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Distribution of prostaglandins E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$, in some animal tissues

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A survey of the distribution of prostaglandins E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$ in fourteen tissues from the dog, cat, rat, rabbit, guinea-pig and chicken has been made. One or more of these prostaglandins are present in varying amounts in most tissues with PGE_2 $PGF_{2\alpha}$ occurring most commonly.

SIX of the naturally occurring "primary" prostaglandins (E_1, E_2, E_3, $F_1\alpha$, $F_2\alpha$, $F_3\alpha$) have been described and the elucidation of their structure has been fully documented and recently reviewed by Bergström & Samuelsson (1965) and Samuelsson (1965). Five of these primary prostaglandins have been isolated from human seminal fluid (Bergström & Samuelsson, 1962; Samuelsson, 1963). Prostaglandins do not only occur in male accessory glands and their secretions. They have been found in thymus, pancreas, brain and kidney (Bergström & Samuelsson, 1965; Samuelsson, 1965). They have also been isolated from human menstrual fluid (Eglinton, Raphael & others, 1963) and from human umbilical cord and amniotic fluid (Karim, 1966, 1967; Karim & Devlin, 1967). Karim,

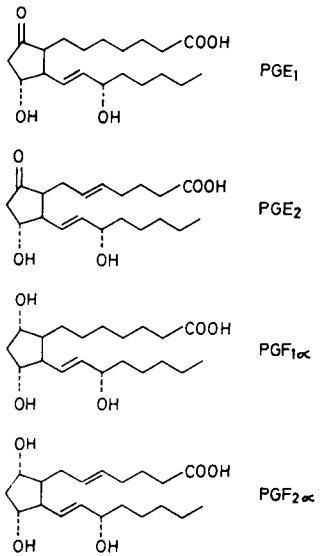

FIG. 1. Formulae of four naturally occurring prostaglandins.

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Sandler & Williams (1967) recently observed prostaglandins to be present in 16 of 23 different human tissues examined. The present investigation is concerned with the distribution of prostaglandins E_1, E_2, $F_1\alpha$ and $F_2\alpha$ in tissues from six widely used laboratory animals.

Experimental

MATERIAL AND METHODS

The animals used were 12 Wistar rats of either sex, 120–150 g; 6 male guinea-pigs, 500–800 g; 3 adult chickens; 3 male rabbits; 2 male cats; 1 male greyhound. The rats, guinea-pigs and chickens were stunned and bled out, and the dog, cats and rabbits were intravenously infused with sodium pentobarbitone until respiration ceased. The selected tissues were removed immediately, pooled for each species and stored at $-10°$ until extracted. The prostaglandins were extracted by the method of Samuelsson (1963). The methods used for the chromatographic separation and identification of the prostaglandins were as described by Karim (1967). Briefly, this consisted of group separation of the E prostaglandins from the F series by chromatography on a column of silicic acid followed by separation of the individual prostaglandins by thin-layer chromatography in solvent system A11 of Green & Samuelsson (1963) using plates coated with silica gel G and containing 7·5% silver nitrate. Markers of known prostaglandins were used. The activity on the plate was located by biological assay. Biological assay of the prostaglandins was on the isolated ascending colon preparation from the jird, *Meriones libycus*. The colon was removed and set up in a 4 ml organ bath of de Jalon solution at 30°, and gassed with oxygen (Karim & others, 1967). Isotonic contractions were recorded on smoked kymograph paper. A dose cycle of 4–5 min with a contact time of $1\frac{1}{2}$–2 min was used depending on the response of the jird preparation. For any one assay, the contact time was constant. The amounts of prostaglandins present in tissue extracts were estimated by the bracket assay method using pure synthetic prostaglandins as standards. For the estimation of some of the extracts the guinea-pig isolated proximal colon preparation (Karim, 1967) was also used.

Results

The survey of different tissues from the six species revealed the presence of the four prostaglandins in varying amounts in most tissues. Identification was based on several characteristics of these substances, including the behaviour of the active material as polar lipid acids on partition between ethyl acetate and water, and also chromatographic properties. Full details of the methods of identification are given by Karim (1967).

The quantitative estimation of small amounts of prostaglandins present in some of the tissues examined has been made possible by the use of the jird isolated colon preparation. Table 1 shows the threshold concentrations of the four prostaglandins required to elicit the contraction of the preparation and the ratio of their biological activity on 60 preparations.

TABLE 1. RATIO OF BIOLOGICAL ACTIVITY OF PROSTAGLANDINS E_1, E_2, $F_1\alpha$ AND $F_2\alpha$ AND THEIR THRESHOLD DOSE ASSESSED USING 60 PREPARATIONS OF THE JIRD ISOLATED COLON. THE ACTIVITY OF E_1 IS TAKEN AS 1.

Prostaglandins	Ratio of activity	Range of threshold doses ng/ml
E_1	1	0·2 -0·7
E_2	2	0·05-0·4
$F_1\alpha$	0·2	1·0 -4·0
$F_2\alpha$	1·5	0·3 -0·5

The concentrations of prostaglandins in ng/g wet weight of tissue, uncorrected for recovery are shown in Table 2. The recovery of known amounts of pure prostaglandins added to various tissues, including those that did not contain any prostaglandins, which were subjected to the standard extraction and separation procedures, was found to be 59% ± 12% (5 experiments).

TABLE 2. DISTRIBUTION (NG/G OF TISSUE) OF PROSTAGLANDINS IN ANIMAL TISSUES

Tissue	Animal					
	Dog	Cat	Rat	Guinea-pig	Rabbit	Chicken
Heart	ND	3·7 $F_2\alpha$	3·8 E_2	ND	ND	3·5 $F_2\alpha$ 51·0 E_2
Thymus	2·5 E_1 2·0 E_2 4·0 $F_2\alpha$	4·0 E_1 5·1 E_2 3·3 $F_2\alpha$	17·5 E_1	6·0 $F_2\alpha$	1·0 $F_2\alpha$	25·8 E_2
Skeletal muscle ..	1·0 E_2 2·7 $F_2\alpha$	1·0 E_1	4·4 E_2 2·1 $F_2\alpha$	1·1 E_2 1·1 $F_2\alpha$	ND	1·8 $F_2\alpha$
Submaxillary salivary glands	1·9 E_2 1·9 $F_2\alpha$	0·75 E_2 1·1 $F_2\alpha$	9·2 E_2 6·9 $F_2\alpha$	4·7 E_2 7·8 $F_2\alpha$	17·5 E_2 2·7 $F_2\alpha$	NE
Spleen	0·4 E_1 18·7 E_2 2·3 $F_2\alpha$	8·75 E_2	37·5 E_2 8·0 $F_2\alpha$	4·0 E_2 6·1 $F_2\alpha$	23·2 E_2 20·0 $F_2\alpha$	180·2 E_2 60·6 $F_2\alpha$
Adrenals	5·0 E_2	80·0 E_2 101·7 $F_2\alpha$	ND	ND	42·0 E_2	40·1 E_2 250·9 $F_2\alpha$
Sympathetic chain	31·7 E_2 57·5 $F_2\alpha$	37·5 E_2 25·6 $F_2\alpha$	NE	NE	NE	NE
Pancreas	1·45 E_2 1·1 $F_2\alpha$	3·3 E_2 3·2 $F_2\alpha$	18·2 E_2 9·7 $F_2\alpha$	ND	5·5 E_2 2·4 $F_2\alpha$	12·5 E_2 10·0 $F_2\alpha$
Thyroid	ND	20·0 E_2 6·0 $F_2\alpha$	154·4 E_2 162·1 $F_2\alpha$	480·8 E_2 160·9 $F_2\alpha$	133·0 E_2 1·83 $F_2\alpha$	192·3 $F_2\alpha$ 160·4 E_2
Kidney	ND	ND	50·4 E_2 9·0 $F_2\alpha$	28·5 E_2 20·2 $F_2\alpha$	32·0 E_2 18·2 $F_2\alpha$	9·2 $F_2\alpha$
Liver	ND	ND	18·2 E_2 9·4 $F_2\alpha$	12·0 $F_2\alpha$	1·75 E_2 8·50 $F_2\alpha$	ND
Blood	ND	ND	ND	ND	ND	ND
Vagus	45·3 E_2 30·4 $F_2\alpha$	90·9 E_2 45·0 $F_2\alpha$	NE	NE	NE	NE
Lungs	ND	65 E_2, 15·5 $F_2\alpha$	16·6 E_2 90·4 $F_2\alpha$	2·5 E_2 375·0 $F_2\alpha$	5·4 E_2, 8 $F_2\alpha$	7·7 E_2 30·4 $F_2\alpha$

ND—Prostaglandins E_1, E_2, $F_1\alpha$, $F_2\alpha$ not detected.
NE—Tissue not extracted.

In addition to the prostaglandins identified in the different tissues, some extracts of rabbit pancreas, cat liver and guinea-pig lung contained other

polar lipid-soluble acidic smooth muscle stimulating substances, which had Rf values, obtained by biological assay, of 0·2–0·3, which were lower than that of $PGF_2\alpha$ (0·45–0·50) on the thin-layer plates. It is conceivable that this activity was due to the presence of PGE_3 or $PGF_3\alpha$. However, pure samples of these two prostaglandins were not available and hence no further attempt was made to identify the substances.

Discussion

Published studies on the distribution of prostaglandins show that there are species differences. Prostaglandins are present in very high concentration in semen of man and sheep but the semen of a number of other species contains none (Bergström, 1963; Bergström & Samuelsson, 1962; Samuelsson, 1966). The presence of prostaglandins has been reported in the dog spleen (Davies, Horton & Withrington, 1966) and the kidney (Lee, Covino & others, 1965). However, human spleen and kidney do not contain any prostaglandins (Karim & others, 1967).

The results of the present investigation show that although the four prostaglandins are widely distributed amongst animal tissues there are differences in their concentrations between similar tissues in different species. Most chicken tissues examined, apart from the liver, contain larger amounts of the prostaglandins than the same tissues from other species. Horton & Main (1967) have reported that concentrations of prostaglandins in the central nervous tissues of the chicken are higher than those in the similar tissues from the dog or the cat. Liver, kidney, heart and thyroid from the dog, the liver and kidney from the cat, rat adrenals, guinea-pig heart and pancreas, rabbit heart and skeletal muscle and chicken liver contain no detectable amounts of the four prostaglandins. In no species were they detected in the blood.

Paasonen (1958), studying the 5-hydroxytryptamine (5-HT) content of rat, dog and rabbit thyroids, reported the presence of a smooth muscle stimulating substance in the rat thyroid which like prostaglandins was soluble in 90% acetone. This activity was shown not to be due to histamine, 5-HT or acetylcholine. Garven (1956) reported a substance with similar properties in extracts or rabbit thyroid. Since prostaglandins E_2 and $F_2\alpha$ have been identified in the thyroids of both these species in moderately high concentrations (Table 2) it is conceivable that the reported activity could well have been due to them. No such smooth muscle stimulating activity was observed in the dog thyroid and we did not detect prostaglandins in dog thyroid.

Prostaglandins were found in the submaxillary glands of all species studied. Stimulation of chorda tympani nerve leads to vasodilatation in these glands in the dog, cat and rabbit (Morley, Schachter & Smaje, 1963; Bhoola, Morley & others, 1965; Schachter, 1966). The cause of this vasodilatation is in dispute. Kallikrein has been suggested to be the vasodilator substance by Hilton & Lewis (1958), Lewis (1959) and Hilton (1960, 1966), but other workers believe that it plays no significant role in this action (Bhoola & others, 1965; Schachter, 1966). Schachter

(1966) suggests that "neurotransmitter substance released in close relation to the receptor sites in the vascular muscle is concerned". The finding that prostaglandins are intense vasodilators in most vascular beds (Horton & Main, 1963; Ånggärd & Bergstrom, 1963; Nakano & McCurdy, 1967) and that they can be released upon nerve stimulation (Ramwell & Shaw, 1963; Ramwell, Shaw & Kucharske, 1965) and that they occur in the submaxillary glands of the six species investigated would make further work in their role as vasodilators in the salivary glands of interest.

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