Prolactin has been claimed to be diabetogenic, because hyperprolactinemia is associated with decreased insulin binding in vitro and insulin resistance in vivo (4). The above mentioned statement is based on the findings obtained in human patients suffering from severe hyperprolactinemia. Cincotta and Meier (1) suggested that prolactin has a permissive role in supporting the hepatic lipogenic activities of insulin and that bromocriptine, a dopaminergic agonist which inhibits prolactin secretion, can be used to reduce lipogenesis. When the prolactin is applied in the bromocriptine treated animals, hypolipidemic effect of bromocriptine is missing. Thus the above mentioned authors claimed the permissive role of prolactin in the lipid metabolism.

In our previous paper (2) we documented that terguride, i.e., dopaminergic agonist is potent to alleviate hyperlipidemia in obese and lean genetically hypertensive Koletsky rats. There remained to be solved the possible role of prolactin in the mentioned alleviation. It is a subject of the recent paper.

Material and methods

Experiments were performed in obese and lean genetically hypertensive rats of Koletsky type (3) of both sexes and in males and females rats of Wistar strain. Lean Koletsky SHR rats represent dominant non-obese homozygotes and heterozygotes whereas their obese siblings are recessive homozygotes. The abnormal animals were obtained by Koletsky (3) when mating spontaneously hypertensive rat (Okamoto -Aoki strain) with normotensive Sprague-Dawley male rat. The genetically obese animals appeared after several generations of selective inbreeding of hypertensive offsprings of the original cross.

After weaning at the age of 30 days the animals were kept in groups of four and supplied with water and ST-1pelleted diet ad libitum.

Plasma insulin

Plasma insulin was determined by radioimmunoassay.

Plasma prolactin

Plasma prolactin was determined by radioimmunoassay using rat prolactin for standard curve and aspecific antibody to rat prolactin.

Plasma lipids

Blood sampled by cardiac puncture (in light ether anesthesia at 7.00 after 14 h starvation) was centrifugated and the serum was stored in plastic tubes at -20 °C. Total plasma cholesterol and plasma triglycerides were determined enzymatically by Hitachi analyzer.
Glucose tolerance

Blood was sampled to heparinized capillaries (from retrolbulbar plexus under light ether anesthesia) before glucose loading (basal glycemia) as well as 30.60,120 and 180 min after glucose loading. Glucose (3g/kg b.w., 30% solution) was applied intragastrically after 14h starvation. Glycemia was analysed enzymatically (Oxochrom glucose, Lachema). Glycose tolerance was expressed as a sum of glycemia obtained 30, 60, 120 and 180 min after glucose loading (area under the glucose tolerance curve).

Teruguride treatment

The drug was applied i.p. in two doses (7:00 and 14:00) for 21 days (when lipemia was investigated) or for 11 days only (when glucose tolerance was monitored).

Teruguride maleate was administered at a dose of 0.1mg/kg.

Statistics

Two correlation computations were used, i.e., Spearman non-parametric and Pearson parametric one.

Results

Considering prolactin in the control animals strain dependence is apparent, i.e., SHR lean rats show higher plasma prolactin than rats of Wistar strain. When comparing the obese and lean Koletsy SHR rats no differences in prolactinemia were found.

Statistically significant hyperprolactinemic effect of teruguride is obvious in all groups of rats except normotensive females.

Considering the total plasma cholesterol in controls (Table 2) sex dependence is obvious in lean as well as in obese Koletsy rats, elevation in is females. Strain dependence is apparent between normotensive and lean Koletsy females in the last mentioned rats there is increase.

Taking into account the effect of teruguride on the total plasma cholesterol sex dependence is expressed, i.e., teruguride decreases cholesterol in females of both strains and substrains of rats.

When we consider plasma triglycerides, strain dependence is obvious (Table 3). Thus lean Koletsy rats of both sexes show higher triglycerides than the rats of Wistar strain and at the same time they show lower triglycerides than obese Koletsy rats of both sexes. Sex dependence in triglycerides is not expressed.

Considering the insulinemia in the control animals sex dependence is apparent in normotensive Wistar rats, insulinaemia being higher in females. Teruguride alleviates triglycerides only in the obese females.

We noted no relationship between prolactinemia and plasma triglycerides is not expressed.

We noted no relationship between prolactinemia and plasma triglycerides is not expressed.
Glucose tolerance
Blood was sampled to heparinized capillaries (from retrolubular plexus under light ether anesthesia) before glucose loading (basal glycemia) as well as at 30,60,120 and 180 min after glucose loading. Glucose (3g/kg b.w. 30% solution) was injected intragastrically after 14h starvation. Glycemia was analyzed enzymatically (Oxochrom glucose, Lachema). Glucose tolerance was expressed as a sum of glycemia obtained 30,60,120 and 180 min after glucose loading (area under the glucose tolerance curve). 

Terguride treatment
The drug was applied i.p. to two groups (7.00 and 14.00) for 21 days (when lipemia was investigated) or for 11 days only (when glucose tolerance was monitored). Terguride maleate was administered at a dose of 0.1mg/kg.

Statistics
Two correlation computation methods were used, i.e., Spearman non-parametric and Pearson parametric one.

Results
Considering prolactin in the control animals strain dependence is apparent, i.e., SHR lean rats show higher plasma prolactin than rats of Wistar strain. When comparing the obese and lean Koletsky SHR rats no differences in prolactinemia were found.

Profound sex dependence in prolactinemia was found in lean as well as in obese Koletsky rats, hyperprolactinemia being elevated in females. Statistically significant hypoprolactinemic effort of terguride is obvious in all groups of rats except normotensive females.

Considering the total plasma cholesterol in controls (Table 2) sex dependence is obvious in lean as well as in obese Koletsky rats, elevation in is females. Strain dependence is apparent between normotensive and lean Koletsky females in the last mentioned rats there is increase. Taking into account the effort of terguride on the total plasma cholesterol sex dependence is expressed, i.e., terguride decreases in females of both strains and substraits of rats.

When we consider plasma triglycerides, strain dependence is obvious (Table 3). Thus lean Koletsky rats of both sexes show higher triglycerides than the rats of Wistar strain, and in the same time they show lower triglycerides than obese Koletsky rats of both sexes. Sex dependence in triglycerides is not expressed.

Terguride alleviates triglycerides only in the obese female of Koletsky rats. Considering control animals in the results of glucose tolerance test, strain dependence is apparent, obese of both sexes show elevated glucose intolerance. Terguride alleviates glucose intolerance in both substrains. But there is a substrain dependence. While in obese rats decrease of the area under the curve represents 44% in both sexes, then in lean Koletsky rats this decrease is represented by 10% (males) or 11% (females).

Table 1: Plasma prolactin effect of long lasting terguride treatment

| Group      | Control | Terguride | Pc |
|------------|---------|-----------|----|
| SHR-M      | 5.64±1.36 | 2.01±1.36 | 0.05 |
| SHR-F      | 2.79±1.76 | 1.91±1.18 | 0.2 |
| SHR-O-F    | 3.71±1.67 | 1.64±0.59 | 0.01 |
| SHR-O-M    | 3.94±2.43 | 0.38±1.24 | 0.02 |
| SHR-O-G    | 1.71±0.35 | 2.72±1.02 | 0.06 |
| SHR-O-F    | 4.61±0.52 | 2.52±1.28 | 0.01 |

Table 2: Total plasma cholesterol: effect of long lasting terguride treatment

| Group      | Control | Terguride | Pc |
|------------|---------|-----------|----|
| SHR-M      | 1.64±0.28 | 1.60±0.21 | 0.05 |
| SHR-F      | 1.79±0.36 | 1.54±0.16 | 0.01 |
| SHR-M      | 1.80±0.16 | 1.84±0.13 | 0.1 |
| SHR-F      | 2.40±0.25 | 1.99±0.25 | 0.05 |
| SHR-O-F    | 2.10±0.37 | 2.39±0.55 | 0.01 |
| SHR-O-G    | 2.56±0.26 | 2.24±0.30 | 0.05 |

Table 3: Plasma triglycerides: effect of long lasting terguride treatment

| Group      | Control | Terguride | Pc |
|------------|---------|-----------|----|
| SHR-M      | 0.59±0.07 | 0.73±0.18 | n.s. |
| SHR-F      | 0.62±0.08 | 0.68±0.12 | n.s. |
| SHR-M      | 0.89±0.15 | 0.80±0.03 | n.s. |
| SHR-F      | 0.96±0.17 | 0.79±0.15 | 0.05 |
| SHR-O-F    | 3.51±0.20 | 4.01±1.79 | 0.05 |
| SHR-O-G    | 3.72±0.30 | 2.81±0.48 | 0.05 |

Discussion
Cincotta and Meyer (1) were the first who directed the attention to the relationship between prolactin and lipid metabolism. They described the fat reducing effect of bromocriptine in several strains of animals. Meier et al. (4) described that bromocriptine administration reduces body fat stores in obese postmenopausal females and alleviates hyperglycemia in type II diabetes in human patients. Scherthanher et al. (5) documented in human patients that severe hyperprolactinemia is associated with decreased insulin binding in vitro and insulin resistance in vivo.

We mentioned data suggest relationship between the prolactin on one side and the lipide and glycide metabolism on the other side. In our series of experiments there can be demonstrated positive correlation between total plasma cholesterol and prolactinemia. When we consider the mean of individual groups of rats then we found r = 0.9049, P<0.02, n = 6 when parametric Pearson correlation coefficient is judged, and r = -0.8286, P<0.05, n = 6 when non-parametric Spearman correlation was calculated. We obtained similar correlation between plasma prolactin and plasma triglycerides, but the correlation did not attain statistical significance (r = +0.7174, n = 6 when Spearman correlation was used, r = +0.4567, n = 6 when Pearson correlation was used). The above mentioned correlations do not exclude the possibility that prolactin takes part in the regulative mechanism of lipid metabolism.

Table 4: Glucose tolerance test. Effect of long lasting terguride treatment

| Group      | Control | Terguride | Pc |
|------------|---------|-----------|----|
| SHR-M      | 533.33±71 | 484.33±83 | 0.05 |
| SHR-F      | 542.66±83 | 492.33±83 | 0.05 |
| SHR-O-F    | 764.20±83 | 531.83±83 | 0.01 |
| SHR-O-G    | 412.60±83 | 253.60±83 | 0.01 |

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Introduction

Developmental changes of abnormalities in genetically hypertensive obese Koletsky rats were originally described by Koletsky (8). He analyzed the body weight from two to ten months of age in the obese rats and in their lean siblings. The author monitored development of plasma triglycerides from two to twelve months. In the period from two months to four months triglycerides elevate from 1.98 mmol/l to 4.67 mmol/l. Total plasma cholesterol in this period is elevated from 2.49 mmol/l to 3.74 mmol/l. In all groups of rats no changes were registered except one, i.e., obese females show decrease.

Summary of results were obtained. Thus during one month insulin is elevated in lean males +19%, in lean females +23%, but in obese males +80%, in obese females +144%. During one month glucose intolerance is elevated as well only in obese rats. Total plasma cholesterol during period of one month shows no changes in both substrains of rats. Similar picture can be found in basal glycemia. In all groups of rats no changes were registered except one, i.e., obese females show decrease.

Key words: Development of glycide and lipid abnormalities; Koletsky obese and lean SHR rats; Insulinemia; Glucose tolerance; Triglycerides; Cholesterol; Basal glycemia

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Diabetes mellitus (NIDDM) came to the conclusion that at the earliest stages of development of NIDDM there is elevated secretion of insulin.