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TOPIC HIGHLIGHT

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Metabolic effects of obesity: A review

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Abstract

With the many recent advances in the biomedical world, vast changes are taking place in our growing knowledge of the physiological aspects of almost all the tissues and organs of the human body. One of the most prevalent topics of discussion is the question of obesity and its effect on the metabolic changes in the human body. The original classical role of adipose tissue as an energy storage organ has been greatly modified. We now know that it is an endocrine organ, producing adipokines like leptin, adiponectin, visfatin, resistin, apelin, *etc*, which modulate metabolic processes in the body. Since obesity is associated with an increase in the adipose tissue mass, these hormones may be expected to be produced in increased concentrations and may thus have a significant impact on the macronutrient metabolism. Further, these adipokines may interact with long term energy modulators like insulin. Even though the scientific community has started unravelling the mysteries of the close linkage between obesity, its hormones and their physiological effects, a lot still remains to be discovered. The present discussion makes an attempt to trace the basic modern day concepts of the role of obesity in various metabolic processes.

INTRODUCTION

Genetic predisposition is a key contributing factor in obesity, as has been demonstrated by familial aggregation, twin and adoption studies[1,2]. Estimates for a genetic basis for obesity range from approximately 40% to 70%. The idea that genetic loci alter body fat content has been substantiated by the identification of mutations that cause low- or high-fat phenotypes in rodents and humans[3]. Obesity comes about when energy intake, principally stored as triglycerides, exceeds energy expenditure[4]. Obesity is a complex trait influenced by diet, developmental stage, age, physical activity and genes[5]. Many recent epidemiological studies have documented the rapid increase in the prevalence of obesity. According to data from the Center for Disease Control Behavioural Risk Factor Surveillance System, in the United States the prevalence of obesity [body mass index (BMI) > 30 kg/m^2] has increased from < 20% a decade earlier to 30% in 2006[6]. Along with the increase in obesity there is a parallel increase in the prevalence of type 2 diabetes, impaired glucose tolerance[7,8], and other complications of obesity, such as hypertension, sleep apnoea, and arthritis. A recent study

has suggested that, due to the increase in obesity, future life expectancy may even decrease[9].

REGULATION OF ENERGY HOMEOSTASIS AND OBESITY

Obesity is characterized by an excess of adipose tissue. The increase of food intake (hyperphagia) triggered by a period of fasting is a simple but compelling example of food-intake regulation. The balance between energy intake (food consumption) and energy expenditure (basal metabolic rate, i.e. biochemical processes required to maintain cellular viability, physical activity and adaptive thermogenesis) is tightly regulated. A homeostatic network maintains energy stores through a complex interplay between the feeding regulatory centres in the central nervous system (CNS), particularly in the hypothalamus and the regulated storage and mobilization of fat stores that maintains the body energy stores[10,11]. Thus, genes that encode the molecular components of this system may underlie obesity and related disorders. A number of recent research groups have encoded the molecular and genetic mysteries that underlie obesity and its related disorders.

Signalling pathways in the hypothalamus

The hypothalamus is the major nervous centre controlling food intake. It has two major areas which play important role in maintaining the normal energy homeostasis of the body by controlling the hunger and satiety centres. The ventro-medial hypothalamic nucleus (VMN), a portion of the hypothalamus, is known as the 'satiety centre'. Stimulation of the VMN causes suppression of food intake, whereas a bilateral VMN lesion induces hyperphagia and obesity. The lateral hypothalamic area is known as the 'hunger centre', and its stimulation or any lesion induces the opposite set of responses[12,13]. Various neuropeptides (e.g. the melanocortin system, neuropeptide Y) and neurotransmitters (e.g. serotonin, dopamine and noradrenaline) along with insulin and leptin molecules function in the hypothalamus and thus coordinate the behavioural, physiological and metabolic responses. These response elements maintain the energy balance *via* both the intake and the expenditure pathways[14].

In addition to these long-term adiposity signals, short-term meal-related signals are also transmitted to the CNS through afferent nerves or gut-secreted peptides (e.g. cholecystokinin, ghrelin[15]). Neurons in the CNS also directly sense carbohydrates and fats[16,17].

Melanocortins

Melanocortins are peptides that are cleaved from the proopiomelanocortin precursor molecule, and thus exert their effects by binding to members of a family of melanocortin receptors[18].

Melanocortins also promote negative energy balance. Among the growing list of melanocortins, the significant ones for these purposes are the α-melanocyte-stimulating hormone[19], the corticotropin-releasing hormone[20], the thyrotropin-releasing hormone[21], cocaine and the amphetamine-regulated transcript[22] along with interleukin-1β. Neuronal synthesis of these peptides increases in response to increased adiposity signalling in the brain[23].

The role of melanocortin signalling in the control of energy homeostasis first emerged after the cloning of the MC3- and MC4-receptor genes, and the discovery that they are expressed primarily in the brain[24]. This discovery was followed by evidence that a synthetic agonist of these receptors suppresses food intake whereas a synthetic antagonist leads to the opposite effect[25].

Neuropeptide effectors

Neuropeptide Y (NPY) is a prominent orixgenic molecule and belongs to the class of anabolic effector pathways. Experimental studies have shown that repeated injection of NPY into cerebral ventricles or directly into the hypothalamus stimulates food intake, decreases the total body energy expenditure and leads to obesity[26-29]. It also induces lipogenic enzymes in the liver and white adipose tissue[27]. NPY gene expression and secretion of the NPY peptide in the hypothalamus are increased during active depletion of body fat stores[30,31] and leptin inhibits arcuate nucleus NPY gene expression[32,33]. NPY meets the criteria for an anabolic signalling molecule. Moreover, the Agouti-related protein (AGRP), orexin (also known as 'hypocretin') and the melanin-concentrating hormone (MCH) have all been added to the list of candidate anabolic effector signalling molecules.

Ghrelin

Ghrelin, a peptide hormone secreted from the stomach, is now known to have a potent appetite-stimulating activity. It has also been suggested that the primary location for the orexigenic activity of ghrelin is through the neuropeptide Y/Agouti-related peptide (NPY/AGRP) neurons within the arcuate nucleus of the hypothalamus[31]. Recently, it has been shown that area postrema, a caudal brain stem center that lacks a blood-brain barrier, is a key site of activity for ghrelin in stimulating appetite and regulating pancreatic protein secretion[32]. Ghrelin is suggested to play a role in long-term regulation of energy balance, as chronic administration of ghrelin causes weight gain by reducing fat utilization as an energy source[33]. Circulating levels of ghrelin are increased in the fasting state and in anticipation of food, and are attenuated by feeding and the presence of nutrients in the stomach. Ghrelin also plays a role in the digestion of food and the stimulation of gastric motility, acid secretion, and pancreatic protein secretion .

ROLE OF ADIPOSE TISSUE AS AN ENDOCRINE ORGAN

Adipose tissue is a major endocrine organ, producing

various hormones that regulate body metabolism. An increase in the fat cell mass leads to imbalances in its release of hormones, which can have various metabolic effects. The metabolic complications of obesity, often referred to as the metabolic syndrome, consist of insulin resistance, often culminating in β-cell failure, impaired glucose tolerance and type 2 diabetes, dyslipidemia, hypertension, and premature heart disease. Abdominal obesity, ectopic lipid accumulation, hepatic steatosis, and sleep apnea can also be included in the metabolic complications of obesity[34].

In mammals, white adipose tissue functions as the main depot for fuel storage. In the past decade, identification of myriad lipid and protein signals secreted from this tissue has led to its recognition as a major endocrine organ[35,36]. Adipocytes secrete a variety of biologically active molecules, termed as adipocytokines[37]. Adipose tissue has been found to be an important source of various hormones. Of these, the hormones which play an important role in body weight regulation are mainly leptin, visfatin, apelin, resistin, and adiponectin.

ROLE OF LEPTIN IN BODY WEIGHT REGULATION

Leptin

Leptin, the 167 amino acid protein, is a cytokine-like hormone secreted from white adipose tissue. It was the first adipocytokine identified, encoded by the *ob* gene. Leptin receptors are expressed in a number of different tissues. Adipocytes have been identified as the primary site for leptin expression, however it is also expressed in the gastric wall, vascular wall, placenta , ovary , in skeletal muscle, and the liver[38-41]. Leptin has several roles, including growth control, metabolic control, immune regulation, insulin sensitivity regulation, and reproduction[42-44]. However, its most important role is in body weight regulation.

Leptin and insulin

The mechanisms involved in leptin secretion are all quite different. The rate of insulin-stimulated glucose utilization in adipocytes is a key factor linking leptin secretion to body fat mass[45]. Although the mechanism is incompletely understood, it may involve glucose flux through the hexosamine pathway[46]. In addition, various observations indicate that leptin has a more important role than insulin in the CNS control of energy homeostasis. Insulin is secreted from the endocrine pancreas and exerts potent effects on peripheral nutrient storage. Insulin is an afferent signal to the CNS that causes long-term inhibitory effects on energy intake. Leptin receptors and insulin receptors are expressed by brain neurons involved in energy intake[47-49], and administration of either peptide directly into the brain reduces food intake[50-52] whereas deficiency of either hormone does the opposite[53-54]. Leptin deficiency causes severe obesity, with hyperphagia that persists despite high insulin levels. In contrast, obesity is not induced by insulin deficiency. However, such comparisons are complicated by the critical role that insulin has in promoting both fat storage and leptin synthesis by fat cells.

Leptin and obesity

Leptin is the chief regulator of the "brain gut axis", which provides a satiety signal through its action on the CNS receptors within the hypothalamus[41,55] Activation of hypothalamic leptin receptors suppresses food intake and promotes energy expenditure pathways[56]. Leptin levels decrease with weight reduction.

The hypothesis that leptin resistance can occur in association with obesity was first suggested by the finding of elevated plasma leptin levels in obese humans[57]. This hypothesis suggests that some cases of human obesity may be due to reduced leptin action in the brain, and affected individuals are unlikely to respond to pharmacological treatment with leptin. Several mechanisms contribute to leptin resistance.

Leptin uptake into the brain is facilitated by leptin receptors expressed by endothelial cells[58] in the blood-brain barrier that function as leptin transporters. Impaired leptin transport across endothelial cells of the blood-brain barrier is one potential mechanism leading to leptin resistance. Whether dysfunction of this transport process can lead to obesity remains to be determined, but it has been seen that in obese humans cerebrospinal fluids demonstrate low levels of leptin in comparison to plasma[59].

Upon activation of leptin receptors in the brain, a series of integrated neuronal responses required for food intake and energy balance are activated, and these neuronal effector pathways play a key role in energy homeostasis. Failure of one or more of these pathways in response to the leptin signalling will manifest as leptin resistance[60].

Reduced leptin-receptor signal transduction is another potential cause of leptin resistance. Like other cytokine receptors, activation of the leptin receptor induces expression of a protein that inhibits any further leptin signal transduction, termed 'suppressor of cytokine signalling-3' (SOCS-3)[61]. The potential contribution of SOCS-3 to acquired forms of leptin resistance and obesity is an active area of study.

Leptin and inflammation

The role of Leptin in inflammation can be summarized as: (1) Pro-inflammatory; (2) Increase in T cell activation, and cytokine release proliferation; (3) Promotes Th1 response; (4) Increases NK cell activation; (5) Increases macrophage activation and cytokine release [tumor necrosis factor (TNF)-α/interleukin (IL-6) *etc*]; and (6) Activates neutrophils and increases their chemotaxis and oxidative burst.

Leptin acts on the monocytes and induces the release of cytokines such as TNF-α or IL-6 as well as CCL2 and VEGF[58]. It leads to increased proliferation and

differentiation of the monocytes. Acting on the neutrophils, leptin leads to an increased expression of CD 11b, as well as increased neutrophil chemotaxis and oxidative burst[58,62,63], all of which are very important in innate immune responses and regulation of pathogen colonization of the skin and mucosa[64].

Visfatin

Visfatin is also known as pre-B cell colony enhancing factor (PBEF). Visfatin also possess nicotinamide phos phoribosyltransferase (Nampt) activity. It is produced by the visceral adipose tissue. The expression of visfatin is increased in abdominal obesity and type 2 DM. Visfatin binds to the insulin receptors at a site distinct from insulin and mimics insulin in exerting a hypoglycemic effect by reducing glucose release from the hepatocytes, and stimulating the glucose utilization in the peripheral tissues[65] .

However, recent studies indicate the association of visfatin with obesity alone and make its metabolic role debatable. Revello *et al* demonstrated that the extracellular form of Nampt (eNampt/Visfatin/PBEF) secreted through the non-classical secretory pathway had nicotinamide adenine dinucleotide (NAD) biosynthetic activity. Haplodeficiency and chemical inhibition of Nampt re sulted in decreased NAD biosynthesis and glucose-stimulated insulin secretion in pancreatic islets *in vitro* and *in vivo*. It has been suggested that supplementation of nicotinamide mononucleotide, a Nampt reaction product, results in an amelioration of these defects. Revello and his co-workers also demonstrated that visfatin does not mimic insulin[66].

Apelin

Apelin is an adipocytokine whose plasma concentration is increased in obesity, insulin resistance and hyperinsulinemia[66]. In the cardiovascular system, apelin elicits endothelium dependent, nitric oxide mediated vasorelaxation and reduces arterial blood pressure[67], along with a positive inotropic activity.

Resistin

Resistin is thus named because it renders resistance to the action of insulin[68]. It is made up of 114 amino acids. It has been observed that circulating resistin levels are increased in obese humans. It is considered a pro-inflammatory molecule. It activates NFκB-dependent cytokine release and adhesion molecule expression including TNF-α and IL-6. It also plays an important role in the pathogenesis of diabetes and its complications. The release of resistin is often associated with stimulation by the inflammatory process, IL-6, hyperglycemia and hormones like the growth hormone and the gonadal hormones. The role of resistin in obesity and insulin resistance in humans is controversial[69].

Adiponectin

Adiponectin is an important adipocytokine, present within cells and in the circulation, in multimeric forms: trimers, hexamers, high-MW oligomers and full-length adiponectin multimers (fAd). The fAd may cleave to liberate a fragment containing the C-terminal globular domain (gAd), which plays an important role in adipose tissue metabolism[70]. Adiponectin oligomers act *via* two receptor subtypes (AdipoR1 and AdipoR2), the stimulation of which results in increased AMP-activated protein kinase (AMP-kinase), PPAR-α ligand activities and activation of a NF-κB signaling pathway[71-73].

Adiponectin has the following metabolic functions in the body: (1)Enhances hepatic insulin actions and suppresses fatty acid influx into the liver[74,75]; (2) Enhances glucose uptake in the liver and skeletal muscles[71]; and (3) Increases fatty acid oxidation[76].

The main difference between adiponectin and the other hormones is that, whereas the other hormones are related to insulin resistance and are increased in obesity, adiponectin production and concentration decreases in obesity[77].

Combined efforts of various researchers have led to the discovery that the adiponectin levels in humans is less in obese individuals than in the lean subjects[78]. In another recent study it has been observed that plasma MMW and LMW adiponectin levels decrease in Type 2 diabetics as compared to the non-diabetic individuals[79]. Various other studies have demonstrated the inverse relationship between plasma adiponectin and serum triglyceride levels as well as fasting and post-prandial plasma glucose concentrations.

Adiponectin and inflammation: The role of adiponectin has been defined beneficial to the body. (1) It is anti-inflammatory[80]; (2) It decreases T cell activation and proliferation; (3) It inhibits NFkB dependent cytokine release and molecule expression including TNF-α/IL-6[81]; (4) It increases IL-10; and (5) It inhibits phagocytosis oxidative burst.

In obesity, concentrations of inflammatory mediators like TNF-α and IL-6 increases. This leads to a decrease in adiponectin expression and release. The main function of adiponectin in an immune metabolism is *via* the NFκB pathway[73]. In the immune system, adiponectin inhibits T cell activation and proliferation.

Adiponectin also inhibits B-cell lymphopoiesis[82]. Adi ponectin induces the production of the anti-inflammatory mediators IL-10 in human monocytes, monocyte-derived macrophages, and dendritic cells. In addition, adiponectin significantly impairs the production of the pro-inflammatory cytokine IFN-γ. Moreover, adiponectin-treated macrophages exhibit reduced phagocytic capacity[83].

Adiponectin and cardiovascular function: Adiponectin has been shown to have various vasculoprotective effects. In obesity, the adiponectin level decreases and it leads to an increase in cardiovascular risk.

Various studies have made an effort to correlate this

adipocytokine to the plasma lipoprotein concentration and its implication on CAD[84-86] but without any conclusive results.

The beneficial role of adiponectin on the cardiovascular system might be related to the following factors: (1) Adipo-vascular axis: It proposes the mechanism of adiponectin induced vascular protection *via* the epidermal growth factor and other endothelial growth factors by augmenting endothelial cell proliferation[87]; and (2) Adiponectin also decreases human aortic smooth muscle cell growth and migration response to growth factors[88].

Adiponectin and the hepatic system: In a recent study on Japanese subjects it was seen that adiponectin concentrations are lower in subjects with increased transaminase activities, indicating that hypoadiponectinemia contributes to an increase in transaminase activity. This may signify that liver diseases could be worsened if associated with metabolic diseases[89]. Moreover, it has been observed that high levels of adiponectin can protect against steato hepatitis[90]: (1) Hypoadiponectinemia→Insulin resistance + Hyperlipidemia→Fatty Liver, and (2) Hypoadiponectinemia→Increase hepatic fatty acid influx→Fatty Liver.

Adiponectin and bone: In recent studies, it has been observed that adiponectin and its receptors are also expressed in osteoblasts[91-93]. Further studies suggest that adiponectin stimulates the proliferation, differentiation and mineralization of osteoblasts *via* the AdipoR1 and AMP kinase signaling pathways in autocrine and/or paracrine fashions[94]. It has been found that the suppression of AdipoR1 expression by its siRNA inhibited the differentiation and mineralization of the cells and that adiponectin promoted these processes through the action of AdipoR1 on the osteoblasts. Recent studies have also shown that adiponectin promotes osteoblast proliferation[91-93] and exerts an enhancing action on human osteoblast differentiation and mineralization[93].

However, despite intensive research being carried out on adiponectin, various issues still remain to be explored further such as the complete identification of the adiponectin receptor and the exact mechanism of adiponectin action.

Acute-phase serum amyloid A: Circulating acute-phase serum amyloid A (A-SAA) levels are elevated in obese individuals as compared to lean[95,96], and the expression of A-SAA is strictly correlated with the BMI and fat cell size. It is a pro-inflammatory and lipolytic adipokine in humans. A-SAA may act locally to alter cytokine production and fat metabolism, as well as systemically on liver, muscle, and cells of the immune metabolism and the vasculature, to impact insulin resistance and atherosclerosis. Research on A-SAA has shown that the increased expression of A-SAA by adipocytes in obesity suggests that it may play a critical role in local and systemic inflammation and free fatty acid production and could be a direct link between obesity and its co-morbities, such as insulin resistance and atherosclerosis[97].

The signaling pathays of the A-SAA mediated inflammation response are not well studied. However, in neutrophils, SAA has been found to induce IL-8 production through the formyl peptide receptor like 1/lipoxin A4 receptor and activates nuclear factor kappa B[98]. The same signaling pathways has recently been shown to be an important mediator of inflammation associated with insulin resistance[99,100].

Since energy balance involves this complex interplay between multiple tissues and signaling pathways, an integrated view of feeding behavior, neuroendocrine signaling, nutrient uptake, transport, storage and utilization is required for understanding fat regulation.

EFFECTS OF OBESITY ON THE MACRONUTRIENT METABOLISM ARE MAINLY MEDIATED BY INSULIN RESISTANCE

Several adipokines like Leptin[101], adiponectin[102] and visfatin[103] have been shown to stimulate insulin sensitivity. On the other hand, resistin[104] and the retinol binding protein[105] induce insulin resistance. Adiponectin is proposed to be essential in insulin sensitivity[106]. In obesity there is a decrease in the Adipo R expression levels, thereby reducing adiponectin sensitivity and enhancing insulin resistance[107].

The term "insulin resistance" is defined as resistance to the effects of insulin on glucose uptake, metabolism, or storage. Insulin resistance in obesity is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle, and by impaired suppression of hepatic glucose output[108].

Insulin is a critical regulator of virtually all aspects of adipocyte biology, and adipocytes are one of the most highly insulin-responsive cell types. The physiological role of insulin includes the metabolism of all 3 macronutrients (carbohydrates, lipids, and proteins) as well as cellular growth. Insulin's action on lipid metabolism is analogous to its role in glucose metabolism, i.e. promoting anabolism and inhibiting catabolism. Insulin stimulates glucose transport and triglyceride synthesis (lipogenesis), as well as inhibiting lipolysis[109]. Specifically, insulin upregulates LPL and stimulates gene expression of intracellular lipogenic enzymes, such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). In addition, insulin inhibits adipocyte HSL through inhibition of its phosphorylation[110,111]. It has also been demonstrated that insulin influences the secretion of proteins from mature adipocytes probably by increasing the production of enzymes necessary for the processing of secreted protein precursors[112].

Mechanism of insulin resistance

Insulin's metabolic effects are mediated by a broad array of tissue-specific actions that involve rapid changes in protein phosphorylation and function, as well as changes

in gene expression. The initial molecular signal for insulin action involves activation of the insulin receptor tyrosine kinase, which results in phosphorylation of insulin receptor substrates (IRSs) on multiple tyrosine residues. These phosphotyrosine residues act as docking sites for many SH2 domain-containing proteins, including the p85 regulatory subunit of phosphoinositide 3' kinase (PI3K). Binding of the p110 catalytic subunit of PI3K to p85 activates the lipid kinase that promotes glucose transport[113].

Insulin action in adipocytes also involves changes in gene transcription. The transcription factor ADD-1/SREBP-1c (adipocyte determination and differentiation factor-1/sterol regulatory element-binding protein-1c) may play a critical role in the actions of insulin to regulate adipocyte gene expression[114-116], by inducing genes involved in lipogenesis and repressing those involved in fatty acid oxidation.

Functional defects in insulin resistance may be due to impaired insulin signalling in all three target tissues i.e. in adipose tissue, skeletal muscle and liver. In both muscle and adipocytes, insulin binding to its receptor, receptor phosphorylation and tyrosine kinase activity, and phosphorylation of IRSs are reduced. Recent studies have indicated that defective signaling from the insulin receptor is an important component of insulin resistance associated with obesity in humans.

There are also tissue-specific alterations observed in adipocytes of obese humans, IRS-1 expression is reduced, resulting in decreased IRS-1-associated PI3K activity, and IRS-2 becomes the main docking protein for PI3K[117]. In contrast, in skeletal muscle of obese individuals, IRS-1 and IRS-2 protein levels are normal but PI3K activity associated with both IRSs are impaired[118].

Mechanism for signaling defects in insulin pathways in obesity

It has been suggested that there is increased expression and activity of several protein tyrosine phosphatases (PTPs), which dephosphorylate and thus terminate signalling propagated through tyrosyl phosphorylation events. Some data indicate that there is increased expression and/or activity of the three PTPs i.e. PTP1B, leukocyte antigen-related phosphatase (LAR), and src-homology-phosphatase 2, in the muscle and adipose tissue of obese humans[119]. PTP1B and LAR have been shown to dephosphorylate the insulin receptor and IRS-1 *in vitro*[120,121]. PTP1B not only has a regulatory role in insulin action, but also has a role in energy homeostasis.

Role of TNF-α in insulin resistance in obesity

TNF-α is a pluripotent cytokine produced from macrophages[122]. Fat tissue is a significant source of endogenous TNF-α production and the expression of this cytokine in adipose tissue is elevated in obesity[123]. This abnormal expression of TNF-α in adipose tissue plays a critical role in peripheral insulin resistance in obesity. It has been studied that neutralization of TNF-α in obese and insulin-resistant animals results in significant increases in peripheral insulin sensitivity[124]. Various studies have demonstrated that TNF-α induces insulin resistance through its ability to inhibit intracellular signalling through serine phosphorylation of IRS-1, and can reduce GLUT4 expression. Moreover, this inhibition can be reversed by neutralizing TNF-α *in vivo*[125,126]. The increased expression of TNF-α is significantly correlated with the hyperinsulinemia in the presence of normoglycemia. It has been demonstrated as a marker of insulin resistance[127]. In addition to its role in host defense, TNF-α also has important effects on whole body lipid and glucose metabolism[128].

Effect of obesity on carbohydrate metabolism

The action of insulin in lowering blood glucose levels results from the suppression of hepatic glucose production and the increased glucose uptake into muscle and adipose tissue *via* GLUT4. Muscle has long been considered the major site of insulin-stimulated glucose uptake *in vivo*, with adipose tissue contributing relatively little to total body glucose disposal. On the other hand, various transgenic studies have raised the possibility of a greater role for glucose uptake into fat in systemic glucose homeostasis. Over-expression of GLUT4 selectively in fat tissue enhances whole body insulin sensitivity and glucose tolerance[129], and knocking out GLUT4 selectively from fat tissue results in a degree of insulin resistance similar to that seen with muscle-specific knockout of GLUT4. In all forms of obesity, there is downregulation of GLUT4, a major factor contributing to the impaired insulin-stimulated glucose transport in adipocytes[130]. However, in the skeletal muscle of obese humans, GLUT4 expression is normal. It has also been suggested that defective glucose transport may be due to impaired translocation, docking, or fusion of GLUT4-containing vesicles with the plasma membrane[131]. With obesity there is reduced glucose disposal in adipose tissue. It has been suggested that obesity leads to the development of hyperglycemia[130], hyperlipemia[132], hyperinsulinemia[133], and insulin resistance[134]. Molecules like FFA, leptin, or TNF-α, all of which are released from adipose tissue, are known to affect glucose homeostasis indirectly. Undoubtedly there are other, as yet undiscovered, molecules from adipose tissue that influence systemic metabolism.

Effect of obesity on lipid metabolism

Obesity is associated with increased basal lipolysis in adipose tissue, and elevated circulating FFAs[135]. Acute-phase serum amyloid A (SAA), a lipolytic adipokine in humans, stimulates basal lipolysis. The lipolysis has been postulated to be an autocrine feedback mechanism by which increased SAA production from enlarged adipocytes A into the circulation may contribute to insulin re sistance. The SAA act through the CLA-1 and the extra-cellular signal regulated kinase signaling pathway to stimulate lipolysis directly[136]. Alternatively, increased

lipolysis by SAA may be indirect, i.e. through the stimulation of the lipolytic cytokines viz IL-6 and TNF-α.

Plasma triglyceride (TG) concentration is another metabolic variable, most affected in obesity. It has been suggested that there is tissue resistance to insulin mediated glucose uptake, which in turn accelerates the very low density lipoprotein (VLDL), TG production rate and leads to endogenous hypertriglyceridemia[137-139]. In obesity there is decreased Lipoprotein lipase-mediated lipolysis of chylomicron-TG and ineffective inhibition of hormone-sensitive lipase-mediated lipolysis in adipose tissue[140]. Postprandial lipemia and elevated plasma FA levels are well-recognized abnormalities in obesity. Excess fatty acid availability early in the postprandial period (when it is normally suppressed by insulin) is estimated to influence glucose uptake by as much as 50%[141]. SAA has also a direct effect on cholesterol metabolism. Being an apolipoprotein by nature, it is the apoprotein of high-density lipoprotein (HDL)[142]. The inter-action of SAA with HDL may impair the function of HDL as an anti-atherogenic molecule[143] and facilitate its degradation[144]. The increase of adipose tissue derived SAA in obesity may be a link between obesity, low HDL and increased coronary Artery Disease risk.

Effect of obesity on protein metabolism

It is a well established fact that human obesity is accompanied by abnormalities in both glucose and lipid metabolism[145-149]. However, it is controversial whether protein metabolism is also disturbed in overweight individuals. Some researchers have reported that moderate obesity and difference in body fat distribution are associated with abnormalities in protein metabolism and have hypothesized that moderate obesity is associated with increased proteolysis, an increased rate of basal leucine turnover[150-152], and the impairment of insulin's antiproteolytic action , whereas others have found similar rates of basal leucine turnover in nonobese and obese subjects[153-156]. Conflicting reports also have appeared about the effect of insulin on protein anabolism. Some studies have indicated that the insulin resistance of obesity extends to protein metabolism[150,157], whereas other reports have challenged this conclusion[152,156].

ROLE OF OBESITY IN INFLAMMATION

Adipose tissue-derived proteins have been defined as adipokines, and have been implicated in the pathogenesis of chronic inflammation in obesity. The study of adipose tissue on inflammation was considerably impacted by the demonstration of resident macrophages in adipose tissue[158]. The possible mechanisms underlying the infiltration of macrophages into adipose tissue may be the chemokines by adipocytes, which would then attract resident macrophages[159]. Recent studies have suggested that macrophages infiltrate adipose tissue as part of a scavenger function in response to adipocyte necrosis[160]. The adipose tissue of obese humans contains an increased number of macrophages, and once activated, these macrophages secrete a host of cytokines, such as TNF-α, IL-6, and IL-1. The adipose tissue-resident macrophages are responsible for the expression of most of the tissue TNF-α and IL-6. The expression of macrophage markers in human adipose tissue was high in subjects with obesity and insulin resistance, and was also correlated with the expression of TNF-α and IL-6[161,162].

With obesity and progressive adipocyte enlargement, the blood supply to adipocytes may be reduced, and the induction of adipocyte hypoxia *in vitro* results in the expression of a number of inflammatory cytokines[163]. Obesity is associated with elevated levels of circulating proinflammatory cytokines such as plasminogen activator inhibitor-1 (PAI-1), C-reactive protein (CRP), TNF-α, and IL-6 and monocyte chemoattractant protein-1 (MCP-1)[164]. Many of these factors are produced by adipose tissue, such as circulating levels of TNF-α, IL-6, and MCP-1. Adipocytes express low levels of the MCP-1, and increased expression has been seen in obese subjects[165]. Adiponectin acts as a key regulator of adipocyte secretory function *via* its autocrine action, which correlates with adiposity and insulin resistance[166].

PAI-1 is elevated in subjects with metabolic complications of obesity, and is expressed in the stromal fraction of adipose tissue, including endothelial cells[167-169]. PAI-1 inhibits both the tissue-type plasminogen activator and the urokinase-type plasminogen activator through its serine protease inhibitor function, and this inhibition of fibrinolysis may contribute to a pro-thrombotic state[170].

The cell types involved in the inflammatory response in obesity are not fully delineated. Recent attention has focused on adipose tissue macrophages (ATMs) as a mediator of inflammatory responses in adipose tissue. In addition to the production of pro-inflammatory cytokines that promote metabolic complications, adipose tissue is the sole source of adiponectin, which is anti-inflammatory and associated with protection from atherosclerosis[171]. From an evolutionary perspective, adipose macrophages may have represented an important part of the host defense against injury or infection.

ROLE OF DIFFERENT FAT DEPOTS IN METABOLISM

Many studies have shown that excess fat in the upper part of the body, i.e. central or abdominal (android or male-type obesity) correlates with increased mortality and risk for disorders such as diabetes, hyperlipidemia, hypertension, and atherosclerosis of coronary, cerebral, and peripheral vessels more than the lower body or gluteofemoral or peripheral depot (gynoid i.e. female-type of fat distribution)[172,173]. Abdominal fat is composed of abdominal subcutaneous fat and intraabdominal fat (which includes visceral or intraperitoneal fat). The visceral fat is associated with disturbances in insulin-glucose homeostasis, alterations in plasma lipoprotein-lipid levels[174], particularly increased plasma triglycerides and low HDL

cholesterol concentrations. These effects on the lipid profile may be due to the association of insulin resistance with disturbances in plasma lipid transport and lipoprotein levels[175]. Mobilization of FFAs is more rapid from visceral than from subcutaneous fat cells because of the higher lipolytic activity in visceral adipocytes compared to subcutaneous adipose tissue. This variation may be due to the increased expression and function of β-adrenoreceptors and a decreased insulin receptor affinity and signal transduction in visceral adipocytes[176,177]. This in turn results in a variation in the action of lipolysis-regulating hormones, catecholamines and insulin[176].

CONCLUSION

The newly identified function of the adipocytes has progressed from a simple energy storage tissue to a major endocrine system. The hormones secreted from adipose tissue influence energy homeostasis, glucose and lipid metabolism, vascular homeostasis, immune response, and reproductive functions. Newly discovered roles include the production of the cytokines IL-6, TNF-α, and leptin, which all play decisive roles in the development of obesity and insulin resistance. Thus, the enlargement of the adipose mass has pleiotropic effects on endocrine and metabolic events at whole body level that may contribute to the pathogenesis of the detrimental complications of obesity.

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