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EFFECT OF FUSARIC ACID ON PHOSPHOINOSITIDE METABOLISM OF ERYTHROCYTE MEMBRANES OF SPONTANEOUSLY HYPERTENSIVE RATS

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A factor which accompanies hypertensive states is high activity of the sympathicoadrenal system, as is shown by the fall of arterial pressure (BP) of hypertensive rats in response to injections of antisympathetic drugs or to immunologic "sympathectomy" [3]. One substance which lowers the level of mediators of the sympathicoadrenal system is fusaric acid (FA, 5-butylpicolinic acid), which was discovered by screening products of fungal metabolism [4]. FA inhibits activity of the enzyme dopamine-β-hydroxylase, which catalyzes the conversion of dopamine into noradrenalin. It lowers the concentrations of noradrenalin and adrenalin in the body tissues and depresses BP both in chronic experiments and after injection of a single dose [5, 8]. Spontaneously hypertensive rats (SHR), whose pathology is evidently determined by a genetic defect of permeability of the tissue plasma membranes for ions [7], are used as a model of human essential hypertension.

Di- and triphosphoinositides (DPI and TPI, respectively: phosphatidyl-myo-inositol-4-phosphate and phosphatidyl-myo-inositol-4,5-diphosphate) participate in regulation of plasma membrane permeability for ions and in the mechanism of activation of cells under the influence of Ca^{++}-mobilizing hormones on plasma membrane receptors [1, 2].

The aim of this investigation was to study the effect of FA on metabolism of TPI, DPI, and monophosphoinositides (MPI, phosphatidyl-myo-inositol) of erythrocyte membranes of SHR of different ages.

EXPERIMENTAL METHOD

Male SHR aged 2 and 4 months were used: These animals are characterized by labile (BP 160/95 mm Hg) and stable (205/130 mm Hg) forms of hypertension respectively. The control group for comparison consisted of normotensive Wistar rats (NWR) of the same age and sex (BP 125/70 mm Hg). FA was injected subcutaneously (50 mg/kg) 150 min before subcutaneous injection of ^{32}P-orthophosphate (^{32}P-OP) without a carrier (74 MBq/kg body weight). The rats were decapitated 90 min after injection of ^{32}P-OP, and 5 min later the native erythro-

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cytes were extracted for isolation of lipids. The procedures of isolation, chromatographic fractionation, and quantitative analysis of the individual fractions of the phosphoinositides were described in detail previously [6]. The lipid concentration was expressed in nanomoles/ml of native erythrocytes. The rate of incorporation of ^{32}P-OP was expressed in the form of relative specific radioactive (RSR), the ratio of specific radioactivity (in cpm/nmole) of each phosphoinositide fraction to the specific radioactivity of inorganic phosphate of the erythrocytes, multiplied by 100.

EXPERIMENTAL RESULTS

Data showing changes in phosphoinositide metabolism in erythrocyte membranes of SHR under the influence of FA, compared with the corresponding values of NWR, are given below. With increase of age, the severity of the hypertension in the SHR increased. In the present experiments a decrease in concentrations of DPI and TPI and an increase in the rate of turnover of these fractions were observed in SHR, by comparison with NWR (the difference was significant at the age of 4 months). Changes in MPI metabolism were not significant.

After injection of FA in a dose of 25-50 mg/kg into SHR, their BP fell sharply during the first hour, virtually to the normal level, after which it continued to normalize slowly for 4 h, but after 6 h it began to return gradually to its original level [5]. Under the influence of FA changes took place in metabolism of DPI and, in particular, of TPI. No marked changes in MPI metabolism were observed. FA caused a significant increase in concentrations of DPI and TPI in erythrocyte membranes of SHR aged 4 months and a decrease in the turnover rate of TPI (with a tendency for the DPI level to fall) in SHR aged 2 and 4 months. Changes in metabolism of the phosphoinositide fractions of erythrocyte membranes in SHR under the influence of FA were in the direction of normalization, and their parameters became close in value to those of NWR of the same age. The most marked changes of metabolism were observed when differences from normal were greatest (TPI, animals aged 4 months).

Thus, under the influence of FA normalization takes place not only of activity of the sympathicoadrenal system and BP in spontaneously hypertensive rats, but also of the phosphoinositide metabolism of their erythrocyte membranes, with respect both to their concentrations and their turnover rates.

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