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DISTRIBUTION OF PROSTAGLANDINS IN HUMAN TISSUES

BY

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It has recently become apparent that prostaglandins are not confined to the genital tract, and that their importance may be much greater than was first envisaged when these fatty acid derivatives were first chemically identified in semen (Samuelsson, 1963). Prostaglandins are known to possess smooth muscle contracting activity and may well have important physiological roles as mediators of local responses. Isolated observations on the prostaglandin content of a few extragenital organs in various animals have been documented, and prostaglandins have been found in lungs in various animals: calf thymus, bovine pancreas (Bergstrom, 1964), sheep iris (Änggård & Samuelsson, 1964), bovine brain (Samuelsson, 1964), human umbilical and placental vessels, human amniotic fluid and decidua (Karim, 1966, 1967; Karim & Devlin, 1967). However, no systematic survey of prostaglandin distribution in a wide variety of tissues has been carried out in any animal, and the occurrence of prostaglandins in human tissues is less well documented than in other species. We have therefore estimated the concentrations of prostaglandins present in 23 types of human tissues.

METHODS

Tissues were obtained from necropsy examinations of adult patients carried out within 24 hr, and in most cases, within 12 hr of death. All tissues were macroscopically free of disease, and in most instances were examined histologically to confirm this. They were stored at $-10°$ C until used. Samples of urine and venous blood were obtained from healthy volunteers; fresh human milk was obtained from the milk bank of Queen Charlotte's Maternity Hospital.

The details of the tissue extraction methods, the chromatographic separation of the different prostaglandins and the identification with markers of known prostaglandins are as detailed in a recent publication (Karim, 1967). Biological assay of prostaglandins was carried out using an ascending colon preparation from the jird, *Meriones libycus*. The colon was removed as described by Ambache, Kavanagh & Whiting (1965) and set up in a 4 ml. organ bath of de Jalons solution at 30° C gassed with oxygen. Isotonic contractions were recorded on smoked kymograph paper. A dose cycle of 3–4 min with a contact time of $1\frac{1}{2}$ min was used. For the assay of some of the extracts, guinea-pig isolated proximal colon preparation (Karim, 1967) was also used.

RESULTS

The preparation used was shown to be sensitive to approximately 0·5 ng/ml. prostaglandins E_1, E_2 and $F_{2\alpha}$, and 2 ng/ml. $F_{1\alpha}$. The responses are shown in Fig. 1. The

TABLE 1

DISTRIBUTION OF PROSTAGLANDINS IN HUMAN TISSUES

Tissue		Prostaglandins			
		E_1	E_2	$F_{1\alpha}$	$F_{2\alpha}$
Thyroid	1	—	4·5	—	50·0
	2	—	—	—	100·0
	3	—	24·5	—	—
	4	—	12·5	—	25·0
	5	—	3·5	—	4·0
Pancreas	1	—	0·75	—	2·0
	2	—	—	—	—
	3	—	1·5	—	7·5
	4	—	0·3	—	0·8
Adrenal cortex	1	—	2·5	—	3·0
	2	—	3·0	—	6·3
Adrenal medulla	1	—	45·0	—	25·5
	2	—	22·5	—	64·0
	3	—	—	—	34·0
Thymus Infant	1	11·3	—	—	—
Infant	2	19·5	—	—	—
Adult	3	9·0	—	—	—
Parotid gland	1	—	0·5	—	2·5
	2	—	5·0	—	0·5
Submandibular salivary gland	1	—	5·5	—	1·0
	2	—	10·0	—	—
	3	—	1·0	—	—
Cardiac muscle	1	—	2·25	—	—
	2	—	3·50	—	—
Rectus abdominis muscle	1	—	1·0	—	—
	2	—	10·5	—	—
Psoas muscle	1	—	1·9	—	—
	2	—	1·3	—	—
Cervical sympathetic chain	1	—	1·9	—	4·0
	2	—	3·0	—	3·9
	3	—	15·0	—	—
Vagus nerve	1	—	5·3	—	5·0
	2	—	3·1	—	9·4
Phrenic nerve	1	10·5	—	—	—
Brachial plexus	1	—	2·0	—	4·2
	2	—	1·6	—	3·9
Bronchi	1	—	4·5	—	1·0
	2	—	7·8	—	2·5
Lung parenchyma	1	—	2·4	—	50·0
	2	—	1·3	—	12·4

The figures refer to concentrations in ng/g tissue. A dash indicates that prostaglandins were not detected.

recovery of known amounts of added prostaglandins of the different types which were subjected to the standard extraction and separation procedures and then assayed was found to be between 46 and 59% (4 experiments).

The prostaglandin concentration in ng/g wet weight of tissue, uncorrected for recovery, are shown in Table 1, and the tissues and fluids in which no prostaglandins could be detected are shown in Table 2.

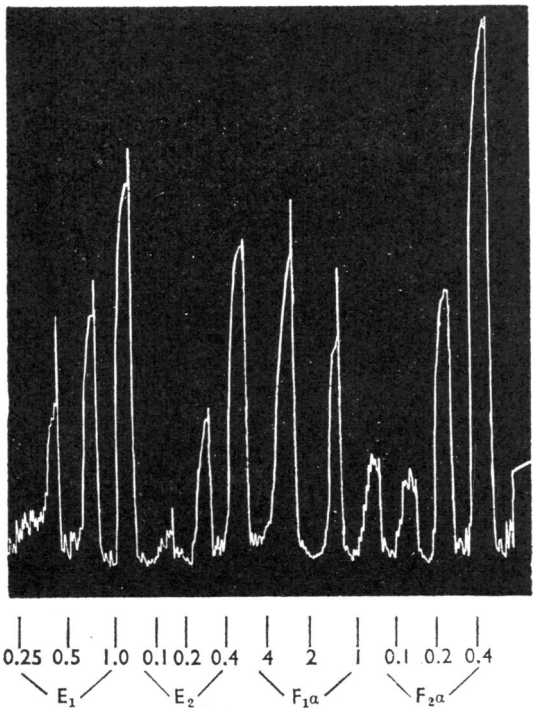

Fig. 1. Isotonic contractions of jird colon (*Meriones libycus*) suspended in 4 ml. organ bath containing de Jalons solution gassed with oxygen. E_1=prostaglandin E_1, E_2=prostaglandin E_2, $F_{1\alpha}$=prostaglandin $F_{1\alpha}$, and $F_{2\alpha}$=prostaglandin $F_{2\alpha}$. Figures indicate concentrations of different prostaglandins in ng/ml. Dose cycle 4 min, contact time 1½ min.

TABLE 2

TISSUES AND FLUIDS IN WHICH PROSTAGLANDINS WERE NOT DETECTED

In all these experiments 100 g tissue or 100 ml. fluid was used for the extraction. Since the assay preparation could detect at least 2 ng PGE_1, PGE_2 and $PGF_{2\alpha}$ in 4 ml. organ bath, tissues and fluids in which prostaglandins were not detected contained less than 0·02 ng/ml. or g of various prostaglandins

Source	Experiments (no.)
Spleen	4
Liver	4
Kidney	3
Subcutaneous fat	4
Milk (2–3 days postpartum)	5
Milk (during menstrual phase of cycle)	2
Urine	2
Venous blood	6

DISCUSSION

The use of the isolated ascending colon preparation of *M. libycus* has made possible the quantitative estimation of small concentrations of the various prostaglandins present in tissue. According to Ambache (1967, personal communication) this preparation contracts in the presence of less than 0·5 ng/ml. prostaglandins E_1, E_2 and $F_{2\alpha}$ and approximately 5 ng/ml. $F_{1\alpha}$. In the present investigation these findings were confirmed.

The finding of prostaglandins E_1 in thymus, and E_2 and $F_{2\alpha}$ in bronchi and lung parenchyma was not unexpected in view of the work of Bergstrom (1964) who found E_1 in calf thymus, and $F_{2\alpha}$ in lungs of various species including man. Similarly, the finding of small amounts of E_2 and $F_{2\alpha}$ in cervical sympathetic chain, vagus nerve and brachial plexus is not surprising as prostaglandins have previously been described in the central nervous system (Samuelsson, 1964). It is interesting that the single specimen of phrenic nerve tested contained detectable amounts of prostaglandin E_1 only, as Ramwell, Shaw & Kucharski (1965) found that E_1 was released from the rat phrenic nerve-diaphragm preparation on nerve stimulation. Both cardiac and skeletal muscle contained small amounts of E_2, while adrenal cortex, pancreas and salivary glands contained small amounts of E_2 and $F_{2\alpha}$. Other observations of interest were that both adrenal medulla and thyroid contained moderate amounts of E_2 and $F_{2\alpha}$. The adrenal medulla is of course of neural origin, but it is interesting that its high catecholamine content is accompanied by a relatively high prostaglandin content when compared with other parts of the peripheral nervous system. There have been no previous reports of the finding of prostaglandins in human or animal thyroid. However, Paasonen (1958), in his study of the 5-hydroxytryptamine (5-HT) content of rat thyroid, did comment on the presence of an acetone soluble substance which caused contraction of the rat uterus. This activity, which was not blocked by lysergic acid diethylamide, was not due to 5-HT or histamine, and in our opinion could well have been due to prostaglandins.

The negative results obtained, listed in Table 2, call for little comment. Two of the samples of human milk were obtained from menstruating mothers. The measurement was carried out because the report of Moncrieff & Thompson (1952), that infants may have diarrhoea if breast fed while the mother has a menstrual period, suggested that a humoral factor might be present in the milk. Pickles, Hall, Best & Smith (1965) have shown that prostaglandins are present in the menstrual fluid and in the circulating blood during the menstrual phase of the cycle only; these substances might increase smooth muscle activity elsewhere in the body. However, no prostaglandins could be detected in human milk obtained during the menstrual period.

The tissue content of prostaglandins may not reflect their rate of formation, and recent work has shown that relatively large amounts may be released after nerve stimulation. The work of Ramwell *et al.* (1965) with the phrenic nerve diaphragm preparation has already been quoted; more recently the same group have demonstrated release of prostaglandins from adrenals stimulated with acetylcholine (Ramwell, Shaw, Douglas & Poisner, 1966). Davies, Horton & Withrington (1966) have shown that electrical stimulation of splenic nerve leads to release of prostaglandins into splenic venous blood, and Shaw (1966) has found a release of prostaglandins from adipose tissue *in vitro* in response to sympathetic nerve stimulation. These findings and our own work do not link prostaglandins with any particular component of the nervous system, as the substances may be found in the central

and peripheral nervous system, including sympathetic and parasympathetic. The low levels in some tissues may represent prostaglandins in the tissue nerve supply, but the concentrations in the thyroid are surprisingly high for this. Also prostaglandins have been found in human umbilical cord vessels, which are free from all innervation (Karim, 1967).

The physiological role played by prostaglandins is still largely unknown. Some of their possible functions have been reviewed by Horton (1965) and Karim (1966). The finding of small amounts of prostaglandins in a wide variety of human tissues suggests that they are of much wider significance than the name would imply.

SUMMARY

1. A survey of the distribution of prostaglandins in 23 types of human tissues and fluid has been carried out.

2. The concentration of prostaglandins in 16 types of tissues in which they were present have been estimated.

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