CONTENT OF PRECURSORS FOR PROSTAGLANDIN BIOSYNTHESIS IN RENAL LIPIDS DURING DEVELOPMENT OF SPONTANEOUS ARTERIAL HYPERTENSION

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UDC 612.12-008.331.1-092-07:616.61-008.939.15:[616.61-008.94:577.175.859

KEY WORDS: prostaglandins, arterial hypertension.

The development of arterial hypertension is linked with changes in renal control over the arterial pressure [2, 5]. The prostaglandin system of the kidneys plays an important role in the mechanism of this control [3, 13, 15]. The development of spontaneous (hereditarily determined) arterial hypertension in rats of the Okamoto-Aoki strain (spontaneously hypertensive rats — SHR) is accompanied by a disturbance of prostaglandin (PG) metabolism in the kidneys [3, 4, 9]. PG synthesis is an intricately controlled process in which the presence of precursors of PG (polyunsaturated fatty acids of the linoleic and linolenic series [14]) are of definite importance. Since most renal PG in rats consist of diene PG [6, 11], in order to characterize the PG system of the kidneys of SHR it is interesting to study the content of arachidonic (20:4ω6) and linoleic (18:2ω6) acids, and also of icosatrienic acid (20:3ω9) of the oleic series, of which the first is a substrate for the synthesis of diene PG, the second the original acid of the linoleic series and a precursor of the first [14], while the third is a compound affecting the spectrum of the PG synthesized [12], in renal lipids during the development of spontaneous hypertension.

The aim of this investigation was to make a comparative analysis of the content of 18:2ω6, 20:4ω6, and 20:3ω9 in lipids of the cortical and internal medullary (papilla) layers of the kidneys in SHR during the development of spontaneous hypertension, and in normotensive Wistar rats (NR) of corresponding ages.

EXPERIMENTAL METHOD

The experimental animals were kept on a standard semisynthetic diet of the following composition (in percent by weight): casein 23, starch 52, brewers' yeast 6, sunflower oil 5, lard 5, cellulose 4, Jones—Foster salt mxiture [8] with the addition of fluorine and aluminum 4, a mixture of lipid-soluble vitamins in oil 1. Pregnant female rats received the diet for 1 week before giving birth and for 1 month after the lactation period, after which male rats were selected from the progeny and these continued to receive the diet until they had reached the necessary age according to the experimental conditions. The rats were decapitated, the kidneys removed, and lipids extracted by Folch's method [7] from the cortex and papilla. The lipids were fractionated and their fatty acid composition analyzed by the method in [1]. The content of 18:2ω6, 20:4ω6, and 20:3ω9 was expressed in percentages by weight of the total fatty acid content. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Data on the content of 18:2ω6 and 20:4ω6 in phospholipids and triglycerides of the renal cortex of SHR and NR of different ages are given in Table 1. The level of 18:2ω6 content in the phospholipids of NR was similar, but the content of 18:2ω6 in the phospholipids of SHR began to fall sooner than in NR. The content of 18:2ω6 in the phospholipids increased with time in the animals of both groups, and no difference was observed between the groups except in the case of rats aged 2 months, in which the level of 20:4ω6 was higher in SHR than in NR. In the triglycerides of the renal cortex at the age of 10 days the content of 16:2ω6 was less in SHR than in NR, but by the age of 1 month the situation was reversed. In animals aged 2 months the level of 18:2ω6 in the SHR group as before was higher than in NR but by 4 months

Laboratory of Pathophysiology, Research Institute of Pediatrics, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR M. Ya. Studenikin.) Translated from Byulletin' Eksperimental'noi Biologii i Meditsiny, Vol. 98, No. 8, pp. 163-165, August, 1984. Original article submitted August 9, 1983.

 0007-4888/84/9808-1042$08.50

TABLE 1. Content of 18:2ω6 and 20:4ω6 in Phospholipids (PL) and Triglycerides (TG) of Renal Cortex of SHR and NR at Different Ages (in percent by weight, M ± m)

Acid		Age of animal	NR	No. of animals	SHR
18:2ω6	PL	10 days	9,43±0,44	10	8,42±0,49
		1 mo.	12,05±0,53	9	13,01±0,58
		2 mo.	13,77±0,25*	9	12,50±0,39
		4 mo.	11,23±0,60*	7	9,82±0,21
	TG	10 days	18,26±0,30**	10	16,34±0,54
		1 mo.	22,09±1,09	9	26,72±0,56**
		2 mo.	20,06±0,98	9	24,69±1,32*
		4 mo.	19,12±0,84	7	17,84±1,40
20:4ω6	PL	10 days	29,89±1,34	10	30,54±1,08
		1 mo.	33,24±1,89	9	33,86±1,46
		2 mo.	31,03±1,15	9	34,05±0,75*
		4 mo.	36,59±1,05	7	37,79±1,74
	TG	10 days	7,13±0,38	10	6,53±0,94
		1 mo.	6,07±0,44**	9	4,45±0,13
		2 mo.	3,15±0,73	9	3,67±0,55
		4 mo.	6,88±1,86	7	6,31±0,55

Legend. *P < 0.05; **P < 0.01.

it had fallen again and was down to the level in NR. At the age of 1 month the content of 29:4ω6 in triglycerides was lower in SHR than in NR, but at all other times no change was observed in the 20:4ω6 content compared with that in NR.

The study of the content of 18:2ω6 and 20:4ω6 in lipids of the papilla is particularly interesting, for it is in this part of the kidneys that extremely active processes of PG synthesis are observed [6, 15], and great importance is attached to this in the antihypertensive function of the kidneys [2]. The curve showing changes in the 18:2ω6 content in SHR in phospholipids of the papilla (Fig. 1a) was almost the mirror image of the corresponding curve for NR. In SHR at the age of 10 days the content of 18:2ω6 was less than in NR, but it subsequently increased, and by the age of 1 month it was higher than in NR. Later, at the ages of 2 and 4 months, the content of this acid, just as in phospholipids of the cortex, decreased and again fell below that in NR. At the age of 10 days the content of 20:4ω6 in SHR was higher than in NR. Later, until the age of 1 month, it remained virtually unchanged whereas in NR it rose sharply, and the end result was that the level of 20:4ω6 in SHR at the age of 1 month was lower than in NR. At the ages of 2 and 4 months the level of 20:4ω6 was the same in SHR and in NR. An important distinguishing feature of phospholipids in the papilla of SHR was a constant increase in the 20:4ω6 content with age. In NR, after a sharp rise until 1 month, the 20:4ω6 level subsequently remained unchanged.

The character of the 18:2ω6 content in triglycerides of the SHR papilla (Fig. 1b) was the same as that in phospholipids at the age of 10 days, and at 2 and 4 months the level of this acid was lower than in NR, whereas at the age of 1 month it was higher. The content of 20:4ω6 in triglycerides of the papilla of SHR of all age groups was higher than in NR.

A definite similarity in the disturbances of the 18:2ω6 content in lipids of the cortex and papilla of SHR must be noted, namely that in the prehypertensive stage (10 days) and in the stage of stable hypertension (4 months) a lower level of 18:2ω6 was observed in the lipids of these layers of the kidneys in SHR than in NR. Comparison of the age dynamics of the content of 18:2ω6 and 20:4ω6 in the renal lipids of SHR and NR shows that the decrease in the 18:2ω6 content in the phospholipids and triglycerides of the renal papilla of SHR at the ages of 10 days and 2 and 4 months corresponded to a higher level of 20:4ω6, whereas the increase in the content of 18:2ω6 in the triglycerides of the cortex and phospholipids of the papilla of the SHR kidney at the age of 1 month corresponded to a fall in the 20:4ω6 level. It is impossible to explain these differences in the content of the principal fatty acids of the linoleic series in the kidneys of SHR by means of the alimentary factor, for the intake of 18:2ω6 by SHR at the age of 1 month with the diet was approximately the same as in NR, and at the ages of 2 and 4 months it actually exceeded that obtained by NR (by 1.34 and 1.24 times respectively; calculation based on the quantity of food consumed by each animal). The reason for the differences described above in the content of 18:2ω6 and 20:4ω6 in SHR kidneys may be change in the metabolism of 18:2ω6. At the ages of 10 days and 2 and 4 months, an increase in metabolism of 18:2ω6 evidently took place in the kidneys of SHR, but not of NR, and this led to a decrease in its concentration, despite the continuous intake with the diet, and

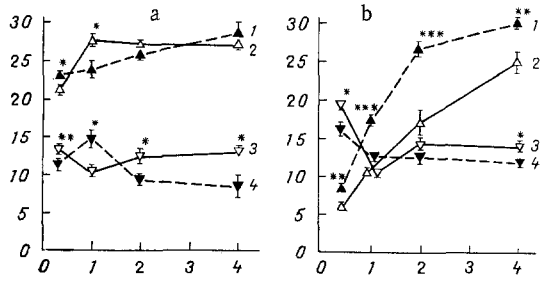

Fig. 1. Content of acids 18:2ω6 and 20:4ω6 in phospholipids (a) and triglycerides (b) of renal papilla in NR and SHR of different ages. Abscissa, age of rats (in months); ordinate, fatty acid content (in percent by weight). 1) 20:4ω6, SHR; 2) 20:4ω6, NR; 3) 18:2ω6, NR; 4) 18:2ω6, SHR. *P < 0.05, **P < 0.1, ***P < 0.001. Data presented in the form of M ± m (each group consisted of 7-10 rats).

also to an increase in the formation of 20:4ω6. These differences in the 18:2ω6 content in SHR kidneys may indicate increased consumption of this essential fatty acid by these animals. The importance of these disturbances in the kidneys for the development of spontaneous hypertension is emphasized by the fact that a fall in the 18:2ω6 level in the renal lipids of SHR at the age of 2 months coincided with the appearance of a high arterial pressure in them (127.66 ± 3.99 mm Hg in SHR, 114.22 ± 3.64 mm Hg in NR; P < 0.05), whereas the diets of SHR, with a high content of 18:2ω6, contributed to the development of a less severe hypertension, as confirmed by data in the literature [4, 10]. In the latter case, the disturbances in the content of 18:2ω6 in SHR were probably abolished.

This investigation showed that the content of 20:3ω9 in phospholipids of the renal cortex of SHR aged 4 months was higher than in NR (P < 0.001) and amounted to 0.18 ± 0.03% of the content of 20:4ω6, whereas in NR its value was close to 0. In lipids of the papilla, 20:3ω9 was absent in both NR and SHR.

In the stage of stable hypertension (4 months) a general increase in the content of 20:4ω6, an immediate precursor of diene PG, thus took place in SHR, as already mentioned, against the background of a fall in the 18:2ω6 level. Of these diene PG, it is PGE_2 which is formed in the largest amount in the renal medulla [4, 6]. Since this PG has a powerful depressor action, its possible increased formation in the presence of an excess of 20:4ω6 must, on the other hand, have inhibited to some degree the development of hypertension in SHR. The causes of this apparent contradiction are evidently connected with two circumstances. First, an increase in the 20:4ω6 level was observed only in triglycerides of the renal medulla of SHR, and not in phospholipids, which are the main source of 20:4ω6, used in PG biosynthesis [4, 14]. Second, these investigations showed an increase in the 20:3ω9 content in SHR. This last acid is an inhibitor of PG formation, including in the kidneys, and it thus leads to a fall in PGE_2 level accompanied by some increase in the output of pressor $PGF_{2\alpha}$ [12], which has also been observed in SHR [4, 10].

The development of spontaneous hypertension in SHR is thus accompanied by disturbance of the content of the principal fatty acids of the linoleic series — 18:2ω6 and 20:4ω6, and also of icosatrienic acids of the oleic series — 20:3ω9, in the renal lipids. Evidently as a result of a disturbance of 18:2ω6 metabolism in the SHR kidney its content and accumulation of its principal metabolite, namely 20:4ω6, in the triglycerides are reduced. Evidence in support of this hypothesis is given by the change in the content of 20:3ω9 in SHR, which takes place particularly often when metabolism of 18:2ω6 is disturbed [12, 14].

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