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LEPTIN AND AGE-RELATED DOWN-REGULATION OF LIPOGENIC ENZYMES GENES EXPRESSION IN RAT WHITE ADIPOSE TISSUE

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The age-related inverse relationship between gene expression of lipogenic enzymes and leptin gene expression as well as inhibitory effect of leptin on lipogenic enzyme's gene expression suggests that leptin could be responsible in part for the low rate of lipogenesis in white adipose (WAT) of old rats. Based on the data published recently we propose a model for the direct inhibitory effect of leptin on lipogenesis. This model may explain the age-related decrease of lipogenic activity in WAT. It is likely that despite of higher concentration of noradrenaline (which inhibits leptin gene expression in WAT) in old animals, the age-dependent decrease of β-adrenergic receptor density in rat adipocytes may lead to the increase of leptin gene expression and to the increase of WAT leptin concentration. High concentration of leptin in adipose tissue decreases sterol regulatory element binding protein–1 (SREBP-1) gene expression by paracrine and/or autocrine action on adipocyte, which leads to the decrease of SREBP-1c level (mature form). The suppression of SREBP-1c synthesis causes a decrease of lipogenic enzyme's gene expression which consequently results in lower rate of fatty acid synthesis in WAT. This model does not exclude the indirect, *via* hypothalamus (by decreasing food consumption), inhibitory action of leptin on WAT lipogenesis. Therefore, it is likely that leptin exerts its inhibitory effect on WAT lipogenesis both directly at the level of adipocytes, and indirectly through hypothalamus by decreasing food intake. The inhibitory effect of high leptin concentration on lipogenesis in WAT of old rats could prevent over-accumulation of triacylglycerols in adipocyte, and by this way could protect against further development of the fat mass.

Key words: *ageing, leptin, lipogenic enzyme gene expression, lipogenesis, white adipose tissue*

OVERVIEW

Leptin is a peptide hormone, produced predominantly in adipose tissue, which suppresses appetite by regulating activities of the appetite and satiety centers in the brain (1). Administration of the hormone to rats or mice causes: a) reduction of food intake; b) increase in energy expenditure, and c) loss of fat mass and body weight (2, 3). The original concept of leptin function was limited to weight gain control. It has been suggested that leptin produced by adipose tissue, secreted to blood reaches the hypothalamus, where after binding to its receptor turns on signal transduction mechanism, that lead to a decrease of food intake and an increase in energy expenditure (4). In this way leptin acts as a feedback signal to maintain the equilibrium of the energy balance and consequently the set point of adiposity. In other words, an increase in adiposity leads to an increase in plasma leptin concentration, which in turn leads to the increase of energy expenditure and the decrease in food intake. Reduced adiposity leads to a decrease in plasma leptin concentration what reduces energy expenditure and increases food intake. Shortly after the discovery of leptin most papers investigated the anti-obesity action of the hormone. The therapeutic response to leptin administration to children with congenital leptin deficiency (5, 6) and in leptin-deficient adults (7) confirmed the importance of leptin in the regulation of human body weight, fat mass and appetite. However, the obese humans display high plasma leptin concentration (8). The obesity-associated hyperleptinemia has been interpreted as a reduced sensitivity to leptin. Some authors suggested that the signal generated by low serum leptin concentrations initiates adaptive changes aimed at conserving energy reserves and preventing reproduction during periods of food scarcity (9, 10).

The leptin gene (*Lep, ob*) encodes a protein of molecular weight of 18 kDa which is cleaved to produce mature hormone (1). Adipose tissue is the principal site of synthesis and the major determinant of the level of circulating leptin. However, biosynthesis of the hormone takes place also in other tissues including stomach, placenta, mammary gland epithelium, muscle, ovarian follicles, brain and some organs during the fetal period of life such as heart and bone (11 - 13). The mature (circulating) leptin is a 16 kDa non-glycosylated protein, presenting structural similarities to members of the long-chain helical cytokine type I superfamily like growth hormone, prolactin, interleukin-3 and many others (14). The body mass reducing effect of leptin (and probably other effects of the hormone) is mediated through interaction with the leptin receptor (15). Several alternatively-spliced forms, designated OB-Ra, OB-Rb, OB-Rc, OB-Rd and OB-Re of the leptin receptor have been reported (16). Only OB-Rb, the full-length isoform, is considered to be the functional receptor since it contains intracellular motifs required for activation of tyrosine kinase called Janus like kinase (JAK) and signal transducers and activators of transcription (STAT) (17). The ability of leptin to regulate body weight is facilitated by downstream signaling events

initiated by the hormone induced activation of functional receptor localized in the hypothalamus (18). The subpopulation of the arcuate nucleus NPY neurons contains the leptin receptor (OB-Rb). It is believed that leptin binding to OB-Rb induces activation of JAK-STAT system to regulate NPY gene transcription. Binding of leptin to its leptin receptor causes receptor homodimerization and activation (phosphorylation) of the JAK (both JAK1 and JAK2) which phosphorylate membrane-proximal sequence of the receptor. The phosphorylated intracellular domain of the leptin receptor provides a binding site for STAT3 which in turn is activated. Activated STAT3 (tyrosine phosphorylated) moves to the nucleus and activates transcription of an inhibitor factor called suppressor of cytokine signaling 3 (SOCS3). The formed SOCS3 antagonizes activation of STAT3 and inhibits directly the transcription of NPY gene promoter (19). Recent data indicated that the SOCS3 mediated suppression of NPY gene transcription might involve active histone deacylase (19).

Regulation of leptin synthesis in adipose tissue and serum leptin concentration

It has been shown that many factors acutely influence leptin biosynthesis. Fasting causes a rapid inhibition of *lep* gene expression, which is associated with fall in the concentration of circulating leptin (13, 20, 21). On the other hand, refeeding or overfeeding leads to an increase of leptin gene expression and the increase of serum leptin concentration (13, 20, 21). Many hormones have been shown to influence leptin gene expression and leptin biosynthesis. Insulin, glucocorticoids, oestrogens and prolactin stimulate leptin gene expression and leptin synthesis (12, 13). Some cytokines such as tumor necrosis factor-α (TNF-α) stimulate, however, other cytokines like interleukin 6 inhibit leptin production (12,13). Androgens, growth hormone and catecholamines, inhibit leptin synthesis (13, 22, 23). It seems that in rodents catecholamines inhibit leptin synthesis through β_3-adrenoreceptor (24 - 26). Based on facts that: a) α-methyl-p-tyrosine (tyrosine hydroxylase inhibitor blocking noradrenaline production) causes rapid increase of serum leptin concentration, which is associated with the increase of leptin mRNA level (27), and b) selective β-adrenorecoptor antagonist (SR59230A) inhibits the fall in serum leptin concentration occurring during cold exposure and on fasting (28), it has been proposed that sympathetic nervous system is the main physiological regulator of leptin synthesis in adipose tissue (29).

Pleiotropic effects of leptin

Initially, leptin actions were thought to be restricted exclusively to the control of food intake and energy expenditure *via* the action on hypothalamus and adjacent brain regions where leptin receptors were discovered. Later on, the almost universal distribution of functional leptin receptor (OB-Rb) was found (13). Leptin receptor is present in adipose tissue, liver, skeletal muscle, pancreas, stomach, small intestine, colon, heart, kidneys, adrenals, endothelium (13).

Functional OB-R was also found in reproductive organs (ovaries, uterus, testes), and in tissues related to the immunological system (spleen, thymus, lymph nodes, hematopoietic cells, T cell) (13). The almost universal distribution of the leptin receptor in the body explains diverse physiological functions of the hormone such as reproduction (30), immune responsiveness (31), bone formation (32), hematopoesis (33), angiogenesis (34), blood pressure control (13), and pancreatic endocrine as well exocrine functions (13, 35, 36).

Leptin, independently of its effect on food intake: a) selectively decreases amount of visceral fat, b) enhances the action of insulin on peripheral glucose uptake and hepatic glucose synthesis, c) modulates gene expression of key hepatic enzymes, and d) determines an intrahepatic redistribution of glucose fluxes that resembles that observed as the result of fasting (37). Moreover, leptin stimulates fatty acid oxidation in skeletal muscle (13), glucose uptake (13), and prevents lipid accumulation in non-adipose tissues (13). In addition, circulating leptin stimulates regional sympathetic nerve activity in a receptor-mediated way (38). Leptin structure, regulation of leptin biosynthesis and molecular action of the hormone has been extensively reviewed (4, 12, 13, 39 - 40). Thus, this review will focus mainly on direct effect of leptin on lipid metabolism in white adipose tissue (WAT), highlighting its role in age-related decrease of lipogenesis.

Effect of leptin on adipose tissue lipolysis

The presence of full-length leptin receptor (OB-Rb) in adipocytes (13) and *in vitro* effects of recombinant leptin on isolated adipocytes (41 - 45), indicate that leptin can directly induce changes in WAT lipid metabolism that occur in rats with hyperleptinemia (46 - 48). The increase of plasma leptin concentration by adenoviral transfer of leptin gene into rat leads to a significant reduction of triacylglycerol stores in adipose tissues (46), and substantial reduction of small quantity of triacylglycerol depots present in other tissues including liver and pancreas (49). Moreover, it has been shown that hyperleptinemia induced by adenoviral transfer of leptin gene into normal rats causes significant reduction of plasma triacylglycerol concentration (46, 49). Interestingly, hyperleptinemic fat loss due to the intracellular triacylglycerol degradation is not associated with elevation of plasma free fatty acids (FFA) and ketone bodies (49), which is characteristic for starvation or insulin deficiency induced lipolysis. Moreover, fat loss in starvation (or conditions of insulin deficiency) is accompanied by proportional release of FFA and glycerol. In the case of hyperleptinemia-induced lipolysis, the release of glycerol is not accompanied by a rise in plasma FFA concentration. These observations led Unger and coworkers (45) to the conclusion that leptin induces an unique form of lipolysis in which glycerol is released from adipose tissue without concomitant release of free fatty acids. One possible explanation for these interesting observations is that FFA are oxidized by mitochondria inside adipocytes. Significant increase of gene expression of

carnitine palmitoyl transferase (a key fatty acids oxidation enzyme) in the adipocyte of hyperleptinemic rats corroborates well with this suggestion (45). Moreover, it has been shown that peroxisome proliferator activated receptor α (PPARα) is necessary for the lipopenic action of hyperleptinemia on adipose tissue (50). It seems that the effect of leptin on lipolysis is mediated by OB-R, since the hormone had no effect on lipolysis in adipocytes with defective receptor (adipocytes of *fa/fa* - obese Zucker diabetic fatty rats) (45). Wang *et al*. (47) showed that the stimulatory effect of high concentration of leptin (caused by adenovirus-mediated transfer of leptin gene into rat) is not mediated by neurotransmitted signals from the central nervous system. These data suggest that leptin stimulates lipolysis without the participation of centrally-mediated pathways. However, the molecular mechanism involved in leptin-stimulated lipolysis is unclear. Since lipolysis is regulated by cAMP and protein kinase A, one can suppose that adenyl cyclase and protein kinase A are involved in the leptin action on lipolysis. The lack of the effect of leptin on forskolin- (activator of adenyl cyclase activity) or dibutyryl-cAMP-induced lipolysis (db-cAMP activates protein kinase A) suggests that direct effect of leptin on adenylate cyclase and/or protein kinase A is unlikely (13). However, Muller *et al.* (43) reported that leptin affects inhibition by insulin of isoproterenol-induced lipolysis and protein kinase A activation. Regarding: a) NO production in adipose tissue, b) involvement of NO in the regulation of lipolysis, c) stimulation of NO synthesis by leptin, and d) prevention by N-nitro-L-arginine methyl ester (inhibitor of NO synthase) of leptin-induced stimulation of lipolysis, one may suppose that NO might facilitate leptin-induced lipolysis (13). In contrast to the above described stimulatory effect of hyperleptinemia (induced by adenovirus leptin gene expression into rat), over-expression of leptin in transgenic mice leads to decreased basal lipolysis, PKA activity, and perilipin levels (51). Interestingly, these transgenic mice secrete approximately 5-fold more leptin than the control mouse, consume less food than normal mice, and have a dramatic reduction (9 to 14 fold) of WAT mass (52). These results suggest that the existence of lean phenotype of these transgenic mice cannot be explained solely by the changes in lipolysis, but that they have to be mediated also by other mechanism(s). In general, the above presented results suggest that short-term leptin treatment causes stimulation of adipose tissue lipolysis, but long-term leptin treatment leads to a decrease of basal lipolysis in adipose tissue. It has been also shown that leptin increases the expression of lipoprotein lipase gene in brown adipose tissue (44), what suggests that the hormone might affect not only intracellular but also extracellular lipolysis.

Evidence that leptin inhibits adipose tissue lipogenesis

Fat accumulation in adipose tissue depends not only on the rate of intracellular lipolysis but also on the rate of lipogenesis. Kim's group (41) was the first to

show that *ob* gene expression in cultured cells (30A5 preadipocyte) suppressed hormone-induced (by insulin and dexamethasone) acetyl-CoA carboxylase gene expression, a rate-limiting enzyme in long-chain fatty acid synthesis. The suppression of acetyl-CoA carboxylase gene expression was associated with the decrease of fatty acid and neutral lipid synthesis (41). Additionally, Kim and coworkers (41) showed that leptin suppressed activity of glycerol 3-phosphate dehydrogenase (41), the enzyme that provides 3-phosphoglycerol for triacylglycerol synthesis. These data indicate that leptin can precisely suppress defined reactions that contribute to lipid accumulation in adipose tissue. This may occur without participation of the brain. Muller *et al.* (43) showed in isolated rat adipocytes that leptin impaired insulin action not only on lipogenesis but also on glycogen synthesis, protein synthesis, and glucose transport. In adipocytes all these processes are stimulated by insulin. Leptin does not affect basal rates of these processes, but inhibits stimulatory effect of insulin (43). Similar results have been reported by Fukuda *et al.* (42) who found that leptin suppressed insulin-stimulated adipose tissue (and liver) fatty acid synthase (and ATP-citrate lyase) gene transcription by reducing the binding capacities of insulin receptors. Leptin administration to young rats, in amounts that caused approximately 5-fold increase of serum leptin concentration, led to a significant decrease of adipose tissue fatty acid synthase (as well as ATP-citrate lyase and 6-phosphogluconate dehydrogenase) gene expression (48). The importance of leptin as an inhibitor of lipogenic enzymes gene expression *in vivo* is also disclosed by differences between wild-type rodents and their counterparts with a single gene mutation that causes either the suppression of normal leptin production (*ob/ob* mice) or the expression of dysfunctional leptin receptor (*fa/fa* Zucker rats or *db/db* mice) (53, 54). Accordingly, these animals display high activity of lipogenic enzymes and high rate of lipogenesis (55 - 57). The over-expression of genes coding lipogenic enzymes and the rate of lipogenesis result presumably from the consequence of the loss of leptin action. Thus, the inhibitory effect of leptin on lipogenesis does not exist in animals with either disturbed production of leptin (*ob/ob* mice) or in leptin-unresponsive animals due to mutation in leptin receptor (*fa/fa* rats and *db/db* mice). These results strongly support the idea that leptin might inhibit gene expression of lipogenic enzymes not only *in vitro* (in tissue culture) but also *in vivo*. However, adenovirus-induced hyperleptinemia led to the down-regulation of acetyl-CoA carboxylase in the liver, but not in the adipose tissue (50). At present it is not known what is the cause of this discrepancy. However, most papers published so far, indicated that hyperleptinemia decreases lipogenic activity not only in rat WAT but also in adipose tissue of other species. For instance, the data reported by Ramsay (58) indicate that porcine leptin inhibits lipogenesis in porcine adipocytes.

Taken together, most results discussed above suggest that leptin is involved in the direct regulation of lipid metabolism in adipose tissue, affecting both lipolysis and lipogenesis. Therefore, white adipose tissue itself is a sensitive target for the

action of its product, leptin. Leptin by auto- or paracrine action, may regulate lipid metabolism in the same or adjacent adipocytes.

Possible role of leptin in ageing associated suppression of lipogenesis

Ageing is commonly associated with relative increase of body weight and adiposity. Usually adults tend to gain body weight until early senescence, after which body weight declines. The mechanism(s) that lead to the accumulation of fat in old animals remain obscure. Ageing is also characterized by a decline in metabolic function of several organs and tissues, what is accompanied in many humans by the development of obesity and occurrence of a variety of age-related diseases. Adipose tissue lipogenesis is one of the metabolic processes significantly reduced in aged animals. Mooradian and Albert (59) showed that in rat WAT ageing is associated with a significant reduction of fatty acid synthase and 6-phosphogluconate dehydrogenase activities. They showed also that the resistance to insulin and triiodothyronine (T3) was not directly related to the significant reduction of the activities of theses lipogenic enzymes (59). We have recently reported that gene expression of WAT lipogenic enzymes (fatty acid synthase, acetyl-CoA carboxylase, ATP-citrate lyase, glucose 6-phoshate dehydrogenase, 6-phosphogluconate dehydrogenase and malic enzyme) are significantly lower in old animals as compared to young rats (48, 60 - 64). Moreover, the age- related decrease in the expression of lipogenic enzymes is strictly correlated with age-associated reduction of the *in vivo* fatty acids biosynthesis (61). These results indicate that despite of increasing adiposity and body weight, lipogenic activity of rat WAT significantly decreases with ageing. However, molecular mechanism and factor(s) responsible for the age-related reduction of lipogenic activity in adipose tissue are not clear. Since ageing is associated with resistance to the action of some hormones (including insulin and T3), one can suppose that endocrine system may be in part responsible for the decrease of lipogenic activity. However, the data published previously suggest that the age-related reduction of WAT lipogenic activity cannot be attributed only to insulin and/or T3 resistance (59). Thus, some other factor(s) contributing to the age-related inhibition of rat WAT lipogenesis must exist. Considering that the gene expression of lipogenic enzymes is under the direct control of leptin (see above), one can assume that leptin could be one possible factor responsible for the age-related inhibition of adipose tissue lipogenesis. It is well established that rat serum leptin concentration and WAT leptin mRNA abundance increase with age (60, 65). Moreover, our results indicate that there are two different phases of changes in white adipose tissue leptin mRNA abundance and serum leptin concentration. Between 1 and 3 months of life (first phase), a strong positive correlation between adiposity and WAT leptin mRNA level as well as between adiposity and serum leptin concentration was found (60). It has been proposed that the increase of *ob* gene expression between 1 and 3 month of life is caused mainly by the increase of food consumption by growing rat

(60). However, these changes might be related also to the development or be secondary to fat accumulation (60). In rats over 3 month old we found no significant increase of leptin mRNA level, what suggests that adult and old rats are characterized by a stationary phase of leptin gene expression (60). Thus, we showed that the responsiveness of adipose tissue leptin gene expression undergoes rapid changes during the growth period of rat development. In mature rats this responsiveness is diminished and the amount of leptin mRNA, and, corresponding serum leptin concentration, were found to be maintained on high, relatively constant level. It is, therefore, likely that under a low serum leptin concentration, young, growing rats consume more food and store fat at a relatively high rate. The increase of lipogenic activity contributes partially to fat accumulation. When serum leptin concentration reaches high, stable level (as in rats older than 3 months), the hormone diminishes increase of food consumption and over-accumulation of fat in adipocytes due to decreased lipogenic activity. This interpretation is in agreement with the hypothesis (discussed above) that serum leptin is a signal molecule that regulates food intake and reflects the size of the fat depots in the body.

The data discussed above indicate also the existence of close inverse correlation between age-related increase of WAT leptin gene expression and the gene expression of WAT lipogenic enzymes. Data presented in *Table 1* indicate that in young rats serum leptin concentration and leptin mRNA level in adipose tissue are lower as compared to the old animals. Activities of WAT lipogenic enzymes and abundance of their mRNA are significantly higher in young than in old rats. In old animals serum leptin concentration and amount of leptin mRNA were higher in old as compare to young rats (*Table 1*). Unlike serum leptin concentration and leptin mRNA level in WAT, activities of lipogenic enzymes and amount of their mRNAs were significantly lower in WAT of old in comparison to young animals (*Table 1*). The pattern of age-related changes in the rate of fatty acids synthesis *in vivo* resembled that of lipogenic enzymes activity, and mRNA level of lipogenic enzymes (*Table 1*). Moreover, the relationship between serum leptin concentration and fatty acid synthase (FAS), and ATP-citrate lyase, activities studied in rats between 2nd and 20th month of life displayed strong negative correlation (60, 61). However, this negative correlation between serum leptin concentration and lipogenic enzymes gene expression was much stronger in rats between 1 and 3 month of life than in rats over 3 moths of life (60, 61). These results support the idea that leptin exerts autocrine (and/or paracrine) effect on the regulation of gene expression of lipogenic enzymes, and, consequently, on the rate of lipogenesis in WAT. To test this hypothesis we increased (by intraperitoneal injection of recombinant leptin) plasma leptin concentration in young rats to the level observed in old animals (*Table 2*). Administration of leptin to young rats significantly decreased FAS activity and FAS mRNA level (*Table 2*). Similar effects of leptin administration to young rats on ATP-citrate lyase and 6-phosphogluconate dehydrogenase mRNA levels in WAT were described (48).

Table 1. Relative serum leptin concentration, white adipose tissue leptin, SREBP-1c, lipogenic enzymes, Glut 4 mRNA levels, lipogenic activity and the rate of *in vivo* fatty acid synthesis in young and old rats.

Parameters studied	**Young rats**	**Old Rats**
Serum leptin concentration	Lover	**Higher**
Leptin mRNA level	Lower	**Higher**
SREBP-1c mRNA level	**Higher**	Lower
FAS mRNA level	**Higher**	Lower
FAS activity	**Higher**	Lower
ACC mRNA level	**Higher**	Lower
ACC activity	**Higher**	Lower
ACL mRNA level	**Higher**	Lower
ACL activity	**Higher**	Lower
ME mRNA level	**Higher**	Lower
ME activity	**Higher**	Lower
6PGDH mRNA level	**Higher**	Lower
6PGDH activity	**Higher**	lower
Rate of fatty acid synthesis *in vivo*	**Higher**	Lower
Glut4 mRNA level	**Higher**	Lower

FAS-fatty acid synthase, ACC-acetyl-CoA carboxylase, ACL-ATP citrate lyase, ME-malic enzyme, 6PGDH-6-phosphogluconate dehydrogenase.

Table 2. Serum leptin concentration and fatty acid synthase gene expression in young rats, young rats treated with leptin and in old rats.

	Young rats	**Young rats treated with leptin**	**Old rats**
Serum leptin concentration	Low	**high**	**high**
FAS activity	**High**	low	low
FAS mRNA level	**High**	low	low

FAS-fatty acid synthase

Considering: a) the results indicate that hyperleptinemia induced inhibition of gene expression of some lipogenic enzymes (41 - 43), b) an inverse relationship between age-related changes in serum leptin concentration and gene expression of lipogenic enzymes (60 - 64), and c) the effect of leptin administration to young rats on lipogenic enzymes gene expression (48), one can suggest that the observed age-dependent reduction of WAT lipogenic enzymes gene expression may result from the increased leptin production.

However, the exact molecular mechanism by which leptin inhibits lipogenic enzymes remains unknown. Based on the data indicating that: a) leptin can inhibit

binding of insulin to adipocytes (67), b) leptin decreases *in vitro* insulin stimulation of some lipogenic enzymes gene expression by reducing the binding capacity of insulin receptor (42), and c) leptin diminishes insulin secretion and induces insulin resistance (68), one can suppose that leptin modulates insulin's action on lipogenesis in adipocytes. However, other mechanism(s) cannot be excluded.

Sterol regulatory element binding proteins (SREBPs) are transcriptions factors, which are involved in the regulation of lipid synthesis (69). Three SREBPs have been described so far: SREBP-1a and SREBP-1c are produced from the same gene (*SREBF-1*) through the use of alternate promoters, and SREBP-2 is encoded by *SREBF-2* gene (69). SREBP-1a and SREBP-1c preferentially activate genes involved in lipid synthesis, whereas SREBP-2 primarily contributes to the transcriptional regulation of genes involved in cholesterol homeostatsis (69). Regulation by SREBPs depends on the amount of membrane-bound SREBP precursor present in the endoplasmic reticulum, and the rate of its cleavage to release the mature form. In the case of SREBP-1 transcriptional regulation appears to play the major role in the regulation of the amount of mature form (69). The mature SREBPs move to the nucleus, bind to sterol regulatory elements (SREs) in the promoters of target genes, and consequently change the transcriptional activity (69). The sterol regulatory elements have been identified in the promoters of the lipogenic enzymes (69). It has been shown that higher leptin level causes a decrease of SREBP-1c in the liver and pancreatic islets (70). On the contrary, leptin deficiency results in an increase of SREBP-1 gene expression in liver of ob/ob mouse (71). Moreover, increased of SREBP-1 gene expression in the adipose tissue of young rhesus monkey and its down-regulation in old animals was found (72). All these data suggest that SREBP-1 could contribute to age-related changes of gene expression of lipogenic enzymes in WAT.

Recently, we have published data indicating that age-related increase of leptin gene expression could in part be responsible for the reduced gene expression of SREBP-1 (63). This conclusion was drawn from the following observations: a) increase of plasma leptin concentration in young rats to the value observed in old animals resulted in the decrease in SREBP-1c mRNA level (63), and b) old rats displayed higher serum leptin concentration and lower level of SREBP-1c mRNA than young animals (63). Based on these observations one may suppose that the increase of leptin gene expression could, in part, account for the reduced SREBP-1c gene expression and, consequently, contribute to the decreased lipogenic activity in old animals. This idea is strongly supported by the results reported by Kakuma *et al.* (73) who found that hyperleptinemia induced in young rats by adenovirus gene transfer of rat leptin cDNA, decreased both liver SREBP-1c and lipogenic enzymes gene expression *in vivo*. Moreover, it has been shown that selective reduction of leptin receptor in adipocytes (induced by antisense RNA)

led to the increase of SREBP-1c mRNA level (74), what suggests that leptin may play a key role in SREBp-1 gene expression.

Taking into account the data discussed above we propose a model for the direct inhibitory effect of leptin on lipogenesis which may explain age-related decrease of WAT lipogenic activity (*Fig. 1*). The increased expression of leptin gene in adipose tissue of old rats leads to the higher synthesis of leptin. High concentration of leptin causes in turn (by paracrine and/or autocrine action on adipocytes) a decrease of SREBP-1 gene expression, what decreases SREBP-1c level (mature form). The suppression of SREBP-1c synthesis leads to the decrease of lipogenic enzymes gene expression, what consequently results in a lower rate of fatty acid synthesis (*Fig. 1*). In young rats opposite events occur. Our model points to the inhibitory effect of leptin on fatty acids synthesis directly

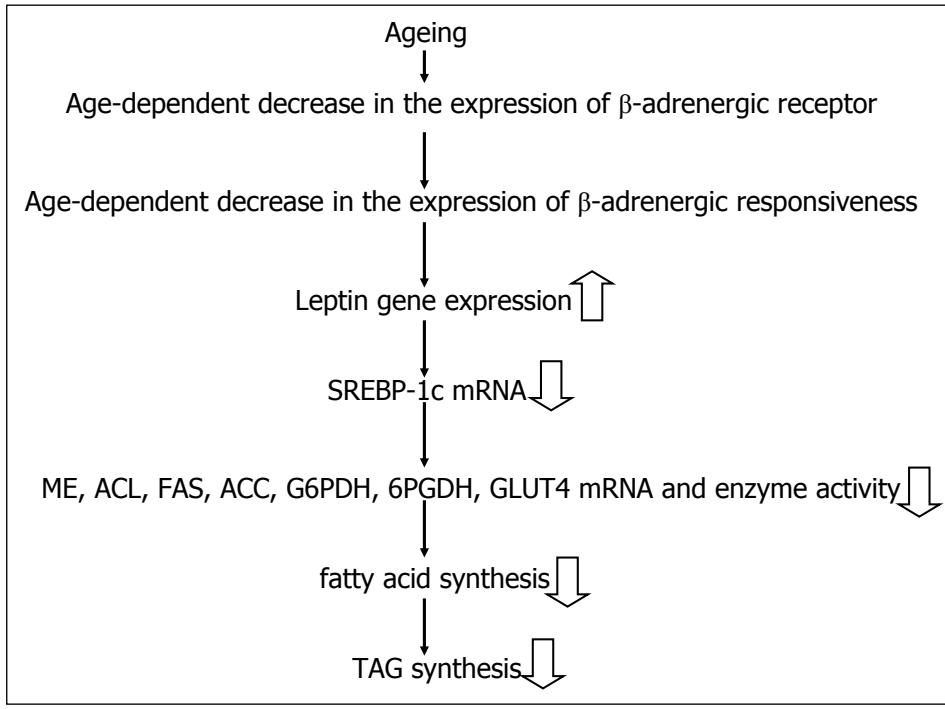

Fig. 1. Proposed mechanism of the involvement of leptin in the age-related inhibition of fatty acids and triacylglycerol (TAG) synthesis in white adipose tissue.
Ageing dependent decrease of β-adrenergic responsiveness leads to the increase in leptin production and secretion. In turn, elevated leptin concentration leads to the inhibition of SREBP-1c synthesis. Decreased level of SREBP-1c is causing the decrease of lipogenic enzymes genes expression and consequently lower rate of fatty acids and TAG synthesis.
FAS (fatty acid synthase); ACC (acetyl-CoA carboxylase); ACL (ATP-citrate lyase); ME (malic enzyme); G6PDH (glucose 6-phosphate dehydrogenase), 6PGDH (6-phosphogluconate dehydrogenase), glut 4 (glucose translocator), TAG (triacylglycerol)

at the level of WAT. *Figure 2* presents overall pathway of triacylglycerols' biosynthesis and sites of leptin inhibitory action on the conversion of glucose to triacylglycerol in rat adipocytes. This model does no exclude the indirect, via hypothalamus, inhibitory action of leptin on WAT lipogenesis. By decreasing food consumption leptin may suppress WAT lipogenesis due to the diminished supply of substrates for the synthesis of triacylglycerols. It is likely, that leptin exerts inhibitory effect on WAT tissue lipogenesis both directly at the level of adipocytes, and also indirectly through its action on hypothalamus, what leads to decreased food intake.

A general conclusion may be formulated about leptin action in aged rat. Inhibitory effect of high leptin concentration on lipogenesis in WAT of old rats (through both direct and/or indirect action) prevents over-accumulation of triacylglycerols in adipocytes and possibly in other tissues. This is important because age-related modulation of lipolytic sensitivity through β-adrenergic receptors leads to the inhibition of lipolysis in rat (75). It seems that compensatory system is required to prevent lipid accretion within adipose tissue of old animals. One can suppose that leptin protects adipocytes from fat overload by inhibiting lipogenesis directly or indirectly. The lack of the inhibitory effect of

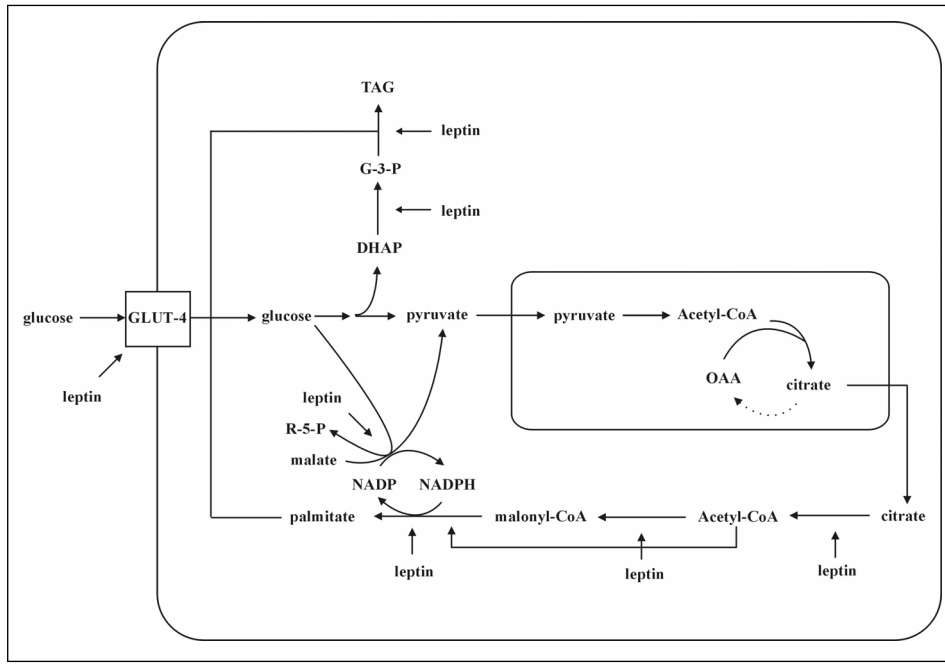

Fig. 2. Potential sites of leptin action in the conversion of glucose to lipids in white adipose tissue. TAG (triacylglycerol); G-3-P (glycerol 3-phosphate), DHAP (dihydroxyacetone phosphate); OAA (oxaloacetate); R-5-P (ribulose 5-phophate).

leptin on WAT lipogenesis could have lead to significantly higher accumulation of triacylglycerols than it really happens in old animals.

Finally, the questions arises: how can leptin contribute to the inhibition of lipogenesis in old rats if these rats are resistant to the effects of leptin (76)? Ma *et al.* (76) suggested that diminished transport of leptin across the blood-brain barrier plays an important role in leptin resistance. This mechanism does not exclude the direct inhibitory effect of leptin on lipogenesis in WAT of old animals. This notion is supported by the results of Wang *et al*. (77), who found that hyperleptinemia in old rats led to the up-regulation of the enzymes of fatty acids oxidation such as acyl-CoA oxidase and carnitine palmitoyl transferase 1. This suggests that despite of the age-related leptin resistance, high serum leptin concentration (as observed in old rats) might regulate gene expression of some enzymes including lipogenic enzymes. This suggestion corroborates with observations that young rats responded to both low and high doses of leptin, whereas old rats showed only a response to high dose (78). Moreover, it has been shown that the treatment of old transgenic mice with high dose of leptin induced increase of body weight loss (52). This suggests that in old rodents responsiveness to leptin still exists, and that high doses of the hormone are required to overcome the age-related leptin resistance.

The next important question is: what is the possible mechanism(s) by which leptin would suppress SREBP-1 gene expression? It has been shown previously that leptin antagonizes insulin action and decreases insulin production by pancreatic β-cells (79). Regarding that in isolated adipocytes the transcription of SREBP-1c is induced by insulin (69), one can suppose that the modulation by leptin of insulin's action on adipocyte and on SREBP-1 gene transcription may represent one of the mechanisms of ageing-dependent modulation of leptin's action on various tissues. The modulation by leptin of insulin's action has been discussed above (42, 67, 68).

Unanswered questions concern the possible mechanism(s) by which ageing inducies WAT tissue leptin gene expression and serum leptin concentration. There is no doubt that higher serum leptin concentration is caused by both increased adiposity and increased leptin abundance in old rats. However, the cause of increased leptin mRNA in WAT of old rats remains obscure. Although several factors may contribute to this phenomenon it seems that sympathetic nervous system may play a key role (29, 80). Many years ago it was recognized that sympathetic nervous system becomes progressively activated with increasing age (81). As already mentioned, in rodents catecholamines inhibit leptin synthesis acting through β_3-adrenoreceptor (24 - 26). However, β-adrenergic receptor density in rat adipocytes decreases with ageing (75). Therefore, we propose that despite higher concentration of serum noradrenaline (which inhibits leptin production) in old rats, the age-related reduction of β-adrenergic receptor density may suppress β-adrenergic inhibition of leptin production, and, consequently, may cause leptin overexpression in white adipose

tissue. However, other mechanism(s) involved in ageing-related WAT leptin overexpression of cannot be excluded.

Finally, the question arises whether the changes described in the adipose tissue of rodents occur also in human adipose tissue? The positive answer is supported by the observation that in humans high serum leptin concentration is associated with low FAS mRNA abundance in the adipose tissue of obese patients (82).

This review focuses mainly on the complex relationship between leptin gene expression and lipogenic enzymes gene expression in WAT in the aim to explore molecular mechanisms of lipogenic activity inhibition in aged animals. It is concluded that the up-regulation of leptin gene in old rat may down-regulate lipogenic enzymes gene expression . However, the discussion of the problem was presented as a working hypothesis that has to be supported by further research.

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