The effect of histamine releasers on the output of prostaglandins from rat diaphragms

Piper & Vane (1969) reported that antigen caused the release of prostaglandins E_2 and $F_2\alpha$ from appropriately sensitized perfused guinea-pig lungs. One of us has demonstrated that (+)-tubocurarine, a well-known releaser of histamine, causes the release of polar acidic lipids from the diaphragm of the rat (Laity, 1969). The same methods have revealed that in all three experiments with tolazoline hydrochloride (100 μg/ml) and morphine sulphate (50 μg/ml) and in duplicate experiments with pethidine hydrochloride (100 μg/ml) there was a release of polar acidic lipids from rat diaphragms. In these experiments, silicic acid column chromatography (Davies, Horton & Withrington, 1968), has separated the polar acidic lipids released by morphine, pethidine and tolazoline. This has shown that these polar acidic lipids consist of prostaglandins of the E and F series. The amount of PGF was larger than that of PGE (Fig. 1). Morphine, pethidine and tolazoline all produced a similar release of prostaglandins.

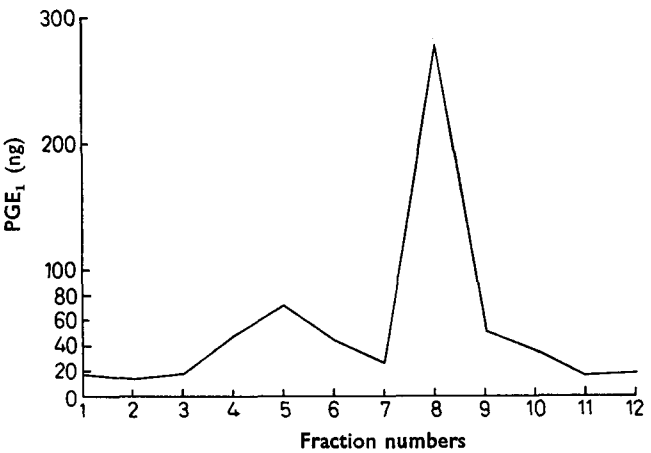

FIG. 1. Silicic acid column chromatogram of material extracted from bath fluid collected after exposure of rat diaphragms to Krebs solution containing pethidine (100 μg/ml) for 60 min at 37° gassed with 5% CO_2 in oxygen. Ordinate, biological activity in terms of PGE_1 assayed on the rat fundal strip. Abscissa, fraction numbers. Fractions were eluted with increasing concentrations of ethyl acetate in benzene: 1 and 2, 30%; 3 to 7, 40%; 8 and 9, 80% and 10, 100%. Fractions 11 and 12 were eluted with methanol.

It would thus appear that histamine releasers cause a similar release of prostaglandins from rat diaphragms to that produced by the antigen-antibody reaction in perfused guinea-pig lungs reported by Piper & Vane (1969).

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REFERENCES

DAVIES, B. N., HORTON, E. W. & WITHRINGTON, P. G. (1968). *Br. J. Pharmac. Chemother.*, **32**, 127–135.

LAITY, J. L. H. (1969). *Ibid.*, **37**, 698–704.

PIPER, P. J. & VANE, J. R. (1969). *Nature, Lond.*, **223**, 29–35.

Oxotremorine: acute tolerence to it and its central "cholinolytic" effect in mice

Decsi, Várszegi & Méhes (1961a, b) reported that tremorine lost much of its analgesic, tremorigenic and narcosis-potentiating properties when given to mice. Keranen, Zaratzian & Coleman (1961) observed a progressive decline of the compound's tremorigenic effect after chronic treatment of unstated duration. Oelszner (1965) was unable to corroborate the observation on the analgesic effect of tremorine made by Decsi & others.

Doses of tremorine and oxotremorine prevent albino mice from clinging for more than 3 to 6 s to a rod operated at 7 rotations/min. Activity was regarded as negative in experiments in which the animal held fast to the rotarod for at least 180 s. The doses given are for oxotremorine oxalate, physostigmine salicylate, nicotine hydrogen tartrate, and tremorine dichlorhydrate.

Table 1 shows that a first injection of tremorine reduces the rotarod activity of a second injection given 16 h later, and totally prevents that of oxotremorine. The rotarod activity of oxotremorine (0·5–1·0 mg/kg, i.p.) wears off within 60–90 min.

Table 1. *Rotarod activity of tremorine and oxotremorine*

First i.p. injection at 0 h	Second i.p. injection at 16 h	n	% mice dropped off the rotarod at 16 h 30 min
0·9% NaCl	20 mg/kg tremorine	24	100
25 mg/kg tremorine	20 mg/kg tremorine	20	45
0·9% NaCl	0·5 mg/kg oxotremorine	10	100
25 mg/kg tremorine	0·5 mg/kg oxotremorine	10	0

Table 2. *Rotarod activity of 3 subsequent oxotremorine injections* (given at 0, at 60 or 90 min, and at 120 or 150 min)

Dose and route	n	% mice dropped off the rotarod 30 min after the: 1st injection	2nd injection	3rd injection
0·5 mg/kg all i.p.	56	89	29	5
1·0 mg/kg all i.p.	40	100	50	25
0·5 mg/kg i.p., i.p., i.v.	16	100	19	13
1·0 mg/kg i.p., i.p., i.v.	16	100	40	13

A second injection of the same dose is much less effective, and a third one almost ineffective (Table 2). Acute tolerance is not the result of decreased absorption, as even intravenous oxotremorine possesses negligible activity. No tremor was observed after the third injection.

A single injection of oxotremorine leaves nicotine lethality unaffected, but a second one given 30 min later inhibits it (Table 3). Similarly, a single dose of