Interactions between prostaglandin E_1 and noradrenaline in anaesthetized rats

The effector response to nerve stimulation in the vas deferens, oviduct and spleen is inhibited by prostaglandins (PG) of the E series (Brundin, 1968; Euler & Hedqvist, 1969; Hedqvist & Brundin, 1969). Hedqvist & Brundin (1969) have shown that the inhibitory effect *in vitro* of PGs on the splenic response to nerve stimulation is accompanied by a reduction in the noradrenaline outflow, suggesting that PG might exert an inhibitory action on the process of noradrenaline release. These results prompted us to study the interactions between PGs and noradrenaline in anaesthetized rats with an intact nervous system.

Male Wistar rats, 200 $\pm$ 10 g, anaesthetized with sodium ethylmethylbutyl barbiturate (Mebubarbital, 30 mg/kg, i.p.) were infused intravenously with PGE_1, dissolved in isotonic glucose, at the subdepressive dose of 1·25 μg/kg min^{-1} (25 μl/min). Blood pressure was recorded throughout the experiment via an indwelling arterial catheter connected to a strain-gauge manometer. (±)-[^{3}H]Noradrenaline hydrochloride* (^{3}H-NA) (25 μCi; specific activity 7·7 Ci/mmol), dissolved in 0·5 ml of isotonic saline was injected 25 min after the PG infusion was begun. Rats were killed 5, 100 or 300 min later, the PG infusion having continued until death. Control experiments were run simultaneously on anaesthetized rats given ^{3}H-NA and infused with isotonic glucose at rate of 25 μl/min. The action of PGE_1 on tyramine-induced noradrenaline release was investigated in another series of rats receiving infusions of both PGE_1 and tyramine hydrochloride (50 μg/min; 25 μl/min) throughout the experimental period; the animals were killed 100 min after the injection of ^{3}H-NA. Controls received the ^{3}H-NA and a tyramine infusion.

^{3}H-NA was estimated in tissue homogenates, prepared according to Robinson & Watts (1965), by alumina column chromatography (Anton & Sayre, 1962). Radioactivity was determined by liquid scintillation on effluents from the alumina column. Endogenous noradrenaline was estimated fluorimetrically (Euler & Lishajko, 1961).

The results (Table 1) indicate that PGE_1 infusion did not alter the endogenous noradrenaline concentration except in the kidney and in the heart. Endogenous noradrenaline was increased in kidney and decreased in heart respectively 5 and 300 min after the injection of ^{3}H-NA. Five min after ^{3}H-NA injection in PGE_1-infused rats, the ^{3}H-NA concentration (Table 2) was significantly increased in kidney, and significantly reduced in adrenals, but after 100 and 300 min it was significantly higher in adrenals. The ^{3}H-NA concentration measured after the simultaneous infusion of tyramine and PGE_1 was significantly higher in heart than that measured during infusion of tyramine alone (Table 3).

These results do not give a clear idea of a possible interaction of PGE_1 with the sympathetic nervous system. In the kidney, PGE_1 was found to increase noradrenaline uptake, a result which may be related to the vasodilator effect of PGE_1 in this tissue (Lee, 1967). In the adrenals, PGE_1 reduced ^{3}H-NA uptake; the increased ^{3}H-NA concentrations observed 100 and 300 min after the ^{3}H-NA injection in PGE_1-infused rats may therefore be secondary to a decrease in noradrenaline release. In the heart, the uptake of the amine was not modified by PGE_1 although the level of endogenous amine was reduced by 300 min. The association of PGE_1 with tyramine markedly reduced the release of noradrenaline by tyramine (Burn & Rand, 1958) in the heart since the ^{3}H-NA concentration was higher than after tyramine alone. The lack of effect on noradrenaline release in the spleen disagrees with the releasing effect demonstrated *in vitro*.

* 2-Amino-1-(3,4-dihydroxyphenyl)-[1-^{3}H]ethanol from the Radiochemical Centre, Amersham.

Table 1. *Effect of PGE_1 on endogenous noradrenaline content.*

		Heart	Spleen	Vas deferens	Kidney	Adrenals
5 min	Control	606 ± 53	233 ± 28	6959 ± 387	106 ± 3	570447 ± 54730
(n = 12)	PGE_1	660 ± 62	283 ± 54	6806 ± 636	132 ± 8*	572177 ± 62012
100 min	Control	571 ± 58	342 ± 60	6241 ± 516	116 ± 8	560837 ± 40909
(n = 26)	PGE_1	495 ± 46	281 ± 30	7187 ± 616	112 ± 6	577179 ± 50103
300 min	Control	408 ± 31	252 ± 42	5482 ± 335	111 ± 17	462038 ± 26699
(n = 26)	PGE_1	210 ± 15*	279 ± 63	4959 ± 332	93 ± 14	459483 ± 37353

Results are expressed in ng/g. Mean ± s.e. $*P < 0.05$.

Table 2. *Effect of PGE_1 on [^3H]noradrenaline content.*

		Heart	Spleen	Vas deferens	Kidney	Adrenals
5 min	Control	270·4 ± 9·0	26·7 ± 2·4	59·3 ± 3·1	50·1 ± 3·0	75·6 ± 6·6
(n = 31)	PGE_1	279·0 ± 17·4	21·5 ± 1·6	61·5 ± 4·5	72·2 ± 4·8*	66·2 ± 3·4*
100 min	Control	208·8 ± 12·3	15·7 ± 1·8	42·7 ± 5·1	15·2 ± 1·3	46·2 ± 3·8
(n = 26)	PGE_1	205·2 ± 14·7	13·9 ± 1·2	41·9 ± 3·3	13·6 ± 0·8	68·2 ± 10·0*
300 min	Control	161·0 ± 9·3	12·5 ± 1·4	31·4 ± 2·7	7·6 ± 0·3	53·9 ± 4·8
(n = 26)	PGE_1	171·0 ± 10·8	14·5 ± 1·5	31·6 ± 2·2	8·0 ± 0·9	63·6 ± 5·8*

Results are expressed in counts/mg tissue; mean ± s.e. $*P < 0.05$.

Table 3. *Effect of PGE_1 on [^3H]noradrenaline content in rats infused with tyramine.*

	Heart	Spleen	Vas deferens	Kidney
Control (tyramine)	74·4 ± 6·3	17·9 ± 1·7	33·1 ± 3·9	9·7 ± 1·2
PGE_1 + tyramine (n = 18) ..	101·2 ± 10·3*	16·5 ± 1·3	38·6 ± 2·8	11·5 ± 1·3

Results are expressed in counts/mg tissue; mean ± s.e. $*P < 0.05$.

It is concluded that PGE_1 at subdepressive doses may reduce *in vivo* the release of noradrenaline in adrenals and heart. That the results were more obvious in previous studies performed *in vitro* may be the consequence of the large inactivation of PGE_1 occurring in the pulmonary circulation (Ferreira & Vane, 1967).

The authors wish to thank Drs J. R. Week and J. R. Pike of the Upjohn Company, Kalamazoo, Mich. who kindly provided PGE_1.

Hypertension Laboratory,
Hospital Broussais,
96, *rue Didot,*
75-*Paris* 14, *France.*

NICOLAS PAPANICOLAOU
PHILIPPE MEYER
PAUL MILLIEZ

March 3, 1971

REFERENCES

ANTON, A. H. & SAYRE, D. F. (1962). *J. Pharmac. exp. Ther.*, **138**, 360–375.
BRUNDIN, J. (1968). *Acta physiol. scand.*, **73**, 54–57.
BURN, J. H. & RAND, M. J. (1958). *J. Physiol., Lond.*, **144**, 314–336.
EULER, U. S. VON & HEDQVIST, P. (1969). *Acta physiol. scand.*, **77**, 510–512.
EULER, U. S. VON & LISHAJKO, F. (1961). *Ibid.*, **51**, 348–385.
FERREIRA, S. H. & VANE, J. R. (1967). *Nature, Lond.*, **216**, 868–873.
HEDQVIST, P. & BRUNDIN, J. (1969). *Life Sci.*, **8**, 389–395.
LEE, J. B. (1967). *New Eng. J. Med.*, **20**, 1073–1079.
ROBINSON, R. L. & WATTS, D. T. (1965). *Clin. Chem.*, **11**, 986–997.