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 twelve months. In the period from two months to four months triglycerides elevate from 1.9 mmol/l to 4.67 mmol/l. Total plasma cholesterol in this period elevated from 2.49 mmol/l to 3.74 mmol/l. Total plasma triglycerides in this period elevated from 2.49 mmol/l to 3.74 mmol/l. At the age of two months Koletsky obese rats show relative to their lean controls elevation of plasma triglycerides (males +184%, females +152%) and insulin (males +169%, females +201%). During one month plasma triglycerides elevated in lean males +9%, in lean females 0%, but in obese males +21%, in obese females +139%. Considering insulinemia similar results were obtained. Thus during one month insulin elevates 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. Considering the strain differences in basal glycemia then at age of one as well as two months obese of both sexes show elevation. As to the body weight at the age of two as well as three months there is increase in obese rats. The changes of body weight during one month are expressively higher in obese rats.

The author analyzed sexual differences.

Summary: Experiments were performed in the genetically hypertensive Koletsky rats and in their lean siblings at the age of two and three months. In the study of development of glycide and lipid abnormalities animal represents control for itself. At the age of two months Koletsky obese rats show relative to their lean controls elevation of plasma triglycerides (males +184%, females +152%) and insulin (males +169%, females +201%). During one month plasma triglycerides elevated in lean males +9%, in lean females 0%, but in obese males +21%, in obese females +139%. Considering insulinemia similar results were obtained. Thus during one month insulin elevates 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. Considering the strain differences in basal glycemia then at age of one as well as two months obese of both sexes show elevation. As to the body weight at the age of two as well as three months there is increase in obese rats. The changes of body weight during one month are expressively higher in obese rats.

The author analyzed sexual differences.

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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Thus our monitoring of development of glycide and lipophilic abnormalities in obese Koletsy rats and in their siblings is well founded.

Material and methods

Animals

Experiments were performed in obese and lean genetically hypertensive rats of Koletsy type (8) of both sexes at the age of two months (54 - 59 days) and three months (92 - 95 days). The animal represents the control for itself. Lean Koletsy rats represent dominant non-obese homozygotes and heterozygotes whereas their obese siblings are recessive homozygotes. The abnormal animals were obtained by Koletsy (8) when mating spontaneously hypertensive female male (Okamoto-Aoki strain) with a normotensive Sprague-Dawley male rat. The genetically obese animals appeared after several generation of selective inbreeding of hypertensive offspring 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-1 pelleted diet ad libitum.

Plasma insulin

Plasma insulin was estimated by radioimmunoassay.

Insulin binding to erythrocytes

Plasma was separated from approximately 3 ml of heparinized blood drawn by cardiac puncture. Erythrocytes were obtained in the presence of constant amount of 125I-insulin (35pM) at 15°C 3 hours. Results were corrected for nonspecific binding. The details of the method were published previously (6).

Plasma lipids

Blood sampled to heparinized capillaries from retrobulbar plexus under light ether anaesthesia was centrifugated and the serum was stored in plastic tubes at -20°C. Total plasma cholesterol and plasma triglycerides were estimated enzymatically by Hitachi analyzer.

Glucose tolerance

Blood 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 estimated enzymatically (Oxochrom glucose, Lachema). Glucose tolerance is expressed as a sum of glycemia obtained 30, 60, 120 and 180 min after glucose loading ("area under the glucose tolerance curve").

Statistic

The data were analyzed by nonparametric tests, i.e., Mann-Whitney two sample (non-matched) test and by Wilcoxon test for matched pairs (10).

Results

Considering the developmental change in plasma triglycerides (Table 1) elevation was found in the obese of both sexes. Taking into account the strain differences at the age of two or three months obese of both sexes show profound increase. Sex dependence of triglycerides was found only at the age of three months and only in obese rats, in females triglycerides being increased.

Table 1. Plasma triglycerides

| Group       | n  | 58 days | 92 days | P    |
|-------------|----|---------|---------|------|
| SHR-M       | 8  | 3.410D35 | 4.590D35 | n.s. |
| SHR-F       | 8  | 2.900D34 | 2.770D34 | n.s. |
| SHR-O-M12   | 8  | 3.990D31 | 3.890D32 | n.s. |

Table 2. Total plasma cholesterol

| Group       | n  | 58 days | 92 days | P    |
|-------------|----|---------|---------|------|
| SHR-M       | 8  | 4.200D26 | 4.400D26 | n.s. |
| SHR-F       | 8  | 2.270D26 | 3.120D26 | n.s. |
| SHR-O-F8    | 8  | 3.020D24 | 2.220D23 | 0.01 |

Mean ± SD. Plasma triglycerides in mmol/l. Abbreviations: SHR-M: genetically hypertensive rats of Koletsy type, SHR-O: obese genetically hypertensive rats of Koletsy type, M: males, F: females. Small letters: inter-sex statistical significance, capital inter-strain statistical significance (obese versus lean) a = P<0.10, b = 0.05, c = 0.01, d = P<0.05, 130 or 92 days: age of animals when measurement was performed.

Total plasma cholesterol (Table 2) was not influenced by the age. Substrain differences were found in females at the age of two months, in males at the age of two months, in obese cholesterol being increased. Sex dependence was expressed in both substrains and at both ages, in females cholesterol being increased.

Table 3. Insulinemia

| Group       | n  | 58 days | 92 days | P    |
|-------------|----|---------|---------|------|
| SHR-M       | 8  | 141D18  | 170D22  | n.s. |
| SHR-F       | 8  | 2.950D24 | 3.180D24 | n.s. |
| SHR-O-M12   | 12 | 3.84D21 | 6.89D21 | 0.01 |
| SHR-O-F8    | 8  | 2.89D19  | 7.05D22 | 0.01 |

Mean ± SD. Plasma insulin. Abbreviations are the same as in Table 1.

Insulinemia (Table 3) was age dependent in the obese of both sexes, at three months being increased. Sex dependence in lean rats is expressed only at the age of two months, being increased in females, and in obese rats is expressed at the age of three months being increased in males. Substrain dependence was found only at the age of three months, elevation is apparent in the obese rats of both sexes.

Table 4: Glucose tolerance

| Group       | n  | 58 days | 92 days | P    |
|-------------|----|---------|---------|------|
| SHR-M       | 7  | 2.540D16 | 2.350D16 | n.s. |
| SHR-F       | 8  | 3.450D17 | 3.410D17 | n.s. |
| SHR-O-M12   | 12 | 5.64D17  | 10.65D22 | 0.01 |
| SHR-O-F8    | 8  | 3.020D17 | 2.220D17 | 0.01 |

Mean ± SD. Glucose tolerance. Abbreviations are the same as in Table 1.

Basal glycemia (Table 5) shows age dependence only in obese females, being lower at the age of three months.

Sex dependence was found only in obese rats at the age of two months where glycemia is increased in females. Substrain dependence was found in both sexes and at the age of two as well as three months, basal glycemia being elevated in obese of both sexes.

Table 5: Basal glycemia

| Group       | n  | 58 days | 92 days | P    |
|-------------|----|---------|---------|------|
| SHR-M       | 8  | 106D11  | 78D12   | n.s. |
| SHR-F       | 8  | 1.29D17  | 1.06D16 | 0.01 |

Mean ± SD. Basal glycemia. Abbreviations are the same as in Table 1.

Body weight (Table 6) shows substrain dependence at the age of two as well as three months, being elevated in obese of both sexes. Sex dependence is apparent in lean as well as in obese rats, body weight being elevated in males. Age dependent changes in body weight shows sex and substrain dependence. In lean rats lower age dependent increase in is in females, in obese rats lower age dependent increase is in males. Age dependent changes are in obese rats twofold (in males) and fourfold (in females) higher than in lean rats.

Table 6: Changes in body weight

| Group       | n  | 58 days | 92 days | change in % |
|-------------|----|---------|---------|-------------|
| SHR-M       | 7  | 170D12  | 246D10  | 44D10       |
| SHR-F       | 8  | 1.40D18  | 1.85D18  | 30D14       |
| SHR-O-M12   | 11 | 215D12  | 416D22  | 93D14       |
| SHR-O-F8    | 8  | 1.62D16  | 3.96D23  | 184D29      |

Mean ± SD. Changes in body weight. Abbreviations are the same as in Table 1.

Insulin specific binding to erythrocytes (Table 7) shows substrate differences in males, being higher in obese rats. Sex dependence is apparent only in obese rats, being higher in males.

Table 7: Specific insulin binding to erythrocytes

| Group       | n  | 58 days | 92 days | % of specific binding |
|-------------|----|---------|---------|-----------------------|
| SHR-M       | 8  | 2.27D10 | 2.57D10 | n.s.                  |
| SHR-F       | 8  | 1.57D10 | 1.66D10 | n.s.                  |
| SHR-O-M12   | 8  | 3.76D15 | 3.12D15 | n.s.                  |
| SHR-O-F8    | 8  | 2.08D10 | 2.56D10 | n.s.                  |

Mean and SD. % of specific binding to erythrocytes. Abbreviations are the same as in Table 1.

Discussion

We have documented that at the age of two months Koletsy obese rats show relative to their lean controls very profound elevation of triglycerides (males +184%, females +152%) and insulin (males +169%, females +201%). Moreover, during one month triglyceride changes were observed in lean males +9%, in females +23%, but in obese males +80%, in obese females +144%.

There are opened two serious questions. The first one, why the greatest differences between obese and lean rats at the age of two months were found in plasma triglycerides and plasma insulin. The second one, to what extent it is possible postulate the causal relationship between elevated plasma insulin and plasma triglyceride.

DeFronzo et al. (1) when summarizing recent knowledge in pathogenesis of non-insulin dependent diabetes mellitus (NIDDM) came to the conclusion that at the earliest stages in the natural history of NIDDM, insulin secretion is augmented compared with age-matched and weight-matched controls. In our previous study (3) we documented that in Koletsky obese rats there is a cluster of abnormalities in lipid and glycide metabolism which resembles deviations described by Reaven (14) and by Friedman et al. (15). We concluded that hyperinsulinemia in our obese rats of both strains can be considered as an expression of developing NIDDM. It would be desirable to monitor insulinemia in our obese rats in earlier stage of development, i.e., at the age of one month. At the age of one month it is possible to distinguish the obese from their lean siblings by＼n
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Thus our monitoring of development of glycemic and lipid abnormalities in obese Koletsky rats and in their siblings is well founded.

**Material and methods**

**Animals**

Experiments were performed in obese and lean genetically hypertensive rats of Koletsky type (8) of both sexes at the age of two months (54 - 59 days) and three months (92 - 95 days). The animal represents the control for itself. Lean Koletsky rats represent dominant non-obese homozygotes and heterozygotes whereas their obese siblings are recessive homozygotes. The abnormal animals were obtained by Koletsky (8) when mating spontaneously hypertensive female male (Okamoto-Aoki strain) with a normotensive Sprague-Dawley male rat. The genetically obese animals appeared after several generation 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-1 pelleted diet ad libitum.

**Plasma insulin**

Plasma insulin was estimated by radioimmunoassay.

**Insulin binding to erythrocytes**

Plasma was separated from approximately 3 ml of heparinized blood drawn by cardiac puncture. Erythrocytes were obtained in the presence of constant amount of 2525T insulin (35pM) at 15°C 3 hours. Results were corrected for nonspecific binding. The details of the method were published previously (6).

**Plasma lipids**

Blood sampled to heparinized capillaries from retrobulbar plexus under light ether anaesthesia was centrifugated and the serum was stored in plastic tubes at -20°C. Total plasma cholesterol and plasma triglycerides were estimated enzymatically by Hitachi analyzer.

**Glucose tolerance**

Blood 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 estimated enzymatically (Oxochrom glucose, Lachema). Glucose tolerance is expressed as a sum of glycemia obtained 30,60,120 and 180 min after glucose loading (‘area under the glucose tolerance curve’).

**Statistic**

The data were analyzed by nonparametric tests, i.e., Mann-Whitney two sample (non-matched) test and by Wilcoxon test for matched pairs (10).

**Results**

Considering the developmental change in plasma triglycerides (Table 1) elevation was found in the obese of both sexes. Taking into account the strain differences at the age of two and/or three month obese of both sexes show profound increase. Sex dependence of triglycerides was found only at the age of three months and only in obese rats, in females triglycerides being increased.

**Table 1: Plasma triglycerides**

| Group | n  | 58 days | 92 days | P   |
|-------|----|---------|---------|-----|
| SHR-M | 7  | 3.20DD30| 3.12DD36| n.s.|
| SHR-F | 8  | 3.20DD20| 3.12DD20| n.s.|
| SHRM-O | 12 | 3.41DD10D| 4.14DD10D| 0.02|
| SHRF-O | 8  | 3.02DD10D| 2.22DD10D| 0.01|

Mean ± SD. Plasma triglycerides in mmol/l. Abbreviations: SHRM-genetically hypertensive rats of Koletsky type, SHRF-obese genetically hypertensive rats of Koletsky type, M-males, F-females. Small letters: inter-sex statistical significance, capital: inter-substrain statistical significance (obese versus lean) = a: P<0.1, b: 0.05, c: 0.02, d: P<0.05. 58 or 92 days: age of animals when measurement was performed.

Total plasma cholesterol (Table 2) was not influenced by the age. Substrain differences were found in females at the age of two months, in males at the age of two months, in obese cholesterol being increased. Sex dependence was expressed in both substrains and at both ages, in females cholesterol being increased.

**Table 2: Total plasma cholesterol**

| Group | n  | 58 days | 92 days | P   |
|-------|----|---------|---------|-----|
| SHR-M | 7  | 3.21DD10D| 4.00DD10D| n.s.|
| SHRF | 8  | 3.41DD15D| 5.49DD15D| n.s.|
| SHRM-O | 12 | 2.90DD10D| 2.77DD10D| n.s.|
| SHRF-O | 8  | 3.99DD10D| 3.89DD10D| n.s.|

Mean ± SD. Total plasma cholesterol. Abbreviations are the same as in Table 1.

Insulinemia (Table 3) was age dependent in the oste of both sexes, at three months being increased. obese rats show pronounced increase at the age of three months. Sex dependence is apparent only in lean rats, insulin being increased in males.

**Table 3: Insulinemia**

| Group | n  | 58 days | 92 days | P   |
|-------|----|---------|---------|-----|
| SHR-M | 7  | 141DD18| 170DD22| n.s.|
| SHRF | 8  | 96DD20| 138DD24| n.s.|
| SHRM-O | 12 | 384DD12D| 689DD12D| 0.01|
| SHRF-O | 8  | 284DD10D| 705DD12D| 0.01|

Mean ± SD. Plasma insulin. Abbreviations are the same as in Table 1.

‘Area under the glucose tolerance curve’ (Table 4) shows age dependence only in obese rats of both sexes, at three months being increased. Sex dependence in lean rats is expressed only at the age of two months, being increased in females, and in obese rats is expressed at the age of three months being increased in males. Substrain dependence was found only at the age of three months, elevation is apparent in the obese rats of both sexes.

**Table 4: Glucose tolerance**

| Group | n  | 58 days | 92 days | P   |
|-------|----|---------|---------|-----|
| SHR-M | 7  | 561DD34| 575DD44| n.s.|
| SHRF | 8  | 628DD34| 622DD36| n.s.|
| SHRM-O | 12 | 543DD36| 1045DD38D| 0.01|
| SHRF-O | 8  | 602DD41| 783DD39D| 0.01|

Mean ± SD. Glucose tolerence. Abbreviations are the same as in Table 1.

Basal glycemia (Table 5) shows age dependence only in obese females, being lower at the age of three months.

Sex dependence was found only in obese rats at the age of two months where glycemia is increased in females. Substrain dependence was found in both sexes and at the age of two as well as three months, basal glycemia being elevated in obese of both sexes.

**Table 5: Basal glycemia**

| Group | n  | 58 days | 92 days | P   |
|-------|----|---------|---------|-----|
| SHR-M | 7  | 82DD11| 97DD13| n.s.|
| SHRF | 8  | 86DD12| 97DD12| n.s.|
| SHRM-O | 12 | 106DD13D| 96DD10D| 0.01|
| SHRF-O | 8  | 129DD17D| 106DD15D| 0.01|

Mean ± SD. Basal glycemia. Abbreviations are the same as in Table 1.

Body weight (Table 6) shows substrain dependence at the age of two as well as three months, being elevated in obe- se of both sexes. Sex dependence is apparent in lean as well as in obese rats, body weight being elevated in males. Age dependent changes in body weight shows sex and substrain dependence. In lean rats lower age dependent increase is in females, in obese rats lower age dependent increase is in males. Age dependent changes are in obese rats twofold (in males) and fourfold (in females) higher than in lean rats.

**Table 6: Changes in body weight**

| Group | n  | 58 days | 92 days | change in % | P   |
|-------|----|---------|---------|-------------|-----|
| SHR-M | 7  | 170DD12| 246DD10| 441D10 | n.s.|
| SHR-F | 8  | 140DD10D| 183DD14D| 30DD14 | n.s.|
| SHRM-O | 12 | 215DD10D| 416DD22D| 93DD18 | 0.01|
| SHRF-O | 8  | 162DD10D| 396DD23D| 148DD19D| 0.01|

Mean ± SD. Changes in body weight. Abbreviations are the same as in Table 1.

Insulin specific binding to erythrocytes (Table 7) shows substrain differences in males, being higher in obese rats. Sex dependence is apparent only in obese rats, being higher in males.

**Table 7: Specific insulin binding to erythrocytes**

| Group | n  | 58 days | 92 days | % of specific binding |
|-------|----|---------|---------|----------------------|
| SHR-M | 6  | 2.7DD84| 2.2DD84| n.s.|
| SHR-F | 12 | 5.7DD21D| 5.6DD21D| 0.01|
| SHRF-O | 8  | 2.6DD74| 7.6DD74| n.s.|

Mean and SD. % of specific binding to erythrocytes. Abbreviations are the same as in Table 1.

**Discussion**

We have documented that at the age of two months Koletsky obese rats show relative to their lean controls very profound elevation of triglycerides (males +184%, females 152%) and insulin (males +169%, females 201%). Moreover, during one month triglyceride levels are increased in lean males +9%, in females +23%, but in obese males +80%, in obese females +139%.

When studying the insulinemia we obtained similar results. Thus, at the age of two months Koletsky obese rats relative to their lean siblings show very profound elevation of insulinemia (males +69%, females +201%). During one month insulin elevates in lean males +19%, in females +23%, but in obese males +80%, in obese females +144%.

There are opened two serious questions. The first one, why the greatest differences between obese and lean rats at the age of two months were found in plasma triglycerides and plasma insulin. The second one, to what extent it is possible postulate the causal relationship between elevated plasma insulin and plasma triglyceride.
Systmic nicotine administration suppresses food intake via reduced meal sizes in both male and female rats

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Summary: The appetite suppressing effect of tobacco products, via the main pharmacological agent nicotine, is a major reason for its usage both by women and man. Food intake (FI) could be changed by altering either meal size (MZ) or meal number (MN), which are regulated dependently in a reciprocal manner. The present study investigated the effect of systemic nicotine administration on the rat feeding pattern. Because of gender differences in the effects of nicotine, both male and female rats were studied. Alzet miniosmotic pumps (Model 2001) and the automated rat eatometer were used to evaluate the feeding pattern of male and female Fischer 344 rats during seven days of systemic nicotine infusion (6 mg/kg b.w. s.c.). The main findings are: 1) systemic nicotine infusion decreased food intake in both sexes; 2) the decreased food intake was due to significantly reduced meal sizes while meal numbers were not altered significantly in either males or females; 3) the cyclical pattern of vaginal smears, food intake, meal number and meal size of female rats was not affected by nicotine administration. We conclude that the feeding suppressive effect of nicotine, which is due to reduced meal sizes and thus satiation, is not sex hormones related.

Key words: Nicotine; rats; Male and female; Feeding pattern; Meal size; Meal number; Food intake; Mini-osmotic pump

Introduction

The appetite suppressing effect of smoking, via its main pharmacological agent nicotine, is a major reason for its usage both by women and man. Food intake (FI) could be changed by altering either meal size (MZ) or meal number (MN), which are regulated dependently in a reciprocal manner. The present study investigated the effect of systemic nicotine administration on the rat feeding pattern. Because of gender differences in the effects of nicotine, both male and female rats were studied. Alzet miniosmotic pumps (Model 2001) and the automated rat eatometer were used to evaluate the feeding pattern of male and female Fischer 344 rats during seven days of systemic nicotine infusion (6 mg/kg b.w. s.c.). The main findings are: 1) systemic nicotine infusion decreased food intake in both sexes; 2) the decreased food intake was due to significantly reduced meal sizes while meal numbers were not altered significantly in either males or females; 3) the cyclical pattern of vaginal smears, food intake, meal number and meal size of female rats was not affected by nicotine administration. We conclude that the feeding suppressive effect of nicotine, which is due to reduced meal sizes and thus satiation, is not sex hormones related.

Additionally, some sex differences in the effects of nicotine per se were reported in human studies of smoking behavior (13) and of sex-dependent metabolism and excretion of nicotine (1, 2, 3, 8, 9, 16, 17, 18, 23, 37). As has been recently reported, the female estrous cycle significantly affects meal number and meal size in a reciprocal fashion (14, 32). The food intake and feeding pattern in the female rat is related to the fluctuations in the circulatory titers of sex-linked hormones (4). Low food intake during proestrus phase matched the smallest MZ and the highest MN during the late proestrus and early estrous phase (4). Therefore, the sex difference in nicotine sensitivity and its effect on feeding may result from endocrinological differences; other possibilities include receptor-biologic differences, drug transport differences, differences in feeding-related neurotransmission or, most probably, combination of several mechanisms (reviewed in 31).

Based on the above observations, the present study was designed using an osmotic mini-osmotic pump implant technique: i) to investigate the manner whereby systemic

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