EFFECT OF A VARIABLE MAGNETIC FIELD ON DEVELOPMENT OF SPONTANEOUS HYPERTENSION IN RATS

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Spontaneous (hereditary) hypertension in Okamoto rats is rightly regarded nowadays as one of the best experimental models of essential hypertension in man. The development of the disease can be studied in these animals from the earliest stages at different age periods, and the effect of various kinds of factors on the degree of elevation of the blood pressure (BP) and on other manifestations of the disease can be investigated. Among the latter particular interest attaches to the effect of geophysical factors, including changes in the magnetic field (MF). It has been shown that exposure of mice to a weak variable MF leads to an increase in succinate dehydrogenase (SDH) activity of the lymphocytes and internal organs, accompanied by a fall in mitochondrial α-glycerophosphate dehydrogenase (GPDH) activity [3]. At the end of exposure a state of simultaneous depression of activity of both dehydrogenases develops for several days, and is reminiscent of the state of histotoxic hypoxia, and lowers the resistance of the animals to infections, toxins, etc. [4, 5]. Clinically, this manifestation of depression of lymphocytic mitochondrial enzymes accompanies myocardial infarction with the severest course [1, 2].

In the investigation described below the effect of changes in MF on the time course of development of spontaneous hypertension was studied in Okamoto rats of different ages. No investigations of this kind have been undertaken previously.

EXPERIMENTAL METHOD

Experiments were carried out on 18 young rats whose mothers had spontaneous hypertension. The pregnant rats and their offspring were kept in a special chamber in which the atmospheric pressure, temperature, and relative humidity were kept constant throughout the experiment. The experimental group consisted of seven young rats, offspring of two mothers kept in an MF for the last 11 days of pregnancy (4 days in MF, an interval of 3 days, followed by 4 days in MF). Newborn rats also were kept in MF from the 5th through the 9th day after birth. Animals of the control group (11 rats) were not exposed to magnetic disturbances. The artificial MF closely resembled in its characteristics the parameters of the geomagnetic field during a period of strong disturbances (frequency 0.1 Hz, amplitude 200-250 G). SDH and GPDH activity of the peripheral blood lymphocytes was determined [6] in experimental and control rats aged 2 weeks by a quantitative cytochemical method. The lymphocyte population was characterized by typical enzyme activity (mean value Q), variation of cells with respect to dehydrogenase activity (coefficient of variation V), balance between pools of cells with high and low enzyme activity (coefficient of asymmetry A), sufficiency of cells with typical (normal for the given population) enzyme activity (coefficient of excess E), and variation among lymphocytes for enzyme activity (relative entropy of information H). The weekly gain in weight of the animals was measured. Starting from the age of 4 weeks and until the end of the experiment BP was measured weekly in the caudal artery of waking rats by means of an automated NK-709 electroplethysmograph ("Natsume," Japan). The animals were decapitated at the age of 3 months. Immediately before decapitation they were weighed, BP was measured, and SDH, GPDH, and lactate dehydrogenase (LDH) activity in the lymphocytes were determined. After decapitation the heart and kidneys were weighed, SDH and GPDH activity

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TABLE 1. Parameters of Population Structure of Lymphocytes for SDH and GPDH Activity in Experimental and Control Rats Aged 2 Weeks (M ± m)

Parameter	Enzyme	Expt.	Control
Typical enzyme activity Q	SDH	10,94±0,88*	8,58±0,33
	GPDH	9,01±0,94*	5,80±0,42
Balance between pools A	SDH	1,28±0,24*	0,67±0,17
	GPDH	0,92±0,15	0,79±0,17
Heterogeneity V	SDH	47,96±2,25	49,87±2,45
	GPDH	53,66±3,17	62,32±4,18
Sufficiency of typical cells E	SDH	2,83±1,12*	—0,09±0,30
	GPDH	1,03±0,53	0,61±0,49
Variation between cells H	SDH	0,719±0,029	0,715±0,012
	GPDH	0,730±0,019	0,667±0,019

Legend. *P < 0.05; Van der Waerden's test.

TABLE 2. Changes in BP in Rats Exposed (I) and Not Exposed (II) to the Action of MF (M ± m)

Age of animals, days	Expt.	Control
28	100,1±7,82	—
35	120,04±9,21*	96,6±4,43
42	142,93±7,54**	109,83±5,10
49	141,40±5,64*	120,52±4,21
56	139,50±4,74	139,50±5,48
63	164,96±3,77	—
70	—	149,77±7,97
93	155,00±5,80	146,82±3,90

Legend. *P < 0.01, Van der Waerden's test; †P < 0.05, Kolmogorov—Smirnov test.

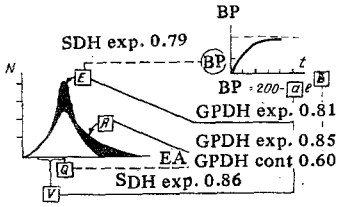

Fig. 1

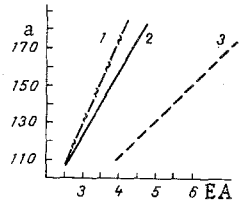

Fig. 2

Fig. 1. Correlation between parameters of population structure of lymphocytes for enzyme activity in young rats aged 2 weeks with constants of rise of BP. EA) Enzyme activity in lymphocytes, BP) BP at 1 month, t) age (in days), e) base of natural logarithms. Continuous lines denote positive correlations, broken lines — negative correlations; numbers of figure indicate values of coefficients of correlation.

Fig. 2. Dependence of constant of rise of BP (a) on GPDH activity of internal organs (in IU.10^{-2}). a) Constant of rise of BP. EA) GPDH activity

$$(1\ \text{IU} = \frac{1\ \text{mole formazan}}{1\ \text{mg protein/min}}\ \text{at } 37°\text{C}).$$

The regression equation is in the form: 1) muscle GPDH = (17.20 + 2.21 a) ± 63; 2) gastric GPDH = (—48.11 + 2.66 a) ± 96; 3) liver GPDH = (181 + 0.16 a) ± 75.

were determined histochemically in the heart, kidney, liver, stomach, and muscle, and LDH activity was determined in the stomach and muscles. Dehydrogenase activity of the internal organs was studied in order to discover the effect of the pathological process on the state (metabolism) of the vital organs and also to obtain a more detailed prognosis for the animal's state. The time course of the rise in diastolic BP in the two experimental groups was described by an asymptotic function, and constants of the curve for each animal were found. The numerical results were subjected to correlation and regression analysis by EC-1022 computer. The significance of differences between the groups was determined by Van der Waerden's and Kolmogorov–Smirnov tests.

EXPERIMENTAL RESULTS

Rats of the experimental group lagged behand the controls in weight from birth. At the age of 2 weeks the rats differed in a number of cytochemical characteristics (Table 1). For instance, the mean SDH and GPDH activity of the experimental animals was higher than that of the controls. A significant difference also was observed between the two experimental groups in the distribution of the lymphocyte population for SDH activity. An excess of cells with typical SDH activity and marked activation of this enzyme in some lymphocyte pools were observed in the experimental animals compared with the controls.

The results of the present experiments show (Table 2) that hypertension developed more rapidly in young rats exposed to the action of magnetic disturbances than in animals not so exposed. The difference in pressure was evident at the age of 42 days.

The time course of the rise in BP was described by the equation $BP = 200 - ae^{bt}$, where BP denotes the actual pressure in the rats, 200 is the upper limit of pressure, t the time (in days) after birth, and a and b are coefficients determined from empirical data for each animal by the method of least squares.

The rise of BP in rats of the different experimental groups is described by the following equations:

$$BP = 200 - 129.591^{-0.02t} \quad \text{with exposure to MF} \tag{1}$$

$$BP = 200 - 222.43e^{-0.02t} \quad \text{(control)} \tag{2}$$

Differences between the constants a in equations (1) and (2) are significant ($P > 0.05$; Van der Waerden's test).

On the basis of the theoretical calculations of the curves it can be postulated that a difference in BP occurs as early as on the first days of life and it disappears by the age of 3 months.

On the basis of enzyme activity of the lymphocytes in rats aged 2 weeks some idea of the rates of development of hypertension may be obtained (Fig. 1).

It is a noteworthy fact that, unlike in the control rats, in the experimental animals the constant a, characterizing the amplitude of pressure, correlates, not with the mean enzyme activity of the lymphocytes, but with the parameters of their distribution. It will be clear from Fig. 1 that the more homogeneous the cells for GPDH activity at the age of 2 weeks, the more rapidly the pathological process develops. Meanwhile the constant a is connected with enzyme activity of the internal organs (Fig. 2). It follows from the regression relationships in Fig. 2 that the higher the GPDH activity in the liver, kidney, and stomach, the higher the value of the constant a.

Analysis of the histochemical data for dehydrogenase activity in the organs showed that levels of SDH activity in the two groups did not differ statistically significantly, but the intensity of functioning of the glycerophosphate shunt in the liver and kidney was lower in the experimental animals than in the controls ($P < 0.05$). It can be tentatively suggested that prolonged exposure of the animals to MF can change the metabolic rate of phospholipids and disturb electron transport from cytosol into mitochondria.

Exposure to MF during intrauterine development thus leads to lasting changes in metabolism of lymphocytes and the internal organs and causes spontanecus hypertension to appear in Okamoto rats. On the basis of cytochemical data at the age of 2 weeks, the prognosis for development of arterial hypertension can be given.

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CHANGES IN β-ADRENORECEPTOR DENSITY IN INTACT LYMPHOCYTES OF HYPERTENSIVE SUBJECTS

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Increased activity of the sympathicoadrenal system is considered to be a trigger mechanism of essential hypertension [4]. The influence of the sympathicoadrenal system of the hemodynamics is exerted through the action of adrenergic mediators and hormones on α- and β-receptors of cells of target organs (heart, blood vessels). More recently, during a study of receptor characteristics of cells of different organs, human peripheral blood lymphocytes have been extensively used as a cell model to reflect the state of the receptors of these cells.

In the case of essential hypertension determination of receptor characteristics of lymphocytes is very important for our understanding of the cellular mechanisms controlling sensitivity to the action of catecholamines and it is of undoubted practical concern.

The aim of this investigation was to determine the density of β-adrenoreceptors of intact lymphocytes from patients with stable essential hypertension and to compare it with that of normal subjects.

EXPERIMENTAL METHOD

A group of patients with stage IIB of essential hypertension (according to the classification in [1]), consisting of 10 men aged from 32 to 44 years, whose diastolic blood pressure (BP) was at or above 110 mm Hg, was chosen for the investigation. For 2 weeks before the tests the patients received no hypotensive drugs including β-blockers. The control group consisted of eight normal men aged from 35 to 42 years (BP below 140/90 mm Hg). Lymphocytes were isolated from heparinized venous blood by centrifugation in a Ficoll–Verografin density gradient [3]. The lymphocyte fraction was washed with phosphate buffer and medium 199 with 0.03% solution of human serum albumin, the erythrocytes were hemolyzed, and the lymphocytes were finally freed from platelets and cell fragments by washing on a column with buffer con-

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