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Adipose Tissue Hypoxia: Effects on Metabolism and Insulin Sensitivity

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Abstract

Obesity is associated with an increased risk of insulin resistance and type 2 diabetes. These risks have been correlated with a chronic inflammatory response of the adipose tissue that affects glucose and lipid metabolism. Hypoxia, stemming from inadequate adipose tissue blood flow in obesity, has been shown to be an important contributor to this inflammatory response. The response to hypoxia includes changes in gene expression that affect glucose uptake, glycolysis, lipid metabolism, inflammation, and angiogenesis. This review describes the effects of obesity on chronic and intermittent hypoxia in white adipose tissue and highlights the resulting effects on gene expression and cell metabolism that can affect the onset of systemic insulin resistance and the development of chronic metabolic dysfunction in type 2 diabetes.

Keywords: Obesity; Glycolysis; Metabolism; Hypoxia; Insulin

Introduction

Adipose tissue is known to be an important endocrine organ that communicates metabolic information to the brain and other tissues. Peripheral insulin resistance and inflammation are evolutionarily conserved responses to preserve glucose supply and eliminate harmful stimuli during localized or systemic stress events. It is becoming increasingly clear that the connection between obesity and the development of diabetes includes signaling by the adipose tissue itself, particularly white adipose tissue. Several lines of evidence support the concept that the changes in adipose tissue signaling are linked to hypoxia-mediated changes in the expression of adipokines and inflammatory cytokines reviewed by Trayhurn [1]. These changes cause a disruption in normal glucose and lipid metabolism, and the expression of inflammatory cytokines stimulates macrophage infiltration, which promotes a chronic inflammatory condition within the tissue. The basis for these changes is discussed along with future possibilities of targeting the hypoxia-mediated inflammatory response as a strategy towards preventing the onset of obesity-related type 2 diabetes.

Adipose hypoxia and transcriptional responses

The accumulation of white adipose tissue that occurs due to obesity has been shown to result in chronic adipose tissue hypoxia. The adipose cell response to hypoxia parallels that seen for other cell types, however the response is magnified because obese adipose tissue exhibits on average a chronic 3-fold lower oxygen level than lean adipose tissue (pO_2 15 *vs.* 45 mm Hg) [2,3]. As the adipose tissue expands, it is unable to compensate for the tissue oxygenation needs and becomes chronically hypoxic.

The adipose tissue response to hypoxia includes two major transcription factor pathways, hypoxia-inducible factor (HIF) and nuclear factor κB (NFκB). The HIF-1α (and less studied HIF-2α) subunits act as oxygen sensors. In normoxia, the HIF-1α subunit is rapidly degraded due to oxygen-dependent proline hydroxylation. The hydroxyl group is bound by the E3 ubiquitin ligase, von Hippel-Lindau, which then targets the protein for ubiquitination and degradation by the proteasome. This fundamental regulation by degradation allows a rapid increase in HIF-α protein levels when oxygen levels decline, preventing hydroxylation [4]. Stabilized HIF-1α can then interact with HIF-1β in the nucleus to stimulate the expression of adipocyte genes which improves glucose utilization (i.e., GLUT1, lactate dehydrogenase), initiates hormone signals (i.e., leptin), and stimulates angiogenesis (i.e., vascular endothelial growth factor (VEGF)). Expression of some genes is inhibited by HIF-1, most notably the anti-inflammatory hormone adiponectin [5].

The NFκB transcription factor pathway is also central to the hypoxia response in adipose tissue. NFκB is held inactive in the cytoplasm by binding the inhibitory protein IκB. NFκB becomes active through several stress-mediated pathways that lead to the degradation of IκB. Several theories exist for the mechanism by which hypoxia activates NFκB, but they all include eventual activation of the IκB kinase that leads to degradation of IκB [6]. In cultured adipocytes, hypoxia leads to NFκB activation and an increase in the expression of pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and monocyte chemo-attractant protein-1 (MCP-1) [7]. These inflammatory signals lead to localized changes in extracellular matrix, vascular permeability, and recruitment of inflammatory cells, especially macrophages. This type of response is seen in many chronic inflammatory pathologies including fibrotic diseases and cancer.

In addition to chronic adipose tissue hypoxia, obese patients are also more likely to suffer from intermittent hypoxia due to sleep apnea, and it is often difficult to determine whether the link to metabolic disorders is due to the commonality of obesity, or due to the intermittent hypoxia. Specific effects of intermittent hypoxia on adipose tissue gene expression in animal models have shown significant changes in metabolic and oxidative stress pathways [8]. Unlike chronic hypoxia,

the overall effect of intermittent hypoxia on gene expression is predominated by oxidative stress and NFκB-regulated responses rather than HIF-mediated gene expression, thus inflammatory cytokines are preferentially produced rather than proteins required for metabolic adaptation.

Effects of adipose hypoxia on angiogenesis and inflammation

With obesity, the white adipose tissue hypoxia leads to transcriptional responses that result in changes in the expression and secretion of adipokines as well as angiogenic and inflammatory mediators. As described above, hypoxia promotes the expression and release of leptin, VEGF, IL-6, and MCP-1, whereas adiponectin production is reduced. Expression and secretion of VEGF affects endothelial cells within local vascular beds resulting in increased permeability and migration. In the context of other vascular growth factors such as platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF), the appropriate VEGF response leads to functional angiogenesis that improves the oxygen supply [4]. Unfortunately, adipose hypoxia in obesity and in many pathologies such as peripheral vascular disease and cancer, the VEGF response leads to leaky vessels and exacerbates local inflammation rather than improving oxygenation [9]. This combination along with the production of the inflammatory cytokine IL-6 and the monocyte-attractant MCP-1 results in edema and a buildup of immune cells, including macrophages, T-lymphocytes, B lymphocytes, natural killer cells, and neutrophils to the localized site [10].

An important question is whether the dysfunctional angiogenesis and inflammation have a causal relationship with insulin resistance. Although obese animal models exhibit reduced adipose tissue blood flow, non-obese insulin resistant animals show increased vascularization, suggesting insulin resistance itself does not directly reduce adipose tissue blood flow [11,12]. Instead, the evidence suggests that obesity leads to chronic hypoxia and inadequate angiogenesis that results in inflammation and contributes to the development of insulin resistance.

This model is supported by recent studies of adipose hypoxia in obese patients. Obese patients exhibit lower adipose tissue oxygenation than lean subjects, but the level of hypoxia is not affected by their insulin resistance status [13]. Patients with insulin resistance also exhibit higher plasma levels of adiponectin and increased HIF-1α and VEGF levels in adipose tissue biopsies, suggesting that insulin resistance itself does not exacerbate the hypoxia-mediated inflammatory response but that adipose tissue dysfunction may promote metabolic disease. Furthermore, in adipocytes isolated from type 2 diabetic patients, administration of an NFκB decoy molecule prevents excess NFκB activity and reduced insulin resistance, suggesting that decreasing the inflammatory response that results from adipose hypoxia could provide therapeutic benefit to the insulin resistance that results from obesity [14].

Effects of adipose hypoxia on glucose metabolism and insulin sensitivity

The development of hypoxia in white adipose tissue results in physiological adaptation in adipocytes, including changes in glucose metabolism. Increasing glucose uptake is the first line of defense against hypoxia in most of cells [4,15], including adipocytes. Hypoxia induced glucose uptake has been observed in human subcutaneous preadipocytes [16] and 3T3-L1 adipocytes [17] and can be blocked by cytochalasin B, an inhibitor of the facilitative glucose transporters (GLUT) [16]. This increase is primarily mediated by the increase in expression of GLUT1 [16,18,19], a ubiquitous GLUT responsible for basal glucose uptake by most of cells, but not GLUT4 and GLUT8 whose expression is reduced by prolonged hypoxia in contrast to GLUT1 [18,20]. There is also a possibility that hypoxia may induce GLUT1 subcellular translocation to the plasma membrane to enhance glucose uptake in adipocytes [17].

In addition to the increase in glucose uptake, another rapid cell response to hypoxia is to induce a metabolic switch from aerobic to anaerobic metabolism. Increased expression of genes encoding enzymes involved in glycolysis, including hexokinase 1 and 2 (HK1 and HK2), glucose-6-phosphate isomerase (GPI), phosphofructokinase (PFK), and aldolase C (ALDOC), has been shown in hypoxic adipocytes by both microarray and proteomic analyses [19,21,22]. More importantly, the production of the major end product of anaerobic glycolysis, lactate, is increased in adipocytes under hypoxia [23,24]. Consistently, the white adipose tissue of obese animals has higher levels of lactate than lean animals *in vivo* [25]. The increase in lactate production may have physiological significance because emerging evidence suggests that lactate is a signaling molecule in many cells. For instance, lactate can stimulate inflammation in macrophages and inhibit lipolysis in adipocytes [26,27]. Thus, the increased lactate under hypoxia may contribute to adipose inflammation and adipose tissue mass increase and obesity.

The metabolic switch toward anaerobic glycolysis leads to less glucose being oxidized through the citric acid cycle to produce ATP in adipocytes during hypoxia. Indeed, microarray analysis has shown a down regulation of a number of genes expressing proteins involved in mitochondrial metabolism and oxidative phosphorylation, such as cytochrome b (CTYB), cytochrome c oxidase subunit Va (COX5A), and ATP synthase, in human adipocytes in response to hypoxia [19]. In addition, reduced ATP production, mitochondrial membrane potential, and NADH dehydrogenase activity have been seen in 3T3-L1 adipocytes after exposed to hypoxia or incubated with hypoxia mimetics $CoCl_2$ [28].

Many of above changes in glucose metabolism in adipocytes under hypoxia are probably primarily mediated by HIFs as many genes involved in glucose metabolism, such as GLUT1, HKs, lactate dehydrogenase A (LDHA), and pyruvate dehydrogenase kinase 1 (PDK1), are well known direct targets of HIF-1 transcriptional regulation [4,15]. However, hypoxia induced changes in insulin and leptin signaling may also be involved.

Insulin is the primary hormone in regulating glucose homeostasis. In adipocytes, in addition to its role to stimulate glucose uptake, insulin stimulates glucose utilization by stimulating glucose oxidation and synthesis of glycerol-phosphate from glucose for triacylglycerol synthesis [29-32]. Increasing evidence has shown that adipose tissue hypoxia inhibits insulin signaling and blocks insulin-stimulated glucose uptake in adipocytes. The adipose tissue of obese mice has decreased insulin receptor-β and insulin receptor substrate-1, consistently with the changes observed in 3T3-L1 adipocytes after hypoxia treatment [33]. In addition, hypoxia reduces phosphorylation of insulin receptor, Akt, and AS160 in 3T3-L1 adipocytes in coupled with blocking insulin-stimulated glucose transport [34,35]. These changes are dependent on the HIF expression because overexpression or down regulation of HIF-1α or HIF-2α can mimic or inhibit the effects of hypoxia, respectively [34]. This evidence suggests that

hypoxia induces insulin resistance in adipose cells, contributing to the metabolic changes in these cells.

Leptin is a hormone primarily produced by adipose tissue and plays an important role in the regulation of body energy balance, mainly food intake and energy expenditure [36,37]. It plays a critical role in the regulation of glucose homeostasis, as demonstrated by the hyperglycemia phenotype in leptin gene knockout mice (ob/ob and db/db) [36]. The specific action of leptin on adipocytes is likely mediated by its inhibition of insulin action, as observed in white adipose tissue [37]. In adipocytes, hypoxia induces leptin expression [18,23]. This increase of leptin signaling may play a role in the above mentioned inhibition of insulin signaling by hypoxia.

The increase of leptin signaling and inhibition of insulin signaling and insulin-stimulated glucose uptake by hypoxia in adipocytes imply that hypoxia plays a role in developing type 2 diabetes in obese subjects. Further effects of hypoxia on insulin sensitivity in adipose tissue also include: 1) the production of several insulin-sensitizing adipokines is reduced under hypoxia [38,39], and 2) expression of GLUT4 is markedly reduced by hypoxia in adipose cells [18]. Consistently, knockout of HIF1α in adipose tissue reduces fat formation and ameliorates insulin resistance in mice [40]. In humans, the more severe the obesity, the greater the relative risk of developing type 2 diabetes. Thus, efforts to control adipose tissue hypoxia or the resulting transcriptional response could provide preventative or treatment options for obesity-related pathologies such as type 2 diabetes.

Effects of hypoxia on lipid metabolism

In normal white adipose tissue, lipolysis is stimulated when the insulin level is low and epinephrine levels are high. Epinephrine binds to cell membrane beta adrenergic receptors activating adenylyl cyclase and generating cAMP. The subsequent activation of protein kinase A leads to phosphorylation of hormone sensitive lipase which facilitates its interaction with the lipid droplet and the formation of free fatty acids and monoacylglycerol [41]. Due to the accumulation of free fatty acids, glucose utilization decreases because free fatty acids block the signal for more glucose uptake [42].

This normal regulation of lipid metabolism in adipocytes is disrupted in obesity due to the effects of hypoxia. In obese mice with measurably significant adipose hypoxia (40-50% reduced PO_2), free fatty acid uptake is reduced and lipolysis is increased. These effects on lipid metabolism are also mimicked by exposure of cultured adipose cells to a hypoxic environment [35]. Many of these changes are attributed to NFκB-mediated TNF-α production that leads to down regulation of the transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ is necessary for the induction of genes that control fatty acid synthesis and sequestration of triglycerides in lipid droplets including phosphoenolpyruvate carboxykinase, fatty acid synthase, and perilipin among others [43]. The hypoxia response of adipocytes also leads to insulin resistance which prevents its inhibitory effect on lipolysis and an increase in free fatty acid levels in the blood stream. The combination of tissue insulin resistance, increased lipolysis and excess leptin production contribute to an increased risk of systemic insulin resistance, lipid-mediated pathologies and the development of type 2 diabetes.

Directions of research and potential for therapy

It is clear that adipose tissue hypoxia results in multiple changes in lipid and glucose metabolism that can contribute to metabolic dysfunction that promotes or exacerbates type 2 diabetes (Figure 1). The findings related to hypoxia-mediated inflammation and metabolic disruption in adipose tissue have moved the research field towards efforts to correct these fundamental changes through possible therapeutic intervention.

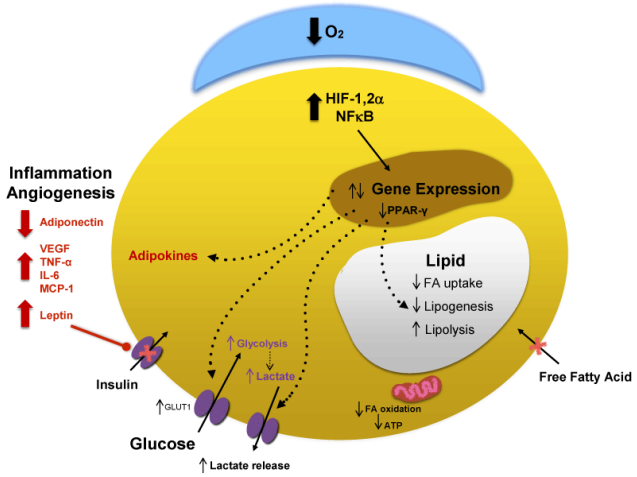

Figure 1: The effects of hypoxia on adipocyte gene expression and metabolism. Low O_2 leads to a stabilization of HIF-1,2α and activation of NFκB. These transcription factors increase the expression of inflammatory and angiogenic adipokines and increase expression of proteins that affect glucose uptake, glycolysis and insulin sensitivity. Inhibition of PPARγ by NFκB also leads to reduced lipogenesis and free fatty acid uptake. These metabolic changes accelerate the onset of systemic insulin resistance and the development of chronic metabolic dysfunction associated with type 2 diabetes.

Many questions remain including the benefit of accelerating vascularization of adipose tissue or perhaps preventing the hypoxic response. Studies using transgenic mouse models have shown conflicting evidence which leads to even more questions. For example, overexpression of VEGF in adipose tissue of animals fed a high-fat diet promotes an increase in vascularization, a decrease in hypoxia and normalization of metabolic indicators [44], and knockdown of HIF-2α in adipose tissue worsens the hypoxia and inflammation. These findings suggest that increasing expression of angiogenic factors to stimulate vascularization will reduce the inflammatory effects of adipose hypoxia. Alternatively, knocking down HIF-1α in a mouse model improves the insulin sensitivity and decreases adiposity in obese mice [45]. Thus, preventing the overall hypoxic transcriptional response may be more important for reducing the inflammation and growth response of adipose tissue. Realistically, there are no current therapies that directly target HIF-1α, and anti-VEGF therapies would likely make the hypoxic situation worse.

Efforts to target the resulting inflammatory response to hypoxia have also been explored. These approaches include targeting NFκB (salicylates, salsalate), TNF-α (entanercept, infliximab, adalimumab),

IL-1β (anakinra, canakinumab) and IL-6 (tocilizumab) [46]. Using agents to modulate NFκB, such as resveratrol have also been proposed [47]. These therapies have shown promise in animal models and have successfully reduced inflammatory markers in patient studies; however, none of the anti-inflammatory therapies have had significant benefit towards improving insulin sensitivity and glucose homeostasis in type 2 diabetic patients [48]. Although there remain many questions related to the appropriate therapeutic target in treating adipose tissue inflammation in obesity, a better understanding of the complex interactions between angiogenic and inflammatory signaling pathways may improve the efforts to reduce chronic adipose hypoxia and prevent the resulting effects on insulin sensitivity and the development of type 2 diabetes.

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