat kidney and called it prostaglandin 9-hydroxydehydrogenase, but in this species it converts a $PGF_{2\alpha}$ metabolite to its PGE_2 equivalent. By contrast, the rabbit enzyme may be an important modulator of renal function, since $PGF_{2\alpha}$ has less potent or different actions than PGE_2 on renal functions (McGiff & Nasjletti, 1973).

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Thyroxine-induced hyperthyroid state in rats suppresses renal prostaglandin metabolism

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15-Hydroxyprostaglandin dehydrogenase (15-PGDH) and prostaglandin Δ-13 reductase (Δ-13 R) in high-speed supernatants from rat kidney metabolise prostaglandin (PG) $F_{2\alpha}$ rapidly to 15-keto $PGF_{2\alpha}$ and then to 13,14-dihydro-15-keto $PGF_{2\alpha}$ (Hoult & Moore, 1977). A prostaglandin 9-hydroxydehydrogenase (9-HDH) further converts PGF metabolites to their PGE derivatives. Since 15-PGDH appears to have a rapid turnover (Blackwell, Flower & Vane, 1975) and its levels are influenced by steroid hormones (Blackwell & Flower, 1976) as well as in pregnancy (Bedwani & Marley, 1975), we examined the effect of altered thyroid status on rat renal PG metabolism.

Groups of 45 g and 275 g male Sprague-Dawley rats were made hyperthyroid or hypothyroid by 18 daily s.c. injections of (−)-thyroxine (200 μg) and methimazole (2 mg) respectively. Hyperthyroid rats showed reduced rates of growth, cardiac hypertrophy, elevated serum thyroxine levels and thyroid atrophy; hypothyroid animals appeared normal apart from thyroid enlargement. 100,000 *g* cytoplasmic supernatants were prepared in pH 7.4 phosphate buffer, incubated with NAD^+ (5 mM) and $PGF_{2\alpha}$ (10 μg/ml) labelled with 0.11 μCi [^{3}H-9β]-$PGF_{2\alpha}$ and extracted for assay of 15-PGDH, Δ-13 R and 9-HDH activity as described previously (Hoult & Moore, 1977).

$PGF_{2\alpha}$ metabolism by both conventional 15-PGDH and Δ-13 R pathways and by conversion to PGE metabolites by 9-HDH was inhibited 40% in hyperthyroid animals. In 10 min incubations of renal supernatants from 45 g rats overall PG metabolism was 68.3 ± 2.3% in saline-injected control rats, but reduced to 40.3 ± 2.9% in hyperthyroid rats ($n = 9$, $P<0.001$). In 275 g rats, metabolism in 75 min incubations was reduced from 83.4 ± 2.6% to 50.1 ± 3.2% ($n = 10$, $P<0.001$). There was no difference between any of the renal supernatants in soluble protein content, rates of utilization of NAD^+ by endogenous enzymes and substrates, or of NAD^+ dependence of 15-PGDH. Thyroxine did not inhibit PG metabolism up to 200 μg/ml.

We conclude that thyroxine treatment reduces endogenous levels of 15-PGDH and other PG metabolising enzymes, probably by a direct effect on protein metabolism, consistent with the known biochemical actions of this hormone (Wolff & Wolff, 1964). The results also show that levels of these enzymes are lower in older rats.

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