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PROSTACYCLIN AND THROMBOXANE LEVELS OF CHILDREN OF PARENTS SUFFERING FROM EARLY ISCHEMIC HEART DISEASE

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Offsprings of parents who had acute myocardial infarction before age of 45 years were investigated. The aim of this examination was to obtain information whether the variation in the balance of prostacyclin/thromboxane ratio is a common cardiovascular risk factor in children.
In children whose parents have had early myocardial infarction, a significant decrease was shown in 6-keto-prostaglandin $F_{1\alpha}$ level while the thromboxane B_2/6-keto-prostaglandin $F_{1\alpha}$ ratio increased in these children. Plasma tromboxane B_2 levels hardly differed from those of the control in that group of children whose one parent and at least one of the grandparents or uncles or aunts suffered from coronary heart disease. Plasma thromboxane concentration was lower in another group of children whose "only" one parent had myocardial infarction. It may be supposed that this is a compensatory mechanism in the offspring of parents suffering from early coronary heart disease.

INTRODUCTION

Coronary heart disease (CHD) mortality of Hungarian middle-aged men is highest in Europe. There is an urgent need to know more of the early stages of its development and of its various risk factors /1/.

As part of a comprehensive cardiovascular prevention program in Hungary a study of risk factors in children, whose parents have had an acute myocardial infarction (AMI) before the age of 45 years, was carried out.

The present work was aimed at the measurement of concentrations of circulating stable hydration products of prostacyclin (PGI_2) and thromboxane (TXA_2)- namely 6-keto-

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prostaglandin - $F_1\alpha$ (6-keto-$PGF_1\alpha$) and thromboxane B_2 (TXB_2). We examined whether the variation of TXA_2/PGI_2 ratio was a common cardiovascular risk factor in children.

MATERIALS AND METHODS

68 children were investigated ranging in age from 3-14 years, and divided into 2 groups. Group I consisted of 31 children, whose one parent had CHD. Group II consisted of 27 children, whose one parent and at least one of the grandparents or uncles or aunts suffered from CHD. We chose a control group of 28 healthy children without any history for CHD. For prostaglandin (PG) analysis venous blood was collected into tubes containing 0.1 volume of 7.4 x 10^{-2}M EDTA and 2.8 x 10^{-5}M indomethacin solution. The blood was centrifuged for 10 min at 1200 g 4°C to obtain plasma. (Plasma samples were stored at -30°C). For PG extraction octadecylsilyl (ODS) cartridges were used (SAMPLEX C 18 Bio-Separation Technologies, Budapest). Plasma samples were acidified to pH 3 by citric-acid and were applied to the cartridges. The columns were washed with 6 ml petroleum-ether and were eluated with 8 ml ethylacetate. The eluate was dried under vacuum and resuspended in assay buffer. The 6-keto-$PGF_1\alpha$ and TXB_2 were determined by radioimmunoassay Izinta RIA KIT, Budapest.
Extraction efficiency calculated from extracted control plasma was 75.6 $\pm$ 15.2 % for 6-keto-$PGF_1\alpha$ and 81.5 $\pm$ 13.2 % for TXB_2. Statistical significance between group means was assessed by Student's t-test.

RESULTS

Plasma 6-keto-$PGF_1\alpha$ concentrations were lower in both groups of affected children. The difference is statistically significant. Plasma TXB_2 levels were lower in group I compared with the controls, and hardly differed from the control in group II. TXB_2/6-keto $PGF_1\alpha$ ratios were elevated in both groups of the examined children. There was a statistically significant difference between the ratio of TXB_2 to 6-keto-$PGF_1\alpha$ in group II (Table).

TABLE

Plasma levels of prostaglandin metabolites and TXB_2/6-keto-$PGF_{1\alpha}$ ratio in examined children compared with controls

	N	6-keto-$PGF_{1\alpha}$ ± SEM (pg/ml)	Thromboxane B_2 ± SEM (pg/ml)	TXB_2/6KPGF$_{1\alpha}$ ± SEM
Control	28	80.9 ± 9.3	325.3 ± 24.0	5.9 ± 0.9
Group I.	31	32.5 ± 7.2^{xx}	197.5 ± 41.4^{x}	29.5 ± 13.2
Group II.	37	14.6 ± 2.5^{xx}	332.8 ± 79.4	56.3 ± 21.8^{x}

^{x}: $p < 0.05$

^{xx}: $p < 0.001$

Group I : one parent had CHD

Group II : one parent and at least one of the grandparents or uncles or aunts suffered from CHD.

Control : healthy children without any history for CHD.

All values are presented as means ± SEM

DISCUSSION

Platelet aggregation and formation of thrombi are important in the pathophysiological mechanism of the development of myocardial ischemia and infarction. The arachidonic acid metabolites thromboxane A_2 and prostacyclin have been recognized to play important roles in platelet function and in the development of the atherosclerotic processes and of CHD /3, 5, 7, 8, 9-11, 19/. PGI_2 inhibits platelet aggregation by stimulating adenylate cyclase, leading to an increase in cAMP levels in the platelets /9, 11/. PGI_2 is a strong hypotensive agent and a vasodilator of all vascular beds. In contrast to PGI_2 the TXA_2 is a vasoconstrictor and platelet aggregator. Balance between formation of PGI_2 by the vessel-wall and of TXA_2 by platelets is important for the control of hemostasis /10/. A number of diseases have been related to an imbalance in the PGI_2 - TXA_2 system /9, 12/. Platelets from patients with hypercholesterolemia have been shown to produce abnormal amounts of TXA_2 /11/. Increased release of TXA_2 has been described in rabbits made atherosclerotic by high-cholesterol diet and patients who survived AMI, and also an elevated level of TXB_2 in blood of patients with Prinzmetal's angina and vasotonic angina /6, 13, 16, 18, 20/. The precise role of TXA_2 in cardio-vascular disease is still unclear. It is possible that multiple factors may be involved in the pathologic etiology.

The results of this study suggest that there is a PGI_2/TXA_2 imbalance in children whose parents had early CHD. A significant decrease was shown in 6-keto-$PGF_1\alpha$ levels while TXB_2/6-keto-$PGF_1\alpha$ ratio increased in both groups of examined children. Plasma TXB_2 concentration in group II hardly differed from that of controls, but it was lower in group I compared with the controls. This may be due to compensatory mechanism in the offspring of parents suffering from early CHD.

Because PGI_2 generation by atherosclerotic arterial tissue has been shown to be lower than by a normal one /15/, our results suggest that childhood is an important prevention stage

of atherosclerotic processes in children with highrisk families.

This PGI_2/TXA_2 imbalance in affected children may contribute to the initiation of atherogenic processes in the blood vessels in childhood and shows the importance of screening examination and of dietary measures that consist of feeding polyunsaturated fatty acids (e.g. eicosapentaenoic acid) to stimulate PGI_2 production of the vessel-walls (2, 4, 14, 17).

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