Skin reactions to prostaglandins

The E-type prostaglandins (PG) have been identified in rat inflammatory exudates and recently Crunkhorn & Willis (1971) reported them to be potent inducers of local vascular permeability in Wistar rats, doses of 100 ng giving consistent and measurable responses. Using their technique, we have tested over 600 responses and found that inter-colony reactions to intradermal prostaglandins are variable and unpredictable.

Intradermal injections of PGE_1 or PGE_2 (each of 0·1 and 1·0 μg), histamine (3 μg), 5-hydroxytryptamine (0·05 μg), bradykinin (1 μg), or dextran (mol wt 67 000, 100 μg) were made into the abdominal skin of male or female Wistar rats, 120–160 g, anaesthetized with different anaesthetics. Increased vascular permeability was visualized by the extravasation of azovan blue dye (20 mg/kg, i.v.) administered immediately before the intradermal injections. Mean diameters (mm) and intensities of the blue areas (on an arbitrary scale from 0 to +++) were assessed from the underside of the skin 30 min after the intradermal injections which were made in volumes of 0·1 ml of Tyrode solution.

Initially, Wistar rats from Tucks, Rayleigh, Essex anaesthetized with ether were used. It became apparent that the animals so tested were poor responders to PGE_1 and PGE_2, and of 35 injections made with 1.0 μg of these compounds, only 8 sites (23%) were considered positive (diameter at least 10 mm and intensity at least +), and these were not dependent on the dose or the animal. Substitution of a barbiturate (thiopentone, pentobarbitone or methohexitone) for ether had the effect of raising the positive responses at injection sites to 70–80% of the total, when there was no significant difference in activity between PGE_1 and PGE_2 (see Table 1), and male and female rats were equally sensitive.

We next tested Wistar rats from other colonies, including the Lilly colony on which the results of Crunkhorn & Willis were based. Using a barbiturate anaesthetic, we found that rats from the Lilly colony (kindly donated by Dr. W. Dawson) were all responders though not always uniformly. For example, the responses to 0·1 and 1·0 μg of either PGE_1 or PGE_2 ranged from 10 (+) to 15 (++) and 15 (++) to 20 (+++) respectively. Four other colonies, however, responded to prostaglandins even more feebly and irregularly than did the rats from the Tuck colony. Compared with the Lilly 100% response (diameter 10 mm or more, intensity at least +), the Tuck response was 44 and 85% for the 0·1 and 1 μg dose respectively, and for the other colonies 32 (range 22–40) and 62 (range 50–81)%.

All rats receiving intradermal prostaglandins also were tested at other sites for reactivity to histamine, 5-hydroxytryptamine, bradykinin and dextran but regardless of the anaesthetic or the colony, consistent responses were always obtained.

From these results it is seen that the E-type prostaglandins do not regularly induce signs of inflammation when injected intradermally into Wistar rats and thus their

Table 1. *Comparison of the potency of prostaglandins E_1 and E_2 in producing increases in vascular permeability when given intradermally to Tuck Wistar rats (anaesthetic-methohexitone).* Responses recorded as numbers obtained giving different diameters (mm) and intensities (0 to +++).

Prostaglandin	Dose (μg)	Response				Positive responses (%)
		Less than 10 (0)	10 (+)	15 (++)	20 (+++)	
E_1	0·1	50	28	7	0	41
	1·0	11	21	29	4	83
E_2	0·1	46	27	8	0	43
	1·0	12	30	18	3	81

importance as mediators of this inflammatory response is limited. Furthermore, they probably do not exert their effect on vascular permeability through histamine release (as suggested by Crunkhorn & Willis) as other histamine releasers (e.g. dextran) respond uniformly when injected intradermally into rats. It is unwise to test compounds for anti-prostaglandin activity by the intradermal route in rats until it has been shown that the particular colony of animals responds in a consistent manner.

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Blockade by pimozide of (+)-amphetamine-induced hyperkinesia in mice

Mediation of (+)-amphetamine's action has been attributed to catecholamine systems (Weissman, Koe & Tenen, 1966). Although there is indirect evidence implicating dopaminergic as well as noradrenergic neurons (Svensson, 1970), a direct test of the importance of dopamine has not as yet been made. Pimozide, a putative dopamine receptor blocker (Janssen, Niemegeers & others, 1968; Andén, Butcher & others, 1970), would appear to provide an opportunity for such a test. There is evidence that pimozide blocks (+)-amphetamine-induced stereotyped behaviours such as "agitation" and "chewing" (Janssen, Niemegeers & others, 1967) and (+)-amphetamine-induced hyperthermia in rats (Matsumoto & Griffin, 1971). We now present quantitative evidence that pimozide also blocks the increased locomotor activity observed in mice after (+)-amphetamine.

Male albino Swiss-Webster mice (Simonsen Laboratories, Gilroy, California, U.S.A.) 24–35 g were given pimozide (0·5 mg/kg) and (+)-amphetamine sulphate (5 mg/kg) intraperitoneally, the doses being expressed in terms of the salt. At 0·5 mg/kg, pimozide apparently blocks only dopamine receptors (Andén & others, 1970). Pimozide was dissolved in a glucose-acetic acid vehicle (cf., Andén & others, 1970), and (+)-amphetamine was dissolved in 0·9% saline. The vehicles were used for control injections. The volume of administered fluid was approximately 0·015 ml per injection.

The 48 mice used were randomly assigned to groups of 12 animals. Two of the groups were given pimozide; the remaining two groups received the glucose-acetic acid vehicle. Four h later, one vehicle and one pimozide group were injected with (+)-amphetamine whilst the remaining two received saline, the (+)-amphetamine vehicle. The mice were then placed individually in stabilimeters (Davis & Ellison, 1964). Five min later activity measurements were begun and continued for 2 h.

As shown in Fig. 1, pimozide completely blocked the (+)-amphetamine-induced hyperkinesia at all intervals measured whereas administration of pimozide alone had no significant effect, compared to control, on spontaneous motor activity. No other differences among the various treatment conditions were statistically significant at any of the time intervals studied (Fig. 1). In view of these results and also those of Svensson (1970) showing only moderate diminution of the locomotor stimulatory