EFFECT OF ATRIAL NATRIURETIC FACTOR ON THE CARDIOVASCULAR SYSTEM AND SOME INDICES OF RENAL EXCRETORY FUNCTION IN SPONTANEOUSLY HYPERTENSIVE RATS

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KEY WORDS: atrial natriuretic factor; hypertension; kidneys

Atrial natriuretic factor (ANF) has a significant effect both on cardiac function and vascular tone, and also on processes taking place in the kidneys [2-6]. However, in the overwhelming majority of studies only the acute effect of a single injection of large doses of ANF has been analyzed.

The aim of this investigation was to study the effect of chronic administration of small doses of ANF to spontaneously hypertensive rats and also to evaluate correlation arising between the blood pressure (BP), heart rate (HR), and some indices of the excretory function of the kidneys.

EXPERIMENTAL METHOD

Experiments were carried out on 29 spontaneously hypertensive Wistar rats. The diuresis, and the concentrations of protein, sodium, potassium, chlorine, and creatinine in the urine and their daily excretion were determined in all animals over a period of 8 days. The systolic BP (BP_{max}) in the caudal artery, HR, and body weight of the animals also were determined on the 1st, 4th, and 8th days of the investigation. On the 8th day, the rats were anesthetized (inactin, 80 mg/kg, intraperitoneally) and an osmotic minipump (model 2001 Alza, Palo Alto, California), connected by polyethylene catheter to the left jugular vein, was implanted subcutaneously in the neck region. Minipumps in the rats of one group (basic, 10 animals) were filled with a solution of synthetic human ANF, which was injected into the jugular vein at a

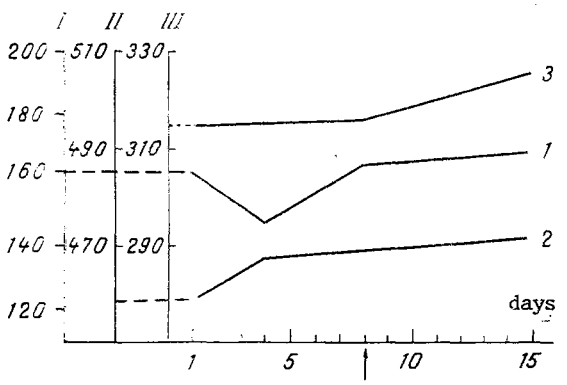

Fig. 1. Changes in BP (1), HR (2), and body weight (3) of spontaneously hypertensive rats before and during administration of ANF. Beginning of injection of ANF indicated by arrow. Abscissa, days of investigation; ordinate: I) BP_{max}, mm Hg; II) HR, beats/min; III) body weight, g.

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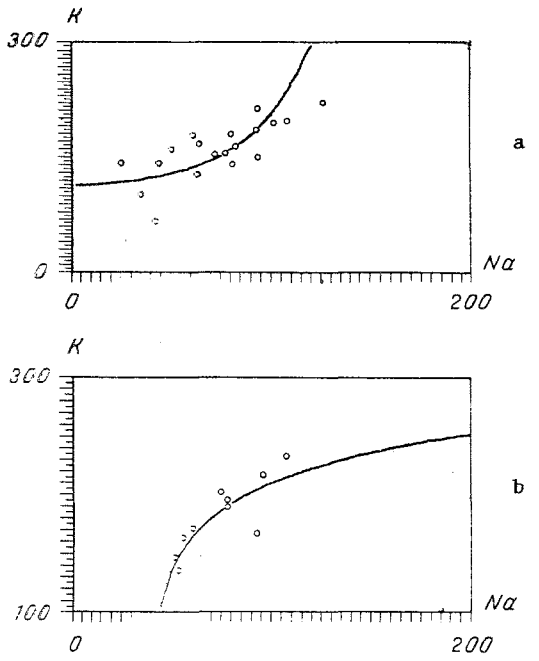

Fig. 2. Character of correlation between Na and K concentrations in urine of spontaneously hypertensive rats before (a) and after (b) administration of ANF for 7 days. Explanation in text.

rate of 100 ng/h (35 pmoles/h) for 7 days, whereas the pumps in the rats of the other group (nine animals, control) were filled with physiological saline. The animals were decapitated at the end of the experiment. The heart and kidneys were weighed, and the hematocrit index and plasma concentrations of Na, K, ANF, and renin were determined. The kidneys were studied histologically. The numerical results were analyzed by Student's test on a "Commodore 64" personal computer and correlation analysis also was carried out. A level of significance of $p < 0.05$ between mean values was accepted. Correlation between events was assessed as strong if the absolute value of the coefficient of correlation (r) ranged between 0.7 and 1.0, average if r was between 0.69 and 0.3, and weak if r was under 0.29. The significance of correlation was determined by Student's test. Confidence limits of r were calculated for 3 degrees of significance (0.05, 0.01, and 0.001).

EXPERIMENTAL RESULTS

After administration of ANF for 7 days to the rats of the basic group its concentration in the plasma was significantly higher (273.5 ± 39 pg/ml) than in the control animals (188.7 ± 16 pg/ml), evidence of an effective supply of ANF from the osmotic minipump into the blood flow.

As regards the effect of ANF on the parameters studied, in the course of the investigation no significant changes were observed in BP_{max}, HR, or body weight in either the control animals or those of the basic group (Fig. 1). No statistically significant changes likewise were observed in the protein, chlorine, and electrolyte concentrations either in single samples of urine or in the total 24-hourly diuresis. The diuresis itself also was unchanged. By the 7th day of injection of ANF, a marked, but not significant ($p > 0.05$) tendency was noted for the creatinine excretion in the 24-hourly urine to decrease.

Correlation analysis of the data (cross correlation between all the parameters studied) gave the following results. Against the background of injection of ANF the confidence limits of correlation were considerably widened (from 116 to 240% compared with the control), and this was observed in 69% of correlated pairs. In 50% of correlated pairs there was a change in the character of correlation (relative to the regression equation), and this was particularly marked in HR—BP_{max}, urinary Na—K (Fig. 2), and urinary K—Cl pairs. In the control animals, significant average correlation ($r = +0.61$; $p < 0.01$) existed between BP_{max} and the diuresis. Against the background of administration of ANF the value of r remained the same but the significance of correlation disappeared, i.e., BP_{max} and diuresis ceased to determine one another. The same was observed in relation to correlation between the Cl concentration and BP_{max}: in the control group $r = +0.94$ ($p < 0.001$), whereas for animals of the basic group $r = -0.28$ (correlation no longer significant).

Histological examination of the kidneys of animals of the basic group showed a significant decrease in the number of unchanged (i.e., without any manifestations of ischemia, exudation, and so on) glomeruli ($p = 0.023$). No significant changes were observed in the plasma levels of renin, K, and Na, or in the hematocrit index after administration of ANF.

The investigation thus showed that chronic permanent administration of ANF for a week to spontaneously hypertensive rats in equivalent to the natural concentration does not affect the parameters of cardiovascular and excretory function which were tested. Evidently a sufficiently stable electrolyte balance was created in the spontaneously hypertensive rats, and the connections between the electrolyte balance and BP are very strong. Against this background, administration of exogenous ANF could not change the established homeostasis, in agreement with views that stable hypertension is a reflection of a new level of regulatory interaction in the body [1].

Meanwhile the results are evidence that administration of exogenous ANF disturbs the stability of the developed system of homeostasis, as is reflected in the much greater scatter of the data, widening of the confidence limits of correlation, and a change in the character of correlation. As a result of this, some parameters, while sufficiently strongly correlating with one another in the control animals, ceased to have a mutually determinant effect after administration of ANF.

Chronic administration of ANF affects the kidneys, as is reflected in a decrease in the number of unchanged glomeruli.

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LIPOXIN B: A FACTOR ENHANCING SPONTANEOUS PLATELET AGGREGATION IN WHOLE BLOOD

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A subject which has recently attracted the attention of research workers is the role of the lipoxygenase metabolites of arachidonic acid (AA) in the regulation of the aggregation state of the blood [4, 9]. It has been shown that 5-hydroxyeicosatetraenoate (5-HETE), if incorporated into phospholipids of endothelial cells, depresses synthesis of prostacycline and prostaglandin E_2 by endotheliocytes [13]. Prostacycline synthesis also is inhibited by 15-hydroperoxyeicosatetraenoate [6]. Leukotrienes C_4, D_4, and E_4 potentiate platelet aggregation and the "platelet factor release reaction" [10], and also potentiate platelet aggregation induced by adrenalin and thrombin [11]. The direct action of lipoxygenase metabolites of arachidonic acid (monohydroperoxy- and monohydroxy-derivatives) on blood clotting has not been established, although it has been shown that they modify eicosanoid metabolism in various tissues and cells, including platelets [5]. Metabolites of arachidonic and eicosapentaenic acid,

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