Inhibition of the pulmonary inactivation of prostaglandins in rabbit *in vivo*

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Prostaglandins (PGs) of the E and F series are efficiently inactivated in the pulmonary circulation of several species *in vivo* (Ferreira & Vane, 1967) and of guinea-pig *in vitro* (Piper, Vane & Wyllie, 1970). This inactivation can be strongly inhibited *in vitro* by di-4-phloretin phosphate (DPP) at concentrations well below those causing antagonism of PG actions (Crutchley & Piper, 1973, 1974). The present study investigates whether DPP inhibits pulmonary inactivation of PGE_2 by rabbits *in vivo*.

Male Dutch rabbits 1.8 to 2.5 kg were anaesthetized by pentobarbitone sodium 40 mg/kg i.v. A polyethylene cannula was introduced retrogradely into the aortic arch via the right carotid artery for i.a. infusions. A similar cannula for i.v. infusion was introduced into the superior vena cava via the right jugular vein. Blood pressure was recorded from the left carotid artery or a femoral artery. Saline, or DPP (in solution, in saline) was infused continuously into the left jugular vein. PGE_2 infusions of 1.5 min duration were given i.a. or i.v. and the resulting falls in blood pressure measured. Control and test measurements were taken in the same animals.

PGE_2 was much more potent via the i.a. route, the difference between i.a. and i.v. responses being taken as a measure of pulmonary inactivation. DPP 25 to 100 $\mu g\ kg^{-1}\ min^{-1}$ potentiated the i.v. responses and shifted the dose responses curve for i.v. PGE_2 to the left, to approximate to that for i.a. doses (n = 18). DPP had no effect on the i.a. responses, suggesting that potentiation of i.v. effects was due to decreased inactivation of PGE_2 in the lung. Potentiation of i.a. responses by DPP was seen, however, with longer infusions of PGE_2 (6 to 8 min). This was presumably due to the cumulative effects of circulating i.a. doses. No direct antagonism of PGE_2 was seen.

DPP 25 to 100 $\mu g\ kg^{-1}\ min^{-1}$ also potentiated the depressor actions of i.v. infusions of $PGF_{2\alpha}$ and the increase in gastrointestinal motility due to i.v. infusions and injections of PGs E_2 and $F_{2\alpha}$ (n = 5). This was presumably due to impaired pulmonary PG inactivation.

The percentage inhibition of pulmonary inactivation by these doses of DPP was 75% at maximum but this caused marked potentiation of PG effects, emphasizing the importance of pulmonary inactivation of PGs.

References

CRUTCHLEY, D.J. & PIPER, PRISCILLA J. (1973). Inhibition of the inactivation of prostaglandins in guinea-pig lungs. *Naunyn-Schmiedeberg's Arch. Pharmac.*, Suppl. to **279**, 27.

CRUTCHLEY, D.J. & PIPER, PRISCILLA J. (1974). Prostaglandin inactivation in guinea-pig lung and its inhibition. *Br. J. Pharmac.*, **52**, 197-203.

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.

Factors influencing the turnover of prostaglandin synthetase

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Evidence is accumulating that prostaglandin generation is of physiological and pathological importance, so the mechanism(s) by which intracellular levels of prostaglandin synthetase are regulated are clearly of interest. Continuous *de novo* synthesis of enzymes is a property of all viable cells and one method by which the cellular concentration of certain types of enzymes can be rapidly regulated (in response to hormone stimulation for example) is by changes in their rate of synthesis or destruction. Lands, LeTellier, Rome & Vanderhoek (1973) have shown that *in vitro* prostaglandin synthetase catalyses its own destruction during substrate oxygenation. If such 'self-destruction' occurs *in vivo*, a tissue such as the kidney which has a high biosynthetic capacity (Somova, 1973) should demonstrate continuous synthesis of the enzyme also.

To test this possibility we injected (i.p.) four male rats (200-250 g) with 4 mg cycloheximide