ORIGINAL ARTICLE

HYPERPROLACTINEMIA IN OBESE AS WELL AS IN LEAN FEMALES OF KOLETSKY RATS: EFFECT OF LONG LASTING TERGURIDE TREATMENT

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Summary: Plasma prolactin was measured in genetically hypertensive obese Koletsky rats, in their lean siblings and in normotensive rats of Wistar strain. Lean as well as obese females show hyperprolactinemia. The males of Wistar strain as well as obese rats and their siblings show comparable prolactinemia except lean males which show higher level than Wistar males. Sex dependence of prolactinemia is missing in the rats of Wistar strain. Long lasting terguride treatment decreases prolactinemia in obese as well as lean rats of both sexes. The drug showed decreased prolactinemia in the males of Wistar strain. When the group of rats are considered in correlation computation positive correlation can be documented between total plasma cholesterol and plasma prolactin. In obese females positive correlation was found between plasma insulin and plasma prolactin.

Key words: *Koletsky SHR obese and lean rats; Prolactinemia; Terguride; Cholesterol; Triglycerides*

Introduction

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 lipide 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 a normotensive Sprague-Dawley male rat. The genetically obese animals appeared after several generations of selective inbreeding of hypertensive off-springs 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-l pelleted diet ad libitum.

Plasma insulin

Plasma insulin was detrmined by radioimmunoassay.

Plasma prolactin

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

Plasma lipids

Blood sampled by cardiac puncture (in light ether anaesthesia at 7.00 after l4 h starvation) was centrifugated and the serum was stored in plastic tubes at -20 °C. Total plasma cholesterol and plasma triglycerides were detrmined enzymatically by Hitachi analyzer.

Glucose tolerance

Blood was sampled to heparinized capillaries (from retrobulbar plexus under light ether anaesthesia) 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). 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. in two daily doses (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 0.1 mg/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 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 effect 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 is in females. Strain dependence is apparent between normotensive and lean Koletsky females,in the last mentioned rats there is increase.

Taking into account the effect of terguride on the total plasma cholesterol sex dependence is expressed, i.e., terguride shows decrease in females of both strains and substrains 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 at 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 females of Koletsky rats.

Considering control animals in the results of glucose tolerance test, substrain 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	P<
NR-M	5.41±4.18(7)	2.10±1.94(8)	0.05
NR-F	2.79±1.78(7)	1.91±1.15(8)	n.s.
SHR-M	18.37±6.86(7)^{D}	1.64±0.38(8)	0.01
SHR-F	39.84±24.63(8)^{Dc}	18.66±11.24(8)	0.02
SHR-O-M	13.76±4.35(10)	2.72±1.02(10)	0.01
SHR-O-F	43.16±.02(11)^{d}	5.25±2.28(10)	0.01

Table 1. Mean±SD. Effect of long lasting terguride treatment on plasma prolactin in the rats of Wistar strain, in the genetically hypertensive obese rats of Koletsky rats and in their lean siblings. Abbreviations: NR - rats of Wistar strain, SHR-O - genetically hypertensive obese rats of Koletsky type, SHR - genetically hypertensive lean rats of Koletsky type.In bracketts - number of rats in the group.Intersex differences: c - P< 0.02, d - P< 0.01. Interstrain differences: D - P< 0.01.

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

Group	Control	Terguride	P<
NR-M	1.66±0.22(8)	1.66±0.20(8)	n.s.
NR-F	1.79±0.34(8)	1.54±0.18(8)	0.05
SHR-M	1.80±0.16(7)	1.84±0.13(8)	n.s.
SHR-F	2.68±0.23(8)^{Dd}	1.99±0.28(8)	0.5
SHR-O-M	2.18±0.37((10)^{D}	2.39±0.55(10)	n.s.
SHR-O-F	2.56±0.26(10)^{d}	2.24±0.30(10)	0.01

Table 2. Mean + SD.Total plasma cholesterol. Effect of long lasting terguride treatment. The abbreviations are the same as in Table 1.

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

Group	Control	Terguride	P<
NR-M	0.59±0.07(8)	0.73±0.21(8)	n.s.
NR-F	0.62±0.09(8)	0.68±0.12(8)	n.s.
SHR-M	0.90±0.15(7)^{D}	0.94±0.19(8)	n.s.
SHR-F	0.96±0.37(8)^{D}	0.79±0.15(8)	n.s.
SHR-O-M	3.50±1.20(10)^{D}	4.05±1.73(9)	n.s.
SHR-O-F	3.72±0.93(11)^{D}	2.81±0.48(10)	0.01

Table 3. Mean±SD. Plasma triglycerides: effect of long lasting terguride treatment. Abbreviations are the same as in Table 1.

Considering the insulinemia in the control animals sex dependence is apparent in normotensive Wistar rats, insulinemia being higher in females. Sex dependence is obvious as well in obese Koletsky rats, insulinemia being higher in males (see Table 4). Strain difference was also found bet-

ween normotensive and lean Koletsky rats of both sexes, insulinemia being elevated in lean Koletsky rats and substrain differences between Koletsky lean rats and Koletsky obese rats of both sexes, insulinemia being elevated in obese Koletsky rats (see Table 4).

Table 4: Plasma insulin. Effect of long lasting terguride treatment.

Group	Control	Terguride	P<
NR-M	87±23(5)	169±36(8)	0.01
NR-F	144±58(7)^{b}	139±42(7)	n.s.
SHR-M	243±77(7)^{D}	179±49(8)	0.05
SHR-F	202±68(8)	169±21(8)	n.s.
SHR-O-M	940±458(10)^{D}	668±228(10)	0.10
SHR-O-F	531±185(9)^{dD}	406±211(9)	0.10

Table 4. Mean±SD. Plasma insulin. Long lasting terguride treatment. Abbreviations:Interstrain differences:D - P 0.0,
Intersex differences: b - P< 0.05, d - P< 0.0l. The other abbreviations are the same as in Table l.

Table 5: Glucose tolerance test. Effect of long lasting terguride treatment

Group	Control	Terguride	P<
SHR-M	533±39(7)	484±52(8)	0.05
SHR-F	542±61(8)	492±33(8)	0.05
SHR-O-M	764±206(10)^{D}	531 ±46(10)	0.0l
SHR-O-F	663±151(11)^{B}	452±42(10)	0.01

Table 5. Mean±SD.Glucose tolerance is expressed as a sum of glycemia obtained 30,60,l20 and l80 min after glucose loading („area under the glucose tolerance curve"). Glucose tolerance was not monitored in the rats of Wistar strain presented in this paper (the results of glucose tolerance test which were obtained in the other group of rats of Wistar strain can be found in paper No 2 - see References). Interstrain differences: B - P< 0.05,D - P< 0.0l. The other abbreviation are the same as in Table l.

Discussion

Cincotta and Meyer (l) were the first who directed the attention to the relationship between prolactin and lipide matabolism. 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 hyperglycaemia in type II diabetes in human patients.

Schernthaner et al. (5) documented in human patients that severe hyperprolactinemia is associated with decreased insulin binding in vitro and insulin resistance in vivo.

The above 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 demostrated 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.l0, n=6 when non-parametric Spearman correlation was calculated.We obtained similar correlation between plasma prolactin and plasma triglycerides, but the correlation did not attained statistical significance (r = +0.7714, 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 a part in the regulative mechanism of lipide metabolism.

The mentioned assumption is not in contradiction with sex dependent elevation of total plasma cholesterol in obese as well as in lean Koletsky rats (see Table 2), where at the same time hyperprolactinemia can be demonstrated (see Table l). In both cases cholesterol as well as prolactin is elevated in females.In the mentioned females terguride alleviates not only the hyperprolactinemia but decreases total plasma cholesterol as well.

Different picture can be found when we analyze plasma triglycerides. The sex dependence in the controls is not present,but strain and substrain dependence is profoundly expressed (see Table 3). Triglycerides in obese rats are three or four times higher than in lean Koletsky rats. Strain dependence is expressed also in the terguride effect. Mentioned drug alleviates hypertriglyceridemia only in obese females. As mentioned above hyperprolactinemia is present in females of both substrains of Koletsky rats (see Table l).

The described pattern of triglyceride events suggests that the participation of prolactin in the regulative mechanism of total plasma cholesterol and plasma triglycerides can be different. For a definite statement more studies in this area are needed.

When we computed correlation between plasma prolactin and plasma insulin in individual groups of rats, we found in obese females r =+0.7667, n = 9, P<0.05 when Spearman non-parametric correlation was calculated, and r=+0.7465, n = 9, P 0.05,and r = +0.7465, n =9, P<0.05. However,two values for statistically significant remoteness had to be excluded.

The last mentioned correlation suggests a possible participation of prolactin in regulative mechanisms of glycide metabolism. It remaines to be solved why the mentioned correlation was found only in obese females.

We noted no relationship between prolactinemia and glucose tolerance as well as between the terguride effect on prolactinemia and on glucose tolerance.

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