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EFFECT OF PHENFORMIN ON FETAL WEIGHT IN RATS PREVIOUSLY IMMUNIZED WITH HOMOLOGOUS THYROID GLAND TISSUE EXTRACT

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It was shown previously that the weight of fetuses of rats immunized at certain times before pregnancy with heterologous or homologous thyroid antigens is above the average value for this parameter in normal pregnant rats [4]. In rats immunized with homologous thyroid antigens, 2-6 weeks after the end of immunization lowering of the glucose tolerance, hyperplasia followed by hypertrophy of the islets of Langerhans in the pancreas, and moderate hyperinsulinemia with a blood insulin concentration 30-40% higher than initially [5] were observed (more marked hyperinsulinemia - a blood insulin level 100-400% higher than initially - was observed in rabbits immunized with thyroglobulin [11]). Injection of the antidiabetic biguanide phenformin during immunization of the rats and for 2-4 weeks thereafter abolished the disturbance of glucose tolerance and the hyperinsulinemia [5].

In the investigation described below the weight of the fetuses was determined in rats immunized with thyroid antigen and simultaneously treated with phenformin in order to determine whether the macrosomia of fetuses in animals subjected to this treatment can be prevented.

EXPERIMENTAL METHOD

Experiments were carried out on female rats from the Rappolovo nursery. The animals were immunized 4 times, at intervals of 1 week, with homologous thyroid antigen [4, 5, 9], divided into two groups: the rats of group 1, starting from the 1st day of immunization and until the 30th day after its end, received phenformin perorally by means of a tube in a dose of 7.5 mg in 1 ml water; the rats of group 2 received the same volume of water. The animals of group 3 were not immunized, but in the course of the experiment they were given 1 ml of water perorally by means of a tube. Mating of the animals began 1.5-2 months after the end of immunization (2-4 weeks after the end of administration of phenformin). The dating of the beginning of pregnancy and the weighing of the fetuses and placenta, removed 21.5 days (516 h) after that moment, were carried out as described previously [2]. The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

Preliminary immunization of the rats with homologous thyroid antigen led to a subsequent increase in the mean weight of the fetuses compared with those of normal pregnant rats (Table 1). Administration of phenformin during immunization and for 30 days after its end led to a significant decrease in the mean weight of the fetuses. No significant differences were observed in the increase in body weight during pregnancy and the weight of the placentas between the groups compared (Table 1). Phenformin had virtually no effect on the weight of the fetuses of the rats if the interval between the end of immunization and parturition was short (12 weeks) and it increased with an increase in the length of that interval (Fig. 1).

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TABLE 1. Effect of Phenformin on Weight of Fetuses of Rats Previously (9-27 weeks before parturition) Immunized with Thyroid Antigen

Group	Interval between end of immunization and parturition, weeks	Increase in body weight of mothers during pregnancy, g	Weight of placenta, mg	Weight of fetuses, g	P (for weight of fetuses)
1	16,1±1,7 (14)	81±5 (14)	749±108 (90)	5,40±0,05 (90)	$P_{1,2} < 0,01$ $P_{2,3} < 0,02$
2	15,2±1,4 (18)	77±4 (18)	808±40 (124)	5,19±0,03 (124)	
3	—	90±6 (14)	721±42 (109)	5,05±0,05 (109)	—

Legend. Number of rats, fetuses, and placentas shown in parentheses.

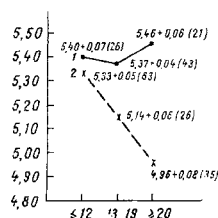


Fig. 1. Dependence of effect of phenformin on weight of fetuses of pregnant rats on interval between end of immunization and parturition: 1) immunization; 2) immunization + phenformin. Abscissa, interval between parturition and end of immunization (in weeks); ordinate, weight of fetuses (in g). Number of fetuses studied given in parentheses.

In children with autoimmune thyroiditis disturbances of carbohydrate metabolism of the diabetes or prediabetes type are not infrequently found [13], and the frequency of appearance of antithyroid antibodies in the blood in the prepubertal period reaches 1-2.3% (according to clinical observations) in the healthy population [10, 12]. These observations, combined with corresponding experimental data, indicating the development of hyperinsulinemia, lowering of the glucose tolerance, and hypertrophy and hyperplasia of the islets of Langerhans in rabbits and rats immunized with thyroid antigen [4, 5, 11], suggested that autoimmune damage to the thyroid gland during childhood and youth could be one possible cause, arising even before the beginning of pregnancy, of the birth of large fetuses [4, 5]. Since it had been shown previously that the antidiabetic biguanide phenformin does not affect the weight of the fetuses in normal pregnant rats [2], but reduces [3] the weight of the fetuses in rats with transient alloxan diabetes, characterized by a tendency to give birth to large fetuses [1], it must be assumed that the effect of the drug found in the present investigation (Table 1) is linked with its normalizing effect on the glucose tolerance and insulin secretion of animals immunized with thyroid antigen [5]*.

The tendency toward birth of fetuses with a mean weight higher than that in control animals was found to be preserved in rats immunized with homologous thyroid antigen at least 5-6 months after the end of immuni-

*Under these circumstances phenformin did not affect the titer of antithyroid antibodies or the character of the morphological changes in the thyroid gland, and it thus weakened the development only of secondary pathological disturbances in the endocrine system [5].

zation (Fig. 1). If these data can be extrapolated to the reproductive period of life in women, calculations show that the metabolic effect of pubertal autoimmune disturbances in the thyroid gland on the outcome of pregnancy may last for 15-20 years. Meanwhile the effect of phenformin on the weight of the fetuses was manifested only in animals with a sufficiently long interval between the last injection of antigen and parturition (Fig. 1). Although the reason for this "delayed" effect of the drug requires further study, it must be supposed that the early prophylactic use of phenformin (a drug widely used to control various manifestations of diseases of compensation [6, 8]), and also of other drugs and dietary measures with a similar effect, in patients with pubertal autoimmune damage to the thyroid gland may prove useful for preventing the development of hormonal-metabolic disorders during pregnancy and may thereby help to reduce the risk of subsequent development of certain endocrine and oncologic diseases [7].

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