Pharmacological Correction of Changes in the Lung—Placenta System under Experimental Conditions

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 140, No. 8, pp. 169-172, August, 2005
Original article submitted March 21, 2005

Pathological changes in the fetoplacental complex and lung—placenta system were observed in rats with experimental gestosis produced by long-term feeding of a high-sodium diet. We revealed a decrease in the weights of the placenta and fetus, pulmonary fibrinolytic dysfunction, and increased production of cortisol. The course of fraxiparine treatment in animals with experimental gestosis decreased coagulation activity of the arterial blood, increased the weights of the placenta and fetus, and reduced the concentration of stress hormone cortisol.

Key Words: *fetoplacental complex; lungs; experimental gestosis; fraxiparine*

Variations in the concentration of hormones in the maternal blood play a key role in the modulation of metabolic and immune systems responsible for prolongation of pregnancy and delivery. High progesterone concentration determines the development of immunological tolerance in pregnancy. Similarly to human chorionic gonadotropin and cortisol, progesterone suppresses T lymphocyte-mediated immune reactions and provides immunological tolerance of the embryo and placenta [9]. Cortisol is also involved in the adaptive response to stress [8]. Previous studies showed that the lungs play a role in the maintenance of blood hormone level and provides the relationship between cortisol production, state of the placenta, and coagulation activity [4]. Some authors reported that the lungs operate as a coagulolytic filter, which decreases the hemostatic potential and increases fibrinolytic activity of the blood [6,10]. The lungs regulate transfer of hormones in the pulmonary circulation and, therefore, modulate their concentration in the effluent blood [2]. Maternal hemostasis is affected by the fetoplacental complex. The blood circulating in the intervillous space does not coagulate due to activity of the placental thrombolytic system [3]. Adaptive dysfunction in pregnancy complicated by gestosis or chronic fetoplacental insufficiency includes significant changes in the lung—placenta system.

Here we studied the possibility of pharmacological correction of changes in the lung—placenta system of rats with experimental gestosis.

MATERIALS AND METHODS

Experiments were performed on pregnant albino rats weighing 170-190 g. The animals were quarantined for 4 days and then were randomly divided into 4 groups (7 rats per group). Control group 1 included intact rats with uncomplicated pregnancy. Control group 2 included animals with uncomplicated pregnancy receiving intracutaneous injections of fraxiparine in a daily dose of 100 U/kg over 7 days starting from the 16th day of gestation. Experimental group 1 included rats with gestosis receiving no pharmacological correction. Experimental group 2 included animals with

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0007-4888/05/1402-0201

gestosis receiving intracutaneous injections of fraxiparine (similarly to rats of control group 2). Experimental gestosis was produced by feeding a high-salt diet starting from day 7 of pregnancy [7]. The concentration of NaCl in drinking water was 1.8%. Pathological signs of experimental gestosis were similar to those observed in clinical practice (hypertension, activation of the renin-angiotensin system, reduction of uteroplacental blood flow, and fetal growth retardation). The samples were obtained as described elsewhere [5]. The data were processed by means of Statistica 5.5A software. The significance of differences and correlation indexes were estimated by parametric (Student's *t* test) and nonparametric tests (Spearman and Wilcoxon tests).

RESULTS

Plasma Na^+ concentration in rats of control group 1 was 140.0±1.0 mmol/liter. By the end of pregnancy Na^+ concentration in animals of experimental groups 1 and 2 increased by 11 and 5.7%, respectively, compared to the control. Na^+ concentration in rats of experimental group 2 was much lower than in animals of experimental group 1. Pharmacological correction with fraxiparine increased the weights of the placenta and fetus at birth by 5.1 and 5.2%, respectively, compared to rats with experimental gestosis (Fig. 1). The course of fraxiparine treatment relieved symptoms of hypernatremia, syndrome of fetal growth retardation, and decrease in the weight of the placenta (Fig. 1).

Feeding of a high-sodium diet contributed to hypercoagulation in pregnant rats. By the end of pregnancy the clotting time of arterial and venous blood decreased by 12 and 5%, respectively, compared to the control. Fibrinogen concentration in the arterial blood increased by 13% compared to rats with uncomplicated pregnancy. Antithrombin III deficiency was observed in the arterial and venous blood (decrease by 12 and 13%, respectively, compared to the control).

Chronic hypernatremia causes not only fetal growth retardation and change in homeostasis toward hypercoagulation, but also hormonal imbalance in the lung—placenta system. Progesterone production by the placenta in rats with experimental gestosis decreased by 20% compared to the control (Table 1). The arteriovenous difference (AVD) in progesterone concentra-

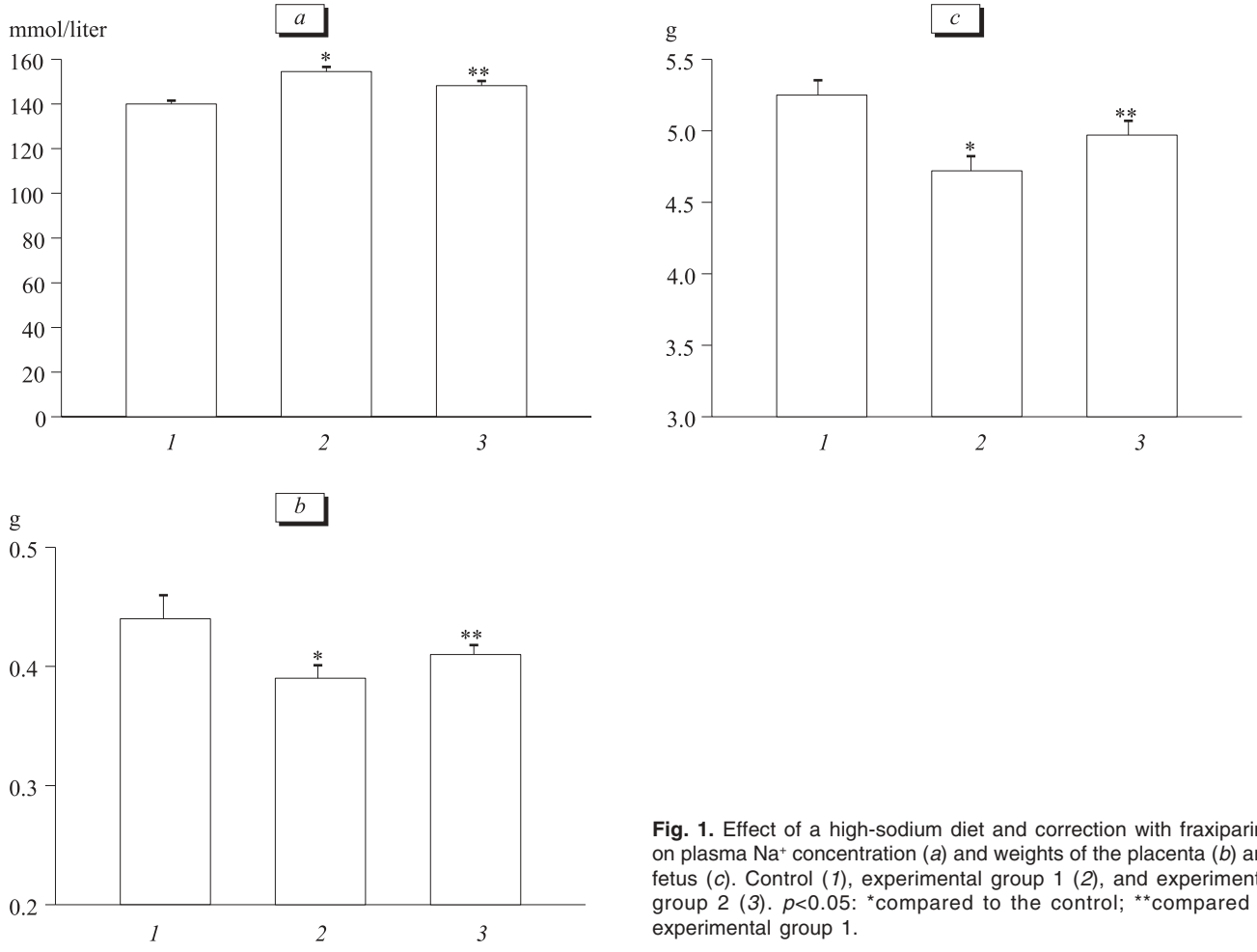

Fig. 1. Effect of a high-sodium diet and correction with fraxiparine on plasma Na^+ concentration (*a*) and weights of the placenta (*b*) and fetus (*c*). Control (*1*), experimental group 1 (*2*), and experimental group 2 (*3*). $p<0.05$: *compared to the control; **compared to experimental group 1.

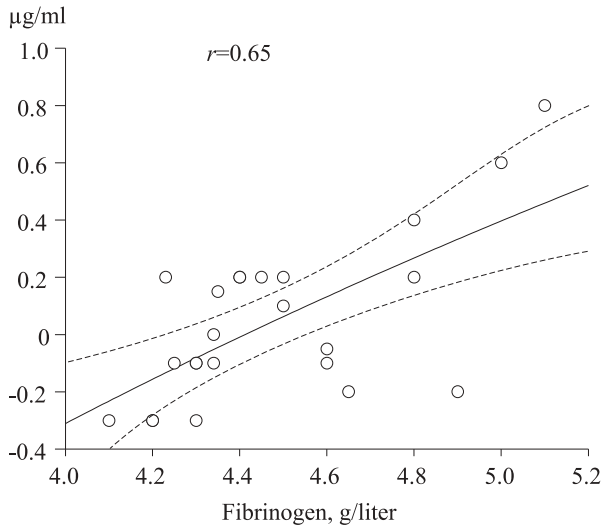

Fig. 2. Correlation between fibrinogen concentration in the arterial blood and arteriovenous difference in cortisol concentration (p<0.001).

tion was positive in most rats, which suggests the release of this hormone from the lungs. A positive value of AVD was revealed in 72% animals with physiological pregnancy and 100% animals with experimental gestosis.

Administration of fraxiparine suppressed progesterone production in control animals and rats with experimental gestosis (by 3 and 8%, respectively). AVD in progesterone concentration remained positive. Cortisol concentration in rats with uncomplicated pregnancy was 2.8±0.1 μg/ml. In animals with experimental gestosis cortisol concentration increased by 32% and reached 3.7±0.2 μg/ml (p<0.05). AVD in cortisol concentration in control and experimental rats remained positive. It should be emphasized that AVD in cortisol concentration in rats with experimental gestosis was higher than in animals with physiological pregnancy (0.3±0.2 and 0.07±0.04 μg/ml, respectively). These changes illustrate intensive release of cortisol from the lungs upon treatment with NaCl.

Administration of fraxiparine was followed by a decrease in cortisol concentration in the arterial blood from control rats and animals with experimental gestosis (by 4 and 5.5%, respectively). Fraxiparine treatment changed the sign of AVD in cortisol concentration in some animals. AVD was negative in 70% rats of control group 2 (-0.07±0.07) and experimental group 2 (-0.1±0.1). Our findings suggest that predominant accumulation of cortisol in the lungs contributes to the decrease in blood hormone concentration after fraxiparine administration.

Blood cortisol concentration and hormone-regulating function of the lungs are associated with changes in coagulation activity of the blood. A positive correlation was revealed between fibrinogen concentration in the arterial blood and AVD in cortisol concentration (r=0.65, p<0.001, Fig. 2). The clotting time of arterial blood negatively correlated with AVD in cortisol concentration (r=-0.44, p<0.05). Administration of fraxiparine is accompanied by hypercoagulation (lengthening of clotting time and decrease in fibrinogen concentration in the arterial blood flowing from the lungs) and decrease in AVD in cortisol concentration. It illustrates predominant accumulation of cortisol in the lungs.

Our results show that correction of changes in the lung—placenta system with fraxiparine is accompanied by a decrease in the concentration of stress hormone cortisol. These changes reflect recovery of the fetoplacental function and decrease in the severity of fetal hypoxia. Fraxiparine treatment decreased AVD in cortisol concentration to normal. Fraxiparine possesses antiaggregant and antiX_a activity and breaks the cascade mechanism of blood coagulation at the stage of thrombin formation. Fraxiparine has the most significant effect on the arterial blood circulating in the intervillous space of the placenta. The improvement of rheological characteristics in the placental area contributes to recovery of the transport and nutritive functions of the placenta, which corrects fetal hypoxia and

TABLE 1. Concentration of Hormones and Hormone-Regulating Function of the Lungs in Rats with Uncomplicated Pregnancy and Experimental Gestosis (n=7, M±m)

Parameter		Control group		Experimental group	
		1	2	1	2
Plasma Na^+ concentration, mmol/liter		140.00±1.08	140.00±2.44	154.50±1.93$^+$	148.25±2.32^o
Progesterone, μg/ml	artery	3.05±0.16	2.97±0.14	2.47±0.05$^+$	2.20±0.04^o
	vein	2.84±0.24	2.69±0.21	2.27±0.11$^+$	1.90±0.04*
Cortisol, μg/ml	artery	2.82±0.15	2.70±0.14	3.77±0.23$^+$	3.50±0.14^o
	vein	2.75±0.14	2.78±0.15	3.40±0.08*	3.60±0.14

Note. p<0.05: *compared to the artery; $^+$compared to the control group; ^{o}compared to group 1.

hypotrophy and increases the weights of the fetus and placenta. It should be emphasized that administration of fraxiparine did not normalize progesterone synthesis by the placenta. Progesterone concentration in rats of experimental group 2 remained low and did not differ from that in animals of experimental group 1.

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