PROSTAGLANDINS, CYCLIC NUCLEOTIDES, AND ADAPTATION OF THE HEART TO ACUTE AND CHRONIC PRESSURE OVERLOADING

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The concentration of prostaglandins (PG) and cyclic nucleotides was determined in the rat heart at different times after coarctation of the abdominal aorta. The animals were divided into three types depending on the rate of development and degree of hypertrophy. Rats best adapted to pressure overloading of the heart (with the greatest degree of hypertrophy) had the highest PG level in the myocardium. Correlation was found between the increase in weight of the heart and the PGE/$PGF_{2\alpha}$ ratio. A connection was demonstrated between PG and cyclic nucleotides in the myocardium in the course of its adaptation to pressure overloading. It is suggested that PG may be an important component of the system of adaptation of the heart to pressure overloading.

KEY WORDS: Pressure overloading of the heart; adaptation; prostaglandins; cyclic nucleotides.

Compensatory hypertrophy of the heart develops in response to increased hemodynamic or metabolic demands [2]. The increase in weight of the heart in hypertrophy is due to stimulation of nucleic acid and protein synthesis [6]. Cyclic AMP is known to take part in the regulation of protein synthesis [14]. In compensatory hypertrophy of the heart an increase in adenylate cyclase activity and in the cyclic AMP concentration is found as early as 5-10 min after coarctation of the aorta [9, 14].

As a result of analysis of data in the literature prostaglandins (PG) can be regarded as integral regulators of primary metabolic processes in the cell [12, 15]. According to Kuehl's hypothesis [8], PG of group E and group F_α exert their action through different mediators. For instance, PGE exerts its effect through cyclic AMP, $PGF_{2\alpha}$ through cyclic GMP. These facts, and also the observation that PG activates adenylate cyclase in the heart [11], suggest a combined role of PG and cyclic nucleotides (CN) in the development of compensatory hypertrophy of the heart.

The object of this investigation was to study the character of relations between PG and CN during adaptation of the heart to pressure overloading. Experiments were carried out to determine the content of PG (E and $F_{2\alpha}$) and CN (cyclic AMP and cyclic GMP) in the rat heart at different times after the beginning of coarctation of the aorta.

METHODS

Eighty male Wistar rats weighing 140-160 g were used. Compensatory hyperfunction and hypertrophy of the myocardium were induced by coarctation of the abdominal aorta by Beznak's method in Kogan's modification [1]. The hypertrophy of the heart muscle was evaluated as the increase in the relative weight of the heart after the creation of experimental aortic stenosis. The control group consisted of 24 rats undergoing a mock operation. At different times (5, 15, and 40 min, 1, 2.5 and 5 h, and 1, 2, 3, 14 and 22 days) after creation of stenosis the tissue of the left ventricle was quickly excised and frozen by means of Wollenberger's forceps cooled in liquid nitrogen. From four to eight animals were used at each time interval. The frozen samples of myocardium were ground in liquid nitrogen and used for quantitative determination of their PG and CN. After extraction [4] and chromatographic separation of PG into groups [5], the content of PGE and $PGF_{2\alpha}$ was determined by radioimmunoanal-

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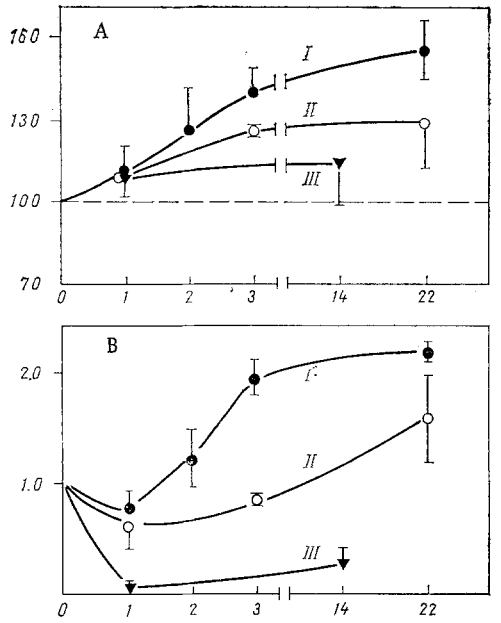

Fig. 1. Changes in relative weight of heart (A) and ratio PGE/$PGF_{2\alpha}$ in myocardium of rats (B) at different time intervals after beginning of coarctation of aorta. I) Group 1, II) group 2, III) group 3. Abscissa, time after stenosis (in days); ordinate, A) weight of ventricles (in percent of control); B) ratio PGE/$PGF_{2\alpha}$.

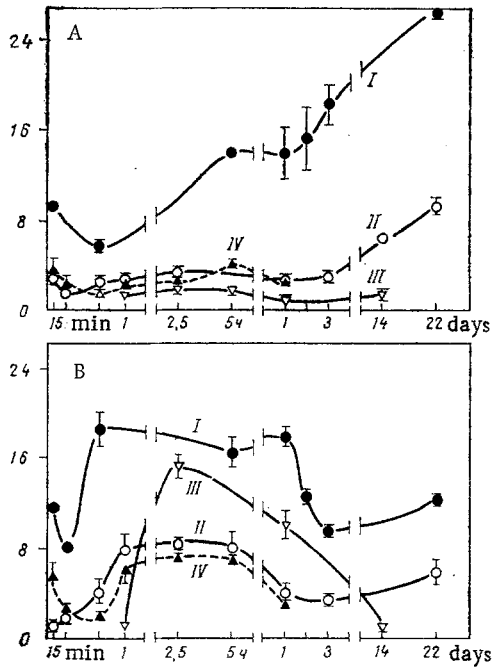

Fig. 2. Dynamics of content of PGE (A) and $PGF_{2\alpha}$ (B) in myocardium of rats at different time intervals after beginning of aortic stenosis. I) Group 1, II) group 2, III) group 3 (unadapted type); IV) control group. Abscissa, time after stenosis; ordinate, A) PGE content (in ng/g tissue); B) $PGF_{2\alpha}$ content (in ng/g tissue).

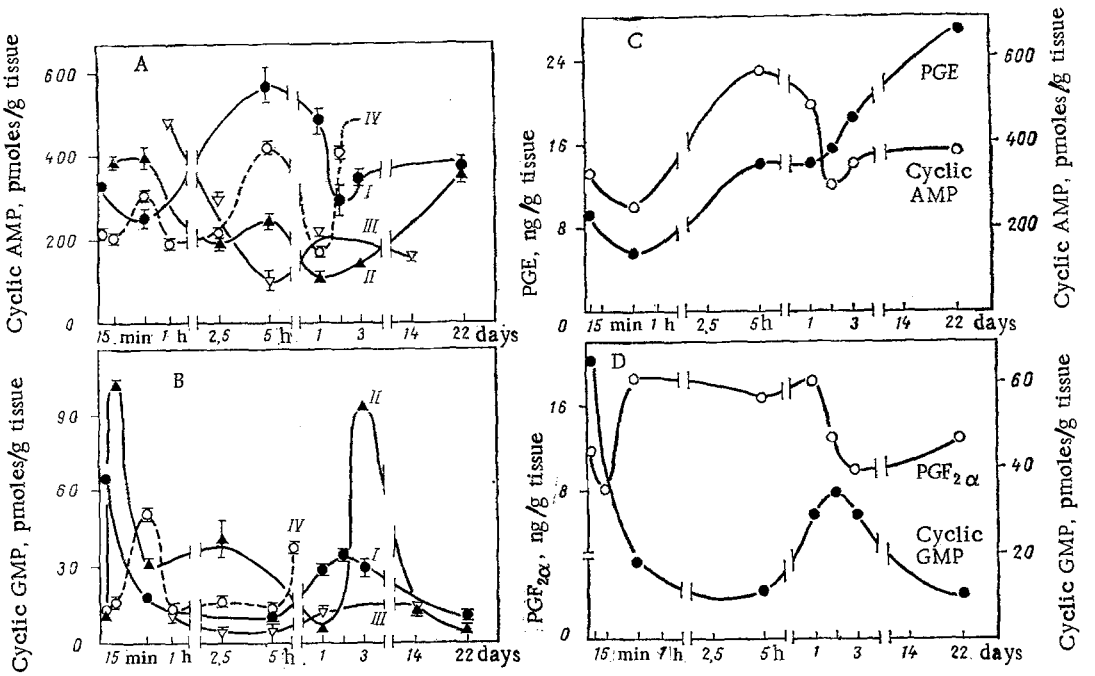

Fig. 3. Dynamics of cyclic AMP (A) and cyclic GMP (B) content at different time intervals after beginning of aortic stenosis. I) Group 1; II) group 2; III) group 3; IV) control group. C) Character of relations between PGE and cyclic AMP for animals of group 1; D) character of relations between $PGF_{2\alpha}$ and cyclic GMP for animals of group 1.

ysis (Clinical Assay, Inc.). The cyclic AMP and cyclic GMP levels in the heart were determined by the method of and using reagents from the Radiochemical Center, Amersham, England.

The results were subjected to statistical analysis by Student's t-test. The values measured are shown in the figures as M ± m.

RESULTS

Coarctation of the aorta caused a distinct and statistically significant increase in the weight of the heart (Fig. 1A). Depending on the rate of development and the degree of hypertrophy of the heart the animals were divided into three groups. Group 1) marked hypertrophy (rapidly adapting type); the rats of this type differed from the other animals in their more active behavior and the absence of visible signs of cardiac failure. Group 2) moderate hypertrophy (slowly adapting type); these animals exhibited little activity and had well-marked features of cardiac failure (dyspnea, ascites). Group 3) the least degree of hypertrophy, rapidly developing decompensation of the heart, 100% mortality after a few hours to 14 days. By this time, signs of compensatory hypertrophy of the myocardium were observed in the animals of the other groups. In rats of this type signs of cardiac failure (severe dyspnea, ascites, and hydrothorax) were advanced.

All three groups of animals differed from each other in the degree of change in the PG content in response to pressure overloading of the heart. The dynamics of the PGE and $PGF_{2\alpha}$ content is illustrated in Fig. 2. Animals of the first type, with the greatest degree and the most rapid development of hypertrophy, and, consequently, the best adapted to the pressure overload, were characterized by a high PG content in the heart. These data are in good agreement with preliminary results obtained in experiments with graduated constriction of the ascending part of the arch of the aorta in rabbits, in which correlation was found between the PG content in the left ventricle of the rabbits and hemodynamic parameters reflecting myocardial contractility. For instance, animals shown by their hemodynamic indices to be more adapted to pressure overloading of the heart also had a higher myocardial PG level [3].

Long-term adaptation of the heart to an increased load is known to be associated with an increase in its weight, i.e., with the development of hypertrophy. This hypertrophy is based on stimulation of nucleic acid and protein synthesis in the early stages after creation of the overload on the heart [6]. On the basis of their experimental data, Limas et al. [9] postulated that activation of PG-synthetase is of the first stages in the chain of biochemical reactions leading to protein synthesis and to the development of hypertrophy. The end result of this activation is the accumulation of both groups of PG (E and F_α) in the myocardium, which was observed also in the present experiments in the animals of the first type (Fig. 2).

There are data in the literature to show differences in the action of PGE and $PGF_{2\alpha}$ on nucleic acid and protein synthesis: PGE_1 has been shown to have a stimulating action, and $PGF_{2\alpha}$ a blocking action [10, 13]. Accordingly we suggested that the development of hypertrophy may perhaps be connected with changes in the $PGE/PGF_{2\alpha}$ ratio in the heart. The results of comparison of the dynamics of this index with changes in the relative weight of the heart demonstrate definite correlation between these two values (Fig. 1A, B). For instance, the greatest increase in the $PGE/PGF_{2\alpha}$ ratio coincides with time with a rapid increase in the weight of the heart.

Since the main aim of this investigation was to establish relations between PG and cyclic nucleotides during adaptation of the heart to acute and chronic pressure overloading, the character of these relations will be examined in the future only for animals of the first type, in which these features were most strongly marked. In the animals of group 1 the dynamics of the cyclic AMP concentration (Fig. 3A) was the mirror image of the dynamics of the cyclic GMP concentration (Fig. 3B) throughout the period of development of compensatory hypertrophy of the heart. This is in agreement with the hypothesis of Goldberg et al. [7] of the opposite role of cyclic AMP and cyclic GMP in the regulation of intracellular metabolic processes. Analysis of the character of correlation between PG and cyclic nucleotides showed that dynamics of the PGE concentration coincided with that of the cyclic AMP concentration. The results are in accordance with the hypothetical scheme of action of PGE through activation of the adenylate cyclase system [8]. Experiments using an agent which blocks PG synthesis, which it is planned to undertake, will provide further confirmation of the correlation between PGE and cyclic AMP. During adaptation of the heart to pressure overloading, the character of the correlation for $PGF_{2\alpha}$ and cyclic GMP was shown to be opposite (Fig. 3D). This fact is difficult to explain at present. Further experiments will help to shed some light on this problem.

Analysis of data in the literature [9-13] and the results now obtained, taken together, suggest that PG are closely linked with the processes of adaptation of the heart to pressure overloading, and that they exert their effect probably through changes in activity of enzymes responsible for synthesis of cyclic AMP and cyclic GMP.

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