Nicotine causes prostaglandin efflux from isolated perfused rat lung

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Bakhle, Hartiala, Toivonen & Uotila (1978) have recently shown that exposure to cigarette smoke reduces the inactivation of prostaglandin (PG) E_2 by rat lung. Furthermore (–)-nicotine, the principal pharmacologically active constituent of cigarette smoke, stimulates PG release from the isolated rabbit heart (Wennmalm, 1977). It seemed important to establish the effect of (–)-nicotine on PG release from the lung.

Male Sprague-Dawley rats (150–250 g) were housed normally ('control') or in inhalation chambers (Littleton & Umney, 1977) in which they were exposed to an aerosol spray for 5 min every 30 min for periods of 10 days or more. The aerosol contained sodium hydrogen tartrate ('sham-exposed') or 6% (–)-nicotine hydrogen tartrate ('nicotine-treated'). After decapitation the lungs were rapidly removed and perfused via the pulmonary artery at a rate of 6 ml/min with well oxygenated Krebs solution at 37° containing combined antagonists (phentolamine 0.2, mepyramine 0.2, methysergide 0.2, atropine 0.6, and practolol 2.0 μg/ml). For assay of PG-like substances the effluent was superfused over a rat colon and two rat fundus strips over which hexamethonium (10 μg/ml) and indomethacin (20 μg/ml) were also perfused.

In 21 experiments, perfusion of (–)-nicotine (2–30 μg through the lung resulted in slow contraction of all 3 assay tissues, but this was not observed if the drug was applied direct to the tissues at the same doses. We attribute these contractions to the presence of stable PGs in the effluent, since (a) they could be replicated by suitable infusions of PGE_2 (15–480 ng over 3 min), (b) the biological activity in the perfusate was recovered from ethyl acetate extracts, (c) 87% of the biological activity was recovered from the same zone as PGE_2 after thin layer chromatography, and (d) this material was inactivated when injected through the lungs.

The amount of PG-like material released after (–)-nicotine perfusion varied considerably between lungs particularly from the 'nicotine-treated' rats. For example, (–)-nicotine (2 μg) released 18.0 ± 4.5, 20.0 ± 19.6 and 45.3 ± 27.4 ng PGE_2 equivalent from lungs of 'control', 'sham-treated' and 'nicotine-treated' rats respectively, and (–)-nicotine (15 μg) released 102.0 ± 26.0, 114.0 ± 43.5 and 154.0 ± 72.3 ng (mean ± s.e. mean, n = 6–8). The increase in PG efflux from the 'nicotine-treated' lungs is not significant at the 5% level and further experiments are in progress.

The mechanism whereby (–)-nicotine releases PG-like material from the rat lung is not known. However, the response shows tachyphylaxis after 4–6 challenges, is blocked by prior infusion of 12 μg hexamethonium or 7 μg indomethacin, and is not elicited by similar doses of (+)-nicotine. These findings suggest that the response may be caused by a receptor-mediated increase in PG synthesis in the lung. (–)-Nicotine may have other effects on PG metabolism. Preliminary experiments suggest that *in vitro* it inhibits $PGF_{2\alpha}$ breakdown by rat lung homogenates ($ID_{50} \simeq 100$ μM). It is possible that these effects of nicotine on PG metabolism may contribute to some of the pathological changes in lung associated with cigarette smoking.

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Sulphasalazine inhibits the pulmonary inactivation of prostaglandins in the rat *in vivo*

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Prostaglandins (PG) of the E and F series are efficiently metabolised in the pulmonary circulation of many species (Piper, Vane & Wyllie, 1970). We have previously shown that sulphasalazine is a potent inhibitor of PG breakdown *in vitro* in 100,000 g supernatants of several organs including rat, guinea-pig, and chick lungs (Moore, Hoult & Laurie, 1978). We have now studied the effect of sulphasalazine on pulmonary PG breakdown in the anaesthetized rat by comparing the vasodepressor potency of prostaglandins injected intravenously (i.v.) and intra-arterially (i.a.).

Male Sprague-Dawley rats weighing 150–250 g were anaesthetized with urethane (650 mg/kg i.p. followed after 5 min by the same dose s.c.).