Some factors affecting inactivation of prostaglandin E_2 (PGE_2) by the rat isolated perfused lung

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Ferreira & Vane (1967) showed that the lungs are a major site for PGE_2 inactivation, this conclusion being confirmed both *in vitro* and *in vivo* by Piper, Vane & Wyllie (1970); Bedwani & Marley (1975); Armstrong, Boura, Hamberg & Samuelsson (1976). Removal may involve an active uptake process (Bito, Wallenstein & Baroody, 1976) and also be influenced by levels of PG15-hydroxydehydrogenase (PGDH), (Blackwell, Flower & Vane, 1975). The work reported below was undertaken to indicate which of these two processes was the major controlling determinant and to study other possibly important factors.

Lungs from Wistar rats (150–250 g) were perfused at 37°C with Krebs solution saturated with 95% oxygen plus 5% carbon dioxide. The effluent was superfused over a rat isolated fundus strip together with mepyramine maleate, methysergide maleate, hyoscine hydrochloride, propranolol hydrochloride and phenoxybenzamine hydrochloride (0.1, 0.2, 0.1, 3.0, 0.1 μg/ml respectively). Concentration-response curves of the fundus were obtained to a series of increasing concentrations of PGE_2 given first directly, then through the lungs and finally directly. PGE_2 inactivation was assessed by comparing the response-curves of the fundus with that obtained after passage through the lungs.

The PGE_2 concentration-response curve of the fundus obtained after passage through the lungs was significantly steeper and to the right of that obtained directly ($P < 0.01$; $n = 10$) indicating that fractional inactivation decreased as the arterial concentration increased. Only 2% of PGE_2, presented at 100 ng/min escaped inactivation in lungs obtained from males and perfused at 10 ml/min but at 4 μg/min more than 55% escaped. Changing the pulmonary flow to 40 ml/min increased escape 1.3 fold ($P < 0.05$; $n = 5$). Cycloheximide (20 mg/kg i.p. 4 h before) increased escape approximately 8 fold ($P < 0.01$) and probenecid (200 mg/kg i.p. 30 min before + 200 μg/ml in perfusate) 2.2 fold ($P < 0.05$). Hydrocortisone (2×10 mg kg^{-1} day^{-1} i.p. for 7 days) increased inactivation 1.8 times. ($P < 0.05$). The lungs from genetic hypertensive rats (New Zealand strain) showed decreased ability to inactivate PGE_2 (2.3 fold; $P < 0.05$) as did those of females (3.8 fold; $P < 0.05$). There was increased inactivation during pregnancy (18–20 days) and 0–8 h post partum (3.4 & 3.0 fold; $P < 0.05$) when compared to virgin female controls.

These experiments indicate that fractional inactivation of PGE_2 in the lung may vary inversely with the rate of presentation and confirm that the processes responsible can be saturated (Armstrong *et al*, 1976b). They support conclusions derived from biochemical studies that PGE_2 removal is influenced by the levels of PGDH (Blackwell *et al*, 1975); it is affected by sex, by genotype (Armstrong, Blackwell, Flower, McGiff, Mullane & Vane, 1976), protein synthesis inhibitors (Blackwell *et al*, 1975) steroids and pregnancy (Bedwani & Marley, 1975; Blackwell & Flower, 1976).

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References

ARMSTRONG, J.M., BLACKWELL, G.J., FLOWER, R.J., McGIFF, J.C., MULLANE, K.M. & VANE, J.R. (1976a). Genetic hypertension in rats is accomplished by a defect in renal prostaglandin catabolism. *Nature, (Lond.),* **260,** 582–586.

ARMSTRONG, J.M., BOURA, A.L.A., HAMBERG, M. & SAMUELSSON, B. (1976b). A comparison of the vasodepressor effects of the cyclic endoperoxides PGG_2 and PGH_2 with those of PGD_2 and PGE_2 in hypertensive and normotensive rats. *Eur. J. Pharmac.,* **39,** 251–258.

BEDWANI, J.R. & MARLEY, P.B. (1975). Enhanced inactivation of prostaglandin E_2 by the rabbit lung during pregnancy or progesterone treatment. *Br. J. Pharmac.,* **53,** 547–554.

BITO, L.Z., WALLENSTEIN, M. & BAROODY, R. (1976). The role of transport processes in the distribution and dispostion of prostaglandins. *Advances in Prostaglandin and Thromboxane Research,* **1,** 297–303, eds. B. Samuelsson & R. Paoletti. Raven Press, New York.

BLACKWELL, G.J., FLOWER, R.J. & VANE, J.R. (1975). Rapid reduction of prostaglandin 15-hydroxydehydrogenase activity in rat tissues after treatment with protein synthesis inhibitors. *Br. J. Pharmac.,* **55,** 233–238.

BLACKWELL, G.J. & FLOWER, R.J. (1976). Effects of steroid hormones on tissue levels of prostaglandin 15-hydroxydehydrogenase in the rat. *Br. J. Pharmac.,* **56,** 343P.

FERREIRA, S.H. & VANE, J.R. (1967). Prostaglandins: their disappearance from and release into the circulation. *Nature (Lond.),* **216,** 868–873.

PIPER, PRISCILLA, J., VANE, J.R. & WYLLIE, J.H. (1970). Inactivation of prostaglandins by the lungs. *Nature (Lond.),* **225,** 600–604.