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The Endocrine Function of Adipose Tissue

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INTRODUCTION

The traditional view of the adipocyte as a passive receptacle for storage and combustion of triacylglycerol is undergoing rapid change. It is now recognized that a variety of adipocyte and adipose stromal cell derived proteins act both locally and distally through autocrine/paracrine and endocrine effects to regulate fat cell differentiation, and sense and adjust systemic energy balance.¹ These adipokines are molecules that were previously identified to be derived from immune cells, while others, cytokines produced by adipocytes, were known to be involved in hemostasis, inflammatory response, vasoregulation, and steroid metabolism (Figure 1). Many of these proteins increase as fat mass accumulates and, thus contribute to the multiple morbidities of obesity. Increased activity of three of these, tumor necrosis factor, interleukin 6, and resistin, play a role in the development of the insulin resistance present in obesity. In contrast, other adipokines, like adiponectin and leptin, are insulin sparing through stimulatory effects on the beta oxidation of fatty acids in skeletal muscle.

The concept of "lipotoxicity" postulates that the accumulation of excess lipids in hepatocytes and skeletal muscle cells interferes with insulin signaling,² and the increased lipolytic activity of visceral fat contributes to this process by shunting fatty acids through the portal vein to the liver. Local overproduction of glucocorticoids in visceral fat ("Cushing's disease of the omentum") is also pathogenic. Increased activity of 11 hydroxysteroid dehydrogenase (11 HSD-1) raises adipose tissue cortisol levels, adversely partitioning fat into visceral sites and stimulating release of metabolically harmful adipokines.² Many of these adipokines also act centrally. Leptin, tumor necrosis factor (TNF) and interleukin (IL-6) enter the hypothalamus where they affect sympathetic tone, feeding behavior, thermogenesis, reproduction, and the activity of various hypothalamic-pituitary axes. Adipocyte

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Letter from the Editor:

The lead article in this issue covers a very current topic, one which pediatric endocrinologists may not be thoroughly familiar or are just beginning to incorporate into their sphere of interest (outline of article at www.gghjournal.com). However, it is a subject about which we all will be hearing a great deal more in the near future as pediatric endocrinologists become more involved in the care of obese patients. The epidemic of obesity is confronting our profession more than ever. Consequently, most readers of *Growth Genetics and Hormones* will benefit from having this article as a source for reference to broaden their knowledge about The Endocrine Function of Adipose Tissue. To serve this purpose the presentation of this article by necessity was very inclusive and written as an introduction to, and compilation about, the existence and known function of the many hormones outlined in the text. Dr. Diamond is to be commended for undertaking a difficult task and achieving the intended goal.

For the Editorial Board
Robert M. Blizzard, MD
Editor-in-Chief

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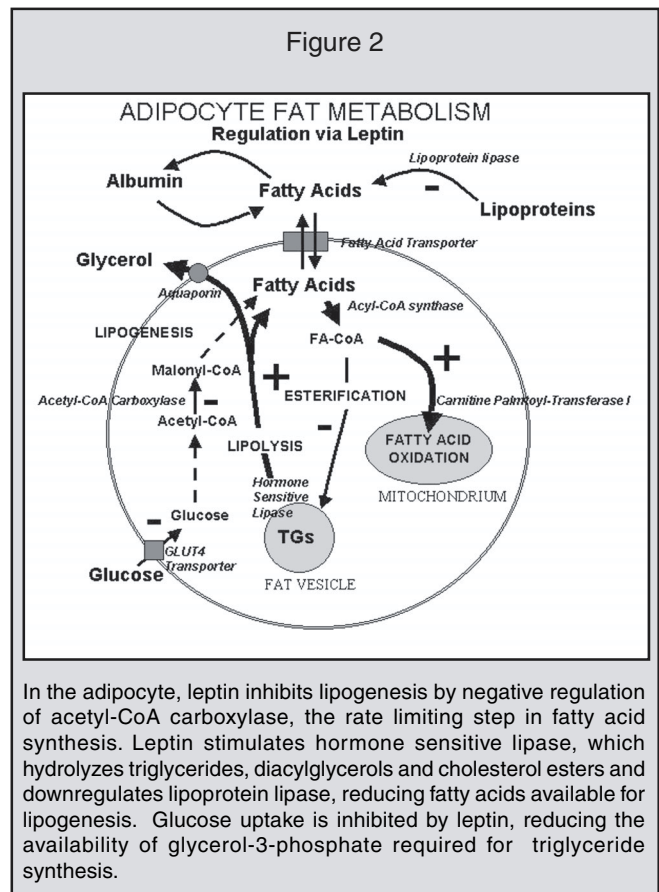
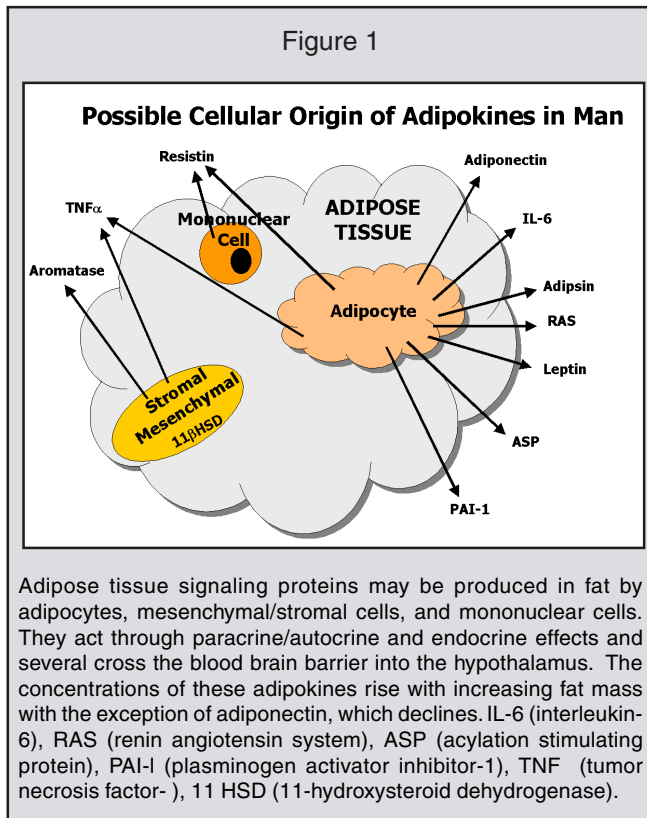
differentiation is controlled by the nuclear transcription factor, peroxisome proliferator activated receptor (PPAR)(Figure 2).³ As energy surplus develops, adipocyte differentiation and lipid accumulation are inhibited through feedback loops of adipocyte-derived factors such as TNF, angiotensinogen (AGT), and resistin (for resistance to insulin). When energy deficit occurs, there is a decline in other adipocyte secreted proteins, such as adiponectin and leptin, and there is activation of trophic proteins such as acylation stimulating protein (ASP) and angiotensin II (AngII). These signal a drive to adipocyte formation and renewed triglyceride accumulation. Insulin is central to this process, promoting lipogenesis and energy storage. The development of insulin resistance which is concomitant with excessive accumulation of body fat may signify a physiologic counter regulation activated to maintain energy homeostasis of the adipocyte. As body fat accumulates beyond that needed for energy balance, and as adipose tissue is chronically exposed to excess dietary fatty acids and glucose, there are further maladaptive responses of adipokines, which result in insulin resistance, inflammation, hypertension, and endothelial disease.

A review of the function and regulation of adipokines is made in this paper to facilitate the understanding by which obesity may contribute to the pathogenesis of the complications of this disease and of the alterations associated with this condition.

ADIPOKINES ASSOCIATED WITH INSULIN SENSITIVITY

Adiponectin

Adiponectin [Adipocyte complement-related protein (ACRP)], a soluble defense collagen, which is a circulating matrix-like protein, is expressed abundantly and exclusively in white adipose tissue.⁴ Adiponectin appears to be an endogenous anti-inflammatory and anti-atherogenic factor that is protective against insulin resistance and macroangiopathy.⁵ Its serum concentrations are reduced in obese mice and humans and rise following weight loss. This suggests that adiponectin plays a negative feedback role in fat storage.⁶ Levels are lower in men compared to women and in individuals with obesity, type II diabetes, and coronary artery disease as compared to healthy subjects.⁷ Its concentrations correlate with the insulin sensitivity state and with steady state plasma glucose, and rise in response to insulin. The protein is not an insulin sensitizer, however, but protects insulin action by accelerating beta oxidation of free fatty acids in skeletal muscle.⁸ Intravenous administration of the "fat burning" c-terminal globular region of AdipoQ, the mouse homologue of adiponectin, reduces circulating free fatty acids and diet induced weight gain and corrects both hyperglycemia and hyperinsulinemia in genetically obese animals.⁹ Hypoadiponectinemia may also



contribute to the insulin resistance of lipoatrophic animals, explaining the apparent paradox of glucose intolerance in both obese and fat depleted models. Adiponectin is highly regulated during adipocyte differentiation and may mediate some of the insulin-sensitizing effects of thiazolidinedione (TZD) binding to PPAR. Clinically, treatment of insulin resistant human subjects with TZDs significantly increases plasma adiponectin concentrations without affecting body weight. Additionally, adiponectin suppresses phagocytic activity, macrophage release of $TNF\alpha$, and transformation of macrophages to foam cells in vitro. It also is deposited in vascular smooth muscle to protect vessel walls and thereby modulates the disease risks of coronary artery disease.¹⁰

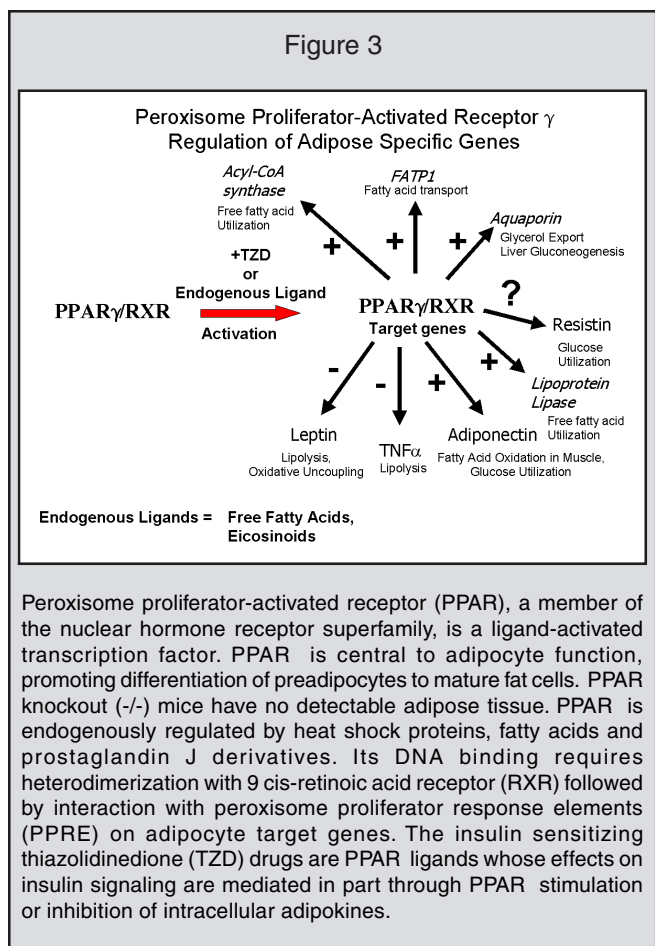
Leptin

Leptin is a 16 kDa adipocyte-derived cytokine synthesized and released from fat cells in response to changes in energy stores and in systemic energy balance. Leptin's primary physiologic function is the defense of body fat. Declining levels in adipose tissue and serum signal the presence of energy deficit to the brain. Leptin circulates partially bound to plasma proteins and enters the CNS by diffusion through capillary junctures in the median eminence and by saturable receptor transport in the choroid plexus. In the hypothalamus leptin binds to long receptor isoforms which stimulate anorexigenic and inhibit orexigenic peptides.^{11,12} Leptin also increases sympathetic nervous system activity and energy expenditure.¹³ Adipocyte levels of leptin mRNA and protein correlate closely with both circulating leptin values and total body fat.

Leptin's lipolytic role in adipocyte metabolism is shown in Figure 3. Leptin reduces the levels of intracellular lipid in skeletal muscle, liver and pancreatic beta cells, thereby improving insulin sensitivity. In muscle this insulin sensitizing effect is achieved through inhibition of malonyl CoA, permitting increased transport of fatty acids into mitochondria for beta oxidation. These changes are partially mediated by central sympathetic activation of adrenergic receptors.²

Leptin synthesis is both constitutive and hormonally controlled. It is influenced by the state of energy reserve, and it is modulated by the sympathetic nervous system through an inhibitory feedback loop. Both adipocyte size and location dictate leptin production, although the mechanism(s) of these paracrine/autocrine modulated effects remain largely undefined. Larger fat cells contain more leptin than smaller ones and subcutaneous fat releases more leptin than visceral fat.^{14,15} Several experimental findings suggest that glucose is an important regulator of adipocyte leptin release.¹⁶ In cultured rat adipocytes, glucose inhibitors block leptin synthesis. In man, glucose infusion attenuates the rapid

Figure 3



fasting decline of leptin. The hexosamine biosynthetic pathway into which 2-3% of cellular glucose uptake enters may mediate this link. Exposure of isolated subcutaneous adipocytes to UDP-N-acetylglucosamine (an end product of hexosamine biosynthesis) increases leptin release. Its inhibition reduces glucose-stimulated leptin release and ob gene expression. UDP-N-acetylglucosamine levels in human subcutaneous adipose tissue correlate significantly with both body mass index (BMI) and serum leptin levels.¹⁷

Insulin stimulates the secretion of leptin when administered to human subjects for several days. In adipocytes from rat white adipose tissue, leptin is present in the endoplasmic reticulum in the absence of insulin, whereas it localizes into the plasma membrane following insulin treatment.¹⁸ Glucocorticoids, whose effects may be primarily permissive, induce leptin synthesis in vitro and in vivo, with greater responsiveness in obese as compared to lean individuals.^{19,20} Females produce more leptin than males when matched for age, weight and body fat. This is probably related to gender differences in fat depots and to the leptin-suppressive effects of testosterone. At birth, the leptin concentrations in umbilical cord blood from girls are double those present in boys.²¹ Pulsatile

leptin secretion correlates with female sex hormones. However, there are conflicting data regarding the influence of ovarian sex steroids on leptin release.^{22,23} Other controlling factors are listed in the addendum.²⁴⁻²⁶

The prevailing evidence of the physiologic role of leptin suggests that it is an anti-obesity hormone, but this concept must be reconciled with the inability of high endogenous leptin levels to prevent most obesity. It appears that in the majority of cases there may be leptin resistance mediated by inhibition of leptin signaling, thereby altering the dominant role of this hormone as a signal to switch between fed and fasted states.

ADIPOKINES ASSOCIATED WITH INSULIN RESISTANCE

Resistin

Resistin is a 12.5 kDa cysteine-rich adipocyte secreted protein which was identified during the screening for genes induced during adipocyte differentiation. This adipokine is down regulated by TZDs. It also is known as Fizz3 (for found in inflammatory zones). Worthy to note is that resistin is one of a family of similar molecules present in fat. Resistin administered to wild type animals induces insulin resistance, but in the obese-insulin resistant mouse it restores normal insulin sensitivity.²⁷ In morbidly obese humans, resistin mRNA from adipose tissue samples is increased as compared to that in lean controls.²⁸ However, a number of clinical and experimental observations suggest that resistin may not be the long sought major link between human obesity and insulin resistance.²⁹

Tumor Necrosing Factor

TNF α is a multi-potential cytokine with diverse immunologic functions. Initially it was described as a cause of tumor necrosis in septic animals and was associated with cachexia-inducing states, such as cancer and infection.³⁰ In obese humans TNF α and its receptors (TNFR1 and TNFR2) are synthesized and secreted in increased amounts by adipocytes and stromovascular cells. Their autocrine effects contribute to the insulin resistance of obesity and diabetes;³¹ TNF α inhibits insulin action by down regulating GLUT4 mRNA in fat and muscle. It also reduces insulin receptor autophosphorylation and phosphorylation by decreasing insulin receptor substrate-1. Circulating free fatty acids (FFA) increase from the lipolytic effects of TNFR1.³² TNF α induces lipolysis which is blocked by PPAR ligands in insulin resistant animals.³³ In man, TNF α concentrations decline with weight loss and treatment with TZDs. The administration of TNF α causes hyperinsulinemia without hypoglycemia.³⁴

TNF α also has important effects on the hypothalamus. In rats, intravenous or intracerebroventricular injection of

TNF α stimulates ACTH secretion through eicosanoid cyclooxygenase mediated release of CRH and inhibits secretion of TSH.³⁵ Thus, TNF appears to have a net effect in prevention of obesity through the inhibition of lipogenesis and increased lipolysis with facilitation of adipocyte death via apoptosis.

Interleukin-6

In man, ~30% of circulating IL-6 originates from adipose tissue.³⁶ Concentrations are higher in visceral fat as compared to subcutaneous fat. They increase with obesity and are stimulated by TNF and IL-1.³⁷ Elevated levels are associated with increased risk of coronary artery disease, athero-sclerosis, and unstable angina.³⁸ Acting on the liver, IL-6 is a primary stimulant of acute phase reactants, such as C-reactive protein, fibrinogen and haptoglobin, thus contributing to a hypercoagulable state. Importantly, IL-6 also promotes the release of endothelial adhesion molecules³⁹ and adversely affects insulin sensitivity by inhibiting GLUT-4, hepatic glycogenesis, and lipoprotein lipase. The resultant lipolysis increases non-esterified free fatty acids (NEFA) which impedes nitric oxide mediated endothelial vasodilation.⁴⁰

IL-6 receptors are present in the hypothalamus where IL-6 stimulates thermogenesis and satiety by increasing prostaglandin synthesis and release of corticotrophin releasing hormone (CRH).⁴¹ It remains to be determined whether IL-6 is a link between obesity and thromboembolic complications.

ADIPOCYTE PROTEINS AND LIPID METABOLISM

Adipsin

Adipsin (ADIPocyte-trypSIN) is a 24-kDa adipocyte secreted protease with close homology to human complement D. This protease is required for the synthesis of acylation stimulating protein (ASP) (*vide infra*), which is described below and which is an important mediator of lipogenesis. Although adipsin concentrations are reduced in rodent models of obesity, paradoxically they are increased in humans with excess adiposity;⁴² for example in obese Pima Indians serum adipsin levels are 45% higher than in non-obese Pimas or other controls. In subjects with anorexia nervosa the adipsin levels are low and rise during refeeding. Insulin stimulated adipsin release is mediated by ADP-ribosylation factor 6 (ARF6) which acts on endocytotic and recycling pathways in the adipocyte; therefore being an important protein in fat metabolism.⁴³ Adrenalectomy of ob/ob mice raises circulating adipsin levels; and corticosterone replacement reverses these changes. Adipsin secretion also is stimulated in animals by sympathomimetic agents, but not by cold stress.⁴⁴

Acylation Stimulating Protein (ASP)

ASP is a 76-amino acid protein that stimulates fatty acid uptake and esterification into triglycerides. Retinoic acid (transported as retinyl ester by transthyretin and chylomicrons) stimulates the C3 gene leading to increased postprandial production of ASP.⁴⁵ Up to a quarter of patients with coronary artery disease have elevated concentrations of ASP. Hyperapobeta-lipoproteinemia, a familial dyslipidemia characterized by increased hepatic release of LDL and VLDL, may result from impaired adipose tissue actions of ASP.⁴⁶ In the ASP-knockout mouse, postprandial triglyceride clearance is delayed and weight gain decreased. Like insulin and additive to it, ASP promotes movement of glucose transporter vesicles in cell membranes in adipose tissue and muscle by activation of the diacylglycerol/protein kinase C pathway.⁴⁷ This provides glucose substrate for glycerol-3-phosphate synthesis of fatty acids and triglycerides. Thus a deficit of ASP results in increased post prandial fatty acids and decreased weight gain and triglyceride synthesis.

Aquaporin Adipose (AQPap)

AQPap is an adipose specific glycerol channel gene abundantly and exclusively expressed in white adipose tissue. AQPap regulates glucose homeostasis by controlling the flux of glycerol into hepatic gluconeogenesis. In wild-type mice, AQPap expression increases during fasting, and declines with refeeding. This takes place through insulin action at the AQPap promoter's negative insulin response element (IRE).⁴⁸ AQPap is increased in adipose tissue from TZD treated mice and reduced in PPAR +/- heterozygous knock-out rodents.

ADIPOKINES & HEMOSTASIS

Plasminogen Activator Inhibitor-1 (PAI-1)

PAI-1, which is synthesized in the liver and in adipose tissue regulates thrombus formation by inhibiting the activity of tissue-type plasminogen activator, an anti-clotting factor. PAI-1 concentrations in serum increase in proportion to visceral adiposity and are entrained by adipocyte size and lipid content.⁴⁹ Omental tissue explants secrete significantly more PAI-1 than subcutaneous tissue from the same subject.⁵⁰ Increased PAI-1 levels are found in patients with coronary artery disease and following myocardial infarction, while levels decline with caloric restriction, exercise, weight loss, and treatment with metformin.⁵¹

THE ADIPOCYTE RENIN-ANGIOTENSIN SYSTEM (RAS)

A renin-angiotensin system (RAS) located in the intra adipose tissue regulates fat cell mass and energy stores through paracrine/autocrine effects on adipocyte

differentiation and lipid storage. Angiotensinogen (AGT), renin, angiotensin-converting enzyme (ACE), angiotensin II (AngII) and its receptors (ATI, AT2), and the non-renin-angiotensin enzymes chymase, cathepsins D and G, and tonin, are all expressed by adipose tissue.⁵² Plasma AGT, renin activity and ACE correlate positively with body mass index while adipose tissue AGT expression correlates significantly with waist-to-hip ratio in man.⁵³ Adipose tissue AngII controls terminal differentiation of preadipocytes to adipocytes through the action of prostacyclin (PGI₂) and regulates adipose tissue blood supply. Adipose tissue AGT also influences adipocyte vascular resistance, but negatively regulates fat mass by decreasing lipogenesis. Ang II and AGT receptors are found in higher concentrations in visceral fat as compared to subcutaneous adipose tissue in both lean and obese individuals.⁵⁴ Glucocorticoids in the presence of insulin, and beta-adrenergic stimulation, and nutritional changes modulate adipocyte AGT gene expression.⁵⁵ In man, the role of the adipocyte RAS in the relationship between obesity and hypertension remains to be further defined.⁵⁶

ADIPOSE AROMATASE AND INTRAADIPOSE GLUCOCORTICOIDS

Aromatase

Sex steroids are not synthesized de novo in fat, but are formed by the action of stromal enzymes on adrenally derived precursors. In human adipose tissue aromatase activity is principally expressed in mesenchymal cells of undifferentiated preadipocyte phenotype.⁵⁷ P450arom, a heme protein product of the CYP 19 gene, converts androstenedione to estrone. Estrogen production in fat rises as body weight increases and as subjects age.⁵⁸ Importantly, adipose tissue-derived estrogens partition fat to subcutaneous and breast tissues, while androgens promote central or visceral fat accumulation.⁵⁹ Aromatase activity varies significantly by region, with greater expression in adipose tissue from buttocks and thighs compared to that from abdomen and breasts.⁶⁰ In vitro, aromatase expression is stimulated by glucocorticoids in the presence of serum, and by class I cytokines. TNF increases aromatase expression in adipose stromal cells exposed to dexamethasone; leptin has little effect.⁶¹ In the aromatase deficient ArKO mouse which lacks a functional Cyp 19 gene, there is a progressive accumulation of intra-abdominal fat and reduced lean body mass.⁶²

11- HYDROXYSTEROID DEHYDROGENASE

11-hydroxysteroid dehydrogenase (11 HSD-1), which regenerates metabolically active cortisol from cortisone in man and corticosterone from 11 dehydrocorticosterone in mice, is increased in adipose tissue from obese

subjects. Adipose tissue corticosterone was overproduced by 30% in a transgenic (Tg) mouse that modestly over expresses 11 HSD in all its adipose tissues. The Tg male animals disproportionately accumulated visceral fat in adipocytes which were three times the size of those of control animals. The mice became hyperphagic, hyperglycemic, and hyperinsulinemic, had reduced levels of adiponectin and uncoupling protein-I, and had increased concentrations of leptin, TNF, angiotensinogen, lipoprotein lipase, and portal free fatty acids. This clinical and biochemical pattern mimics the human "metabolic syndrome".⁶³ In humans thiazolidinediones significantly reduce 11 HSD-I mRNA in vitro and in vivo, and preferentially reduce visceral fat.⁶⁴

OTHER ADIPOCYTE PROTEINS

Metallothionein is an adipocyte secreted low molecular weight metal binding and stress response protein which may function to protect fatty acids from oxidative damage.⁶⁵ The metallothionein genes (MT-I, MT-2) are expressed in adipocytes early in their differentiation process. In vitro, MT-I transcription is stimulated by dexamethasone, forskolin and bromo-cAMP, and to lesser extent by insulin and leptin. Fasting-induced adipose factor (FIAP), a circulating fibrinogen-angiopoietin-related protein, is an adipocyte derived protein which increases during caloric deprivation and interacts with PPAR.⁶⁶ Lipoprotein lipase, cholesteryl ester transferase, apolipoprotein E, and retinol binding protein are other adipocyte proteins important for lipid metabolism which are under study.

CONCLUSION

The mechanisms by which obesity contributes to insulin resistance, hypertension, and endothelial disease are among the most important scientific questions facing medical investigators today. Research into the function and regulation of adipocyte signaling proteins, adipocyte differentiation, and the control of fat partitioning will likely result in further insight into these mechanisms and the discovery of targeted therapies for treatment of obesity and obesity related diseases.

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Addendum (re Leptin)

Many regulatory sites for leptin are found within the ob gene promoter, including cyclic AMP and glucocorticoid response elements, as well as loci for CCATT/enhancer and SP-1 binding.^{24,25} Thiazolidenediones reduce leptin mRNA in adipocyte 3T3-L1 cells through negative PPAR effect at the leptin promoter.²⁶ Peripheral leptin administration activates suppression of cytokine signaling-3 (SOCS-3) which is co-expressed in hypothalamic nuclei with long-form leptin receptors. Increased SOCS-3 expression in vitro has been shown to blunt leptin receptor signal transduction by inhibiting JAK activity. SH2-containing phosphatase 2 (SHP-2) also blocks STAT-3 mediated leptin transcription. Moreover leptin is negatively regulated by the sympathetic nervous system via beta-2 and beta-3 catecholaminergic input at the adipocyte. The increased sympathetic enervation in visceral fat may thus partly explain its reduced leptin content compared to subcutaneous fat tissue. Infusion of isoprenaline or epinephrine in man acutely suppresses leptin release, as does cold exposure. Growth hormone, thyroid hormone, and melatonin have also been shown to decrease leptin secretion.

Abstracts from the Literature

Celiac Disease in Children with Autoimmune Thyroid Disease

This study was designed to test for the presence of celiac disease among children with autoimmune thyroid disease (ATD). Ninety patients (78 females) ages 1.8 to 17.3 years with ATD were studied; 20 of them had Graves' disease, and 16 had other associated conditions i.e. alopecia (4), vitiligo (2), juvenile rheumatoid arthritis (2), autoimmune hepatitis (2), Down's syndrome (1) and other miscellaneous autoimmune alterations (5). Screening for IgA antiendomysium antibodies (EMA) and HLA typing for Class I and II DQA1 and DQA2 heterodimers were done. There were 7 patients with positive EMA; an intestinal biopsy in these patients revealed intestinal villi alterations, with partial or total atrophy, crypt hyperplasia and intraepithelial lymphocytes. Clinically, one of the celiac disease patients had iron deficiency, one had diarrhea, and one had short stature, while the others were asymptomatic. A significant positive correlation was present for celiac-susceptible heterodimers in the patients with celiac disease. The authors concluded that screening for celiac disease should be done on all patients with ATD.

Larizza D, et al. *J Pediatr* 2001;139:738-740.

Editor's Comments: *This report is one more in the recent literature documenting the presence of celiac disease among patients with endocrinopathies. The prevalence of celiac disease in patients with ATD was 7.7% which is higher than that observed in other studies of adults with ATD, and of course much higher than the 1% reported in normal populations.¹⁻³ In Vol 17 No 2 of Growth Genetics & Hormones, I abstracted and commented upon the article describing the presence of celiac disease in 4.6% of children with type I diabetes.⁴ Celiac disease was a significant factor in the development of hypoglycemia complicating the course of the diabetic illness. The presence of celiac disease in the patients in this study, as well as those in other reports, was without clinical evidence of malabsorption and the patients were largely asymptomatic.*

Nonetheless, it has been suggested that the presence of unidentified celiac disease could play a role in the development of autoimmune disorders, and the prompt diagnosis and treatment of this disease could prevent the onset of other alterations.⁵ The availability of an accurate, sensitive and specific test (IgA antiendomysium antibodies) to screen for celiac disease should not be overlooked by Pediatric Endocrinologists who in my opinion should test all patients with autoimmune endocrine disorders regularly for antibodies reflecting the presence of celiac disease.

Fima Lifshitz, MD

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