appeared to be a metabolic product, the experiment was repeated at a ten-fold increased level of substrate. In addition, [^{14}C]-PGE_1 (at the same substrate concentration) was also compared in parallel with the PGE_2.

Following column chromatography further evidence of identification was obtained by thin layer chromatography in two solvent systems. In addition the trimethylsilyl ether methyl ester derivative of the material eluted in the $PGF_{1\alpha}$ zones had a retention time for ^{14}C corresponding to authentic [^{14}C]-$PGF_{1\alpha}$ on radio gas chromatography.

Conclusive evidence of identification for both $PGF_{1\alpha}$ and $PGF_{2\alpha}$ was obtained by combined gas liquid chromatography mass spectrometry.

Of the tissues studied, only the livers of guinea-pig, rabbit and horse and heart of the horse have been found to produce the corresponding PGF_α on incubation with PGE. At no time has any evidence for the production of the corresponding PGF_β been obtained. In addition PGE has been found to be metabolized to products other than the PGF_α in all tissues so far studied. These other metabolites have provisionally been identified as the corresponding 13,14-dihydro PGE, 13,14-dihydro 15-oxo PGE and 15-oxo PGE.

To date the majority of experiments have been performed using rabbit liver homogenates and the results indicate that there is a wide range of 9-oxo reductase activity within the liver of any one species. In rabbit liver the yield of $PGF_{2\alpha}$, formed from PGE_2, has ranged from 25 to 48% of the total radioactivity recovered.

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Biological activity of prostaglandin D_2 on smooth muscle

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The 9,11-cyclic endoperoxide formed during prostaglandin (PG) biosynthesis can be converted to either PGE, PGF_α or PGD (Fig. 1) (Granström, Lands & Samuelsson, 1968; Nugteren & Hazelhof, 1973; Hamberg & Samuelsson, 1973). It has been reported that PGD_1 and PGD_2, in contrast to PGE_1, possess negligible biological activity (Nugteren & Hazelhof, 1973).

Our initial experiments indicated that PGD_2 is active on smooth muscle. We have therefore compared PGD_2 with PGE_2 and $PGF_{2\alpha}$ upon a variety of biological preparations, a number of which are known to give qualitatively different responses to E and F type prostaglandins.

On preparations in which PGE_2 is a more powerful inhibitor than $PGF_{2\alpha}$ (equipotent molar ratio 300 to 3,000). PGD_2 was less active than PGE_2 but two to four times more active than $PGF_{2\alpha}$. Such relative activities were found on cat tracheal muscle *in vitro*, dog hind limb vessels *in vivo* and rabbit oviduct *in vivo*.

In the sheep, PGD_2, like $PGF_{2\alpha}$, is pressor whereas PGE_2 is depressor. PGD_2, however, is 20 to 140 times ($n = 5$) more active than $PGF_{2\alpha}$, producing effects at threshold doses from 0.4 to 20 ng/kg. These pressor responses were not abolished by phenoxybenzamine hydrochloride (3 mg/kg). On the sheep hind limb, perfused at constant flow, the pressure was increased by PGD_2 injected intra-arterially. In the rabbit, PGD_2 was

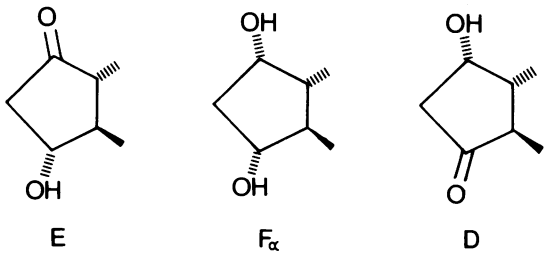

Fig. 1 Structural differences between prostaglandins of the E, F_α and D series.

also pressor, whereas PGE_2 is depressor and $PGF_{2\alpha}$ tends to produce a biphasic response.

On the rabbit oviduct, PGE_2 (0.02 to 0.2 μg/kg) reduces, whereas $PGF_{2\alpha}$ (0.3 to 6 μg/kg), in most experiments, raises intra-luminal pressure (Horton & Main, 1963; 1965), PGD_2 (6 to 13 μg/kg) caused relaxation, sometimes preceded by a contraction. Like PGE_2 and $PGF_{2\alpha}$, PGD_2 contracted the rat fundus and the isolated rabbit jejunum. The equipotent molar ratios for $PGF_{2\alpha}$ and PGD_2 were 3.5 and 47 with respect to PGE_2 (=1.0) on the rat fundus. The ratio of PGD_2 to $PGF_{2\alpha}$ (=1.0) was 7.8 on the rabbit jejunum.

These results establish that PGD_2 has significant pharmacological activity on some smooth muscle preparations. Moreover, its spectrum of activity differs from both PGE_2 and $PGF_{2\alpha}$. Since PGD_2 can be formed enzymatically from the same precursor as PGE_2 and $PGF_{2\alpha}$, its possible biological role merits further study.

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Potentiation by certain amino acids of hypotension induced by arachidonate

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Intravascular injection of arachidonate is followed, after a short latency, by a temporary fall of blood pressure in the hypertensive rat (Cohen, Sztokalo & Hinsch, 1973) and the rabbit (Larsson & Änggård, 1973). As this effect is inhibited by indomethacin it is interpreted as due to a temporary increase in the biosynthesis of prostaglandins from the excess of natural substrate. We have found that in the rabbit and the dog, the hypotension induced by arachidonate is markedly increased by heparin and by tryptophan (Deby and Damas, 1974; Deby, Barac & Bacq, 1974).

We have studied the action of various amino acids on arachidonate-induced hypotension in heparinized rabbits. Well-fed 2.5 kg male rabbits of the same strain were anaesthetized by urethane (80-100 mg/kg). Heparin (20 mg/kg) was injected 1 h before the start of control arachidonate intrajugular injections (arachidonic acid Sigma 99% purity, neutralized to pH 7.6 by NaOH) at doses (50-200 μg/kg) adapted to the sensitivity of each animal. Amino acids (Hoffmann-La Roche or Sigma) 20 mg/kg were injected i.v. in 0.5 ml of 0.15 M sodium phosphate buffer pH 7.6. Injections of arachidonate were repeated after a delay of 10 minutes.

Amino acids fall into three categories: (1) histidine, cysteine, lysine and arginine, like tryptophan, markedly increased the hypotensive effect of arachidonate; (2) leucine and proline were weakly active; (3) glycine, alanine, phenylalanine, tyrosine, glutamic and aspartic acids were inactive.

Our interpretation is that the level of certain amino acids in the blood is one of the factors which controls the synthesis of prostaglandins *in vivo*.