PHARMACOLOGY AND TOXICOLOGY

Congenital Hemineurin Diabetes in Rats

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Intragastral administration of hemineurin in a daily dose of 60 mg/kg for 70 days suppresses insulin secretion by the pancreas, increases glucose and lipid blood levels, and decreases glucose tolerance in female rats. Adult progeny of these females mated with intact males develops increased insulinemic reaction to glucose and glucose intolerance. The progeny of rats administered hemineurin in the same dose on days 11-19 of pregnancy develops latent dysfunction of β-cells manifesting itself after alimentary carbohydrate loading.

Key Words: *congenital diabetes mellitus; hemineurin*

Drugs which in addition to their specific effects suppress the pancreatic β-cell function are widely used in clinical practice [3,11]. The probability of inducing congenital diabetes mellitus by these drugs has not been studied. Previously, we showed that the progeny of female rats fed the diabetogenic agent verapamil before pregnancy developed hyperlipidemia and increased insulinemic reaction to glucose [5]. We failed to find any other reports on this problem.

Our aim was to assess the probability of congenital diabetes in the progeny of female rats administered hemineurin (synonyms: clomethiazole, hemithiamine; chemical name: 5-(2-chloroethyl)-4-methylthiazole ethanedisulfonate), an anticonvulsive and sedative drug exerting a diabetogenic effect.

MATERIALS AND METHODS

Experiments were carried out on 70 outbred albino rats weighing 180-200 g bred at the *Kryukovo* Breeding Center in the Moscow Region.

The rats were kept 10 per cage at 21-22°C and standard 12-h light regimen in standard 2145 cm^2 cages. Rats with normal glucose levels, normal values of the oral glucose tolerance test, and normal estral cycle were used.

Two series of experiments were carried out. In the first series, hemineurin was administered to females in a daily dose of 60 mg/kg intragastrally for 70 days (2% starch emulsion, 1 ml per 100 g); controls were fed the same volume of starch gel. One day after the last administration, experimental and control females were mated to intact males. In the second series, hemineurin in the same dose was administered to pregnant rats from day 11 to day 19 of gestation.

Carbohydrate and lipid metabolism and insulin-secretory function of the pancreas were assessed 2 h after the last administration of hemineurin. The progeny was examined at the age of 2-6 months. In order to detect the probable latent dysfunction of β cells in the progeny of experimental and control rats, carbohydrate loading was added to the ration of adult animals [7]: 40% glucose solution (4 g/kg, 1 ml per 100 g intragastrally, every day for 6 weeks). These rats were examined no earlier than 15 days after glucose was discontinued. The level of glycemia was assessed, glucose tolerance was studied by the oral glucose tolerance test, total cholesterol (CS) and triglycerides (TG) were measured in the serum, and basal serum immunoreactive insulin (IRI) was mea-

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sured 30 min after glucose loading. The animals were not fed 18 h before the test. During oral glucose tolerance test, 40% glucose solution was administered intragastrally in a dose of 4 mg/kg, and blood was collected from the tail vein (0.1 ml). For measuring CS, TG, and IRI, blood was collected from the sublingual vein. Glucose level was assessed using o-toluidine, CS was measured by the method of Ilca, and TG by the acetylacetone method. IRI was assayed by the commercial RIA kits manufactured by the Byelorussian Academy of Sciences.

The results were statistically processed by standard methods, the differences were considered significant at a probability level of at least 95%.

RESULTS

Table 1 shows that prolonged intake of hemineurin induced an increase in blood glucose level and a decrease in glucose tolerance. Blood CS level increased 17%, TG increased 30-50%, and the secretory response of β cells to glucose stimulation was suppressed (Table 2).

At the age of 2.5-6 months the females but not males from the offspring of these rats showed a slight increase in blood glucose level, decrease in glucose tolerance (Fig. 1), and enhanced insulinemic reaction to glucose loading (Table 3).

Both males and females from the offspring of mothers fed hemineurin during pregnancy, which were fed carbohydrate-rich rations (but not standard diets), had increased basal IRI levels and more pronounced insulinemic reaction to glucose in adult age (Fig. 2).

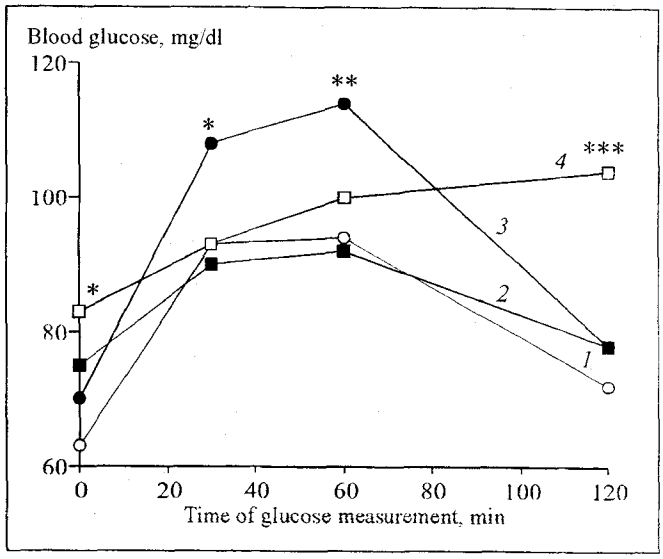

Fig. 1. Glycemia level and oral glucose tolerance test values in rats aged 2.5 and 6 months born to mothers administered hemineurin before pregnancy. *1*) control (2.5 months, n=10); *2*) control (6 months, n=10); *3*) experiment (2.5 months, n=9); *4*) experiment (6 months, n=10). *p<0.01, **p<0.02, ***p<0.001 *vs.* the relevant control.

These results indicate that adult females from the progeny of mothers with hemineurin-induced diabetogenic disorders before mating develop symptoms of relative insulin insufficiency: hyperactivity of β cells and glucose intolerance. Similar changes in the

TABLE 1. Level of Glycemia and Oral Glucose Tolerance Test in Female Rats Treated with Hemineurin ($M\pm m$, n=7-10)

Group	Duration of treatment, days	Blood glucose levels (mg/dl) after glucose loading, min			
		0	30	60	120
Control	—	67.1±2.1	107.1±4.6	126.2±4.6	70.9±3.3
Experiment	30	74.2±2.1*	120.8±2.8*	124.6±4.1	72.5±1.6
Control	—	63.2±1.6	99.4±4.4	83.2±4.5	71.6±2.1
Experiment	70	77.3±3.4*	110.3±11.5	84.0±3.2	87.2±4.1*

Note. Here and in Tables 2 and 3: asterisk indicates values significantly different from the control.

TABLE 2. Pancreatic Insulin Secretion and Serum Lipid Level in Female Rats Fed Hemineurin ($M\pm m$, n=8-11)

Group	Duration of treatment, days	Serum IRI level (μU/ml) after glucose loading, min		Serum lipid level, mg/dl	
		0	30	CS	TG
Control	—	21.7±2.6	132.3±17.9	—	46.3±1.7
Experiment	30	18.7±3.7	31.1±4.1*	—	71.0±6.6*
Control	—	40.8±7.3	131.1±16.9	84.3±2.1	66.9±7.8
Experiment	70	35.3±3.7	57.2±7.4*	97.3±2.7*	86.8±5.0*

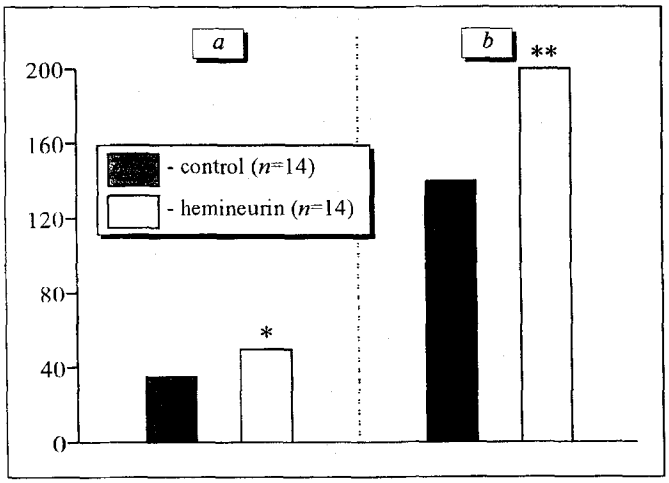

Fig. 2. Pancreatic insulin secretion in females and males born to mothers treated with hemineurin during pregnancy (carbohydrate loading in addition to the ration). Ordinate: serum immunoreactive insulin (IRI) level, μU/ml. *a*) basal IRI level; *b*) 30 min after glucose loading. *$p<0.02$, **$p<0.01$ *vs.* the control.

TABLE 3. Pancreatic Insulin Secretion in Females Born to Mothers Treated with Hemineurin before Pregnancy (*M±m*, *n*=8-12)

Group of animals	Age, months	Serum IRI level (mU/ml) after glucose loading, min	
		0	30
Control	2.5	10.9±2.3	35.1±5.1
Experiment	2.5	21.8±2.7*	81.4±16.2*
Control	6	26.2±2.7	44.9±4.1
Experiment	6	27.0±3.6	61.8±5.4*

insular system function were detected in the females from the progeny of mothers fed verapamil before pregnancy [5]. These data indicate that administration of drugs suppressing the function of β cells to females immediately before pregnancy can cause congenital diabetes in the progeny.

Studies using the model of "chemical diabetes" revealed increased activity of the insular system paralleled by disorders of carbohydrate metabolism in the offspring of female rats with streptozotocin- and alloxan-induced diabetes; these disorders augment in every subsequent generation, and eventuate in the development of severe diabetes [2,9,12]. The majority of researchers believe that the effects of impaired metabolism in the mother on fetal systems regulating carbohydrate metabolism play the crucial role in the development of insular system hyperactivity in the progeny of diabetogenic mothers [1,4,10].

Our findings indicate that the symptoms of congenital diabetes are manifested only in females but not in males born to mothers administered diabetogenic drugs before pregnancy. Similar sex differences were observed in the progeny of female rats with chemical diabetes [8,12].

There were no sex-specific differences in the pancreatic insulin production in the progeny of rats treated with hemineurin during pregnancy: latent disorders of this function were revealed both in males and females. Obviously, during pregnancy diabetogenic drugs damage the fetal β cells.

The results of this study and our previous data on the development of congenital dysfunction of the pituitary-gonadal system under the action of piracetam [6] prove the necessity of studying the relationship between drug effects and congenital dysfunctions of the endocrine system.

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