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Effects of cigarette smoke on metabolism of vasoactive hormones in rat isolated lungs

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Exposure of rats to an atmosphere containing tobacco smoke alters the activity of enzymes metabolizing polycyclic hydrocarbons like benzo[a]pyrene (Welch, Loh & Conney, 1971; Uotila, Pelkonen & Cohen, 1977). We have recently studied the effects of smoke exposure on pulmonary enzymes metabolizing the endogenous substrates, 5-hydroxytryptamine (5-HT), angiotensin I, bradykinin and prostaglandin E_2.

Male rats were exposed to cigarette smoke for 1 h per day for 1 day or for 10 consecutive days. 'Sham exposed' animals were treated identically except that no smoke was added to their environment (Uotilla & Marniemi, 1976). The day after the last exposure, the lungs were removed and perfused through the pulmonary circulation with oxygenated, warmed Krebs solution (Alabaster & Bakhle, 1970). The activation of angiotensin I (by hydrolysis to angiotensin II) and inactivation of bradykinin and prostaglandin E_2 were measured by bioassay on the rat colon, guinea-pig ileum and hamster stomach strip respectively, superfused with the lung effluent. Metabolism of 5-HT was measured by a radiochemical method using [^{14}C]-5-HT (Southgate & Collins, 1969).

The results summarized in the table show a significant increase in angiotensin I conversion and decrease in prostaglandin E_2 inactivation after 1 day's exposure when compared with control, i.e. untreated animals, and with 'sham exposed' animals. After 10 days' exposure, angiotensin I conversion returned to control levels whereas prostaglandin inactivation was still considerably less than normal. However, in the latter case the 'sham exposed' animals also showed decreased inactivation and the change cannot be reliably attributed to the smoke exposure. Bradykinin and 5-HT metabolism were unchanged throughout the experiment.

Our results show that it is possible to alter the metabolism of some endogenous vasoactive substances by exposure of animals to cigarette smoke. Such changes may be relevant to the cardiovascular changes shown by habitual smokers (U.S. Department of Health, Education and Welfare, 1975).

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Table 1 Metabolism of endogenous substrates on passage through the pulmonary circulation of isolated rat lung

Treatment	*Angiotensin I (100–200 ng)†* *(% conversion)*		*Bradykinin (1000–2000 ng)* *(% survival)*		*Prostaglandin E_2 (500–1500 ng)* *(% survival)*		*5-Hydroxytryptamine (3.75 μM)* *(% metabolite)*	
	1 day	10 day	1 day	10 day	1 day	10 day	1 day	10 day
Control	20 ± 4		1.6 ± 0.3		4.4 ± 0.6		79 ± 1	
Sham exposed	33 ± 6	26 ± 3	2.2 ± 0.1	0.9 ± 0.1	4.3 ± 0.7	12.3 ± 3.5	74 ± 6	74 ± 2
Smoke exposed	51 ± 4*	33 ± 4	1.6 ± 0.3	1.0 ± 0.2	8.8 ± 1.4*	17.9 ± 4.0	76 ± 6	77 ± 3

Values shown are the means (±s.e. mean) of 4–17 animals (usually 6).
* Significantly different from sham exposed rats; $P < 0.05$, t-test.
† Level of substrate used.

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Tumour growth and response to treatment: beneficial effect of the prostaglandin synthesis inhibitor flurbiprofen

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Prostaglandins (PG) are implicated in the growth and spread of some tumours. It is important to study inhibitors of PG synthesis for this reason, and because patients may take such drugs. Indomethacin reduces the growth of tumours induced in mice by Moloney sarcoma virus (Strausser & Humes, 1975). We report a similar effect with flurbiprofen, and show in addition a tendency to increased survival time and a significant enhancement of the tumour response to radiotherapy and chemotherapy.

WHT/Ht albino mice of either sex were injected sc into the right flank with 10^6 cells of the spontaneous non-immunogenic murine WHT-NC tumour. Flurbiprofen (5 mg/kg) was given orally once each day, where indicated, in 0.1 ml raspberry syrup (V. Eisen & D.I. Walker, personal communication). Tumours, metastases, and recurrences were removed, weighed, and homogenized in Krebs solution. PGs were extracted and bioassayed on the rat gastric fundus strip preparation against PGE_2 (see Bennett, Stamford & Unger, 1973). Unless stated otherwise, the results are means ± s.e. mean.

Tumour growth and mouse survival were studied in the following groups: (1) tumour inoculation only ($n = 10$); (2) tumour inoculation + flurbiprofen treatment throughout ($n = 10$); (3) tumour excision at 3 weeks ($n = 30$); (4) tumour excision at 3 weeks, then flurbiprofen treatment ($n = 10$); (5) tumour excision at 3 weeks, flurbiprofen treatment throughout ($n = 19$). Primary tumour widths (W) and lengths (L) (groups 1 and 2) were measured weekly, and volumes calculated as $\pi.W^2.L/6$. Flurbiprofen treatment reduced the tumour weights, and tended to prolong survival in mice whose primary tumour was removed (Table 1).

The response of tumours to treatment was studied in groups of mice given 1, 2, or 3 of the following: chemotherapy (melphalan 0.15 mg/kg, days 30–32 and 37–39 after tumour inoculation, and methotrexate

Table 1 The effect of flurbiprofen on tumour weight and mouse survival time

Group	*Primary tumour weight (g) (at 3 weeks groups 3–5, or at death groups 1 and 2)*	*Primary tumour PGs (ng PGE_2 equivalents/g)*	*Survival (days) medians and semi-quartile ranges*
1	3.66 ± 0.15	85 ± 26	73(70–77)
	($P < 0.05$)	($0.1 > P > 0.05$)	($P = 0.327$)
2	1.89 ± 0.21	32 ± 5	76(67–82)
3	0.25 ± 0.03	469 ± 53	70(68–84)*
	($P < 0.005$)	($P < 0.001$)	
4			77(62–86)
5	0.14 ± 0.03	36 ± 13	83(70–91)*†

* $P = 0.068$, Mann–Whitney U-test.
† Two still alive at 127 days.