Skeletal muscle insulin resistance: role of inflammatory cytokines and reactive oxygen species

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Wei Y, Chen K, Whaley-Connell AT, Stump CS, Ibdah JA, Sowers JR. Skeletal muscle insulin resistance: role of inflammatory cytokines and reactive oxygen species. Am J Physiol Regul Integr Comp Physiol 294: R673–R680, 2008. First published December 19, 2007; doi:10.1152/ajpregu.00561.2007.—The cardiometabolic syndrome (CMS), with its increased risk for cardiovascular disease (CVD), nonalcoholic fatty liver disease (NAFLD), and chronic kidney disease (CKD), has become a growing worldwide health problem. Insulin resistance is a key factor for the development of the CMS and is strongly related to obesity, hyperlipidemia, hypertension, type 2 diabetes mellitus (T2DM), CKD, and NAFLD. Insulin resistance in skeletal muscle is particularly important since it is normally responsible for more than 75% of all insulin-mediated glucose disposal. However, the molecular mechanisms responsible for skeletal muscle insulin resistance remain poorly defined. Accumulating evidence indicates that low-grade chronic inflammation and oxidative stress play fundamental roles in the development of insulin resistance, and inflammatory cytokines likely contribute to the link between inflammation, oxidative stress, and skeletal muscle insulin resistance. Understanding the mechanisms by which skeletal muscle tissue develops resistance to insulin will provide attractive targets for interventions, which may ultimately curb this serious problem. This review is focused on the effects of inflammatory cytokines and oxidative stress on insulin signaling in skeletal muscle and consequent development of insulin resistance.

Impaired glucose metabolism, hypertension, obesity, lipid abnormalities, vascular dysfunction, and inflammation are key components of the cardiometabolic syndrome (CMS). The cardinal feature of the CMS is insulin resistance (reduced tissue responses to insulin), and the syndrome is strongly linked to excess caloric consumption, physical inactivity, and genetic factors. The CMS is emerging as an urgent public health dilemma due to its prevalence and the risk for development of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD).

The ability to maintain normal blood glucose levels involves a complex interplay between insulin secretion by pancreatic beta cells and insulin metabolic responsiveness in skeletal muscle, liver, adipose and other tissues. Skeletal muscle is particularly important since it comprises ~40–50% of body mass and is responsible for ~20–30% of resting oxygen consumption and mediates over 75% of all insulin-mediated glucose disposal under normal physiological conditions (82). Significant progress in understanding the development of insulin resistance has been made in the last decade; however, the precise molecular mechanisms responsible for insulin resistance, particularly in skeletal muscle, still remain incompletely understood.

Emerging data indicate that immune mediating inflammatory molecules play an important role in regulating glucose metabolism, and the excessive activation of inflammatory pathways may represent a fundamental step in the development of insulin resistance (40, 76, 82, 97). Oxidative stress due to increased reactive oxygen species (ROS) generation and/or compromised antioxidant systems represents another important factor in the progression of insulin resistance (82). Indeed, clinical conditions such as obesity, T2DM, hypertension, NAFLD, CVD, and CKD have all been associated with chronic low-grade inflammation and oxidative stress (17, 82, 97). The etiology of the CMS is a complex multifactorial process with both lifestyle and genetic origins. Accumulating evidence in-
Indicates that overnutrition and physical inactivity can lead to low-grade inflammation and oxidative stress, important preursors for insulin resistance and the CMS.

**Insulin Actions in Skeletal Muscle**

Insulin binds to the insulin receptor on the sarcolemma of skeletal muscle, increases insulin receptor tyrosine kinase activity, phosphorylates insulin receptor substrates (IRS-1, 2). Tyrosine phosphorylation of IRS-1 results in engagement of the p85 regulatory subunit of PI3K and activates the p110 catalytic subunit, which increases phosphoinositides such as phosphatidylinositol 3,4,5-trisphosphate. This leads to the activation of phosphoinositide-dependent protein kinase and downstream PKB (Akt) and/or atypical PKC (33). Phosphorylation of Akt substrate 160 (AS160), which has a GTPase-activating domain (Rab4), facilitates translocation of GLUT4 to the sarcolemma to facilitate glucose entry into the cell (Fig. 1). Intracellular glucose is then rapidly phosphorylated by hexokinase and directed to oxidative or nonoxidative (glycogen synthesis) pathways. Therefore, maintaining proper responses of the IRS-PI3K-Akt pathway is crucial for normal insulin-mediated glucose metabolism in skeletal muscle. Studies have shown that many other signaling pathways can crosstalk with the insulin metabolic signaling via the IRS-PI3K-Akt pathway leading to reduced skeletal muscle responses to insulin, thereby contributing to systemic insulin resistance. These potential mechanisms include 1) low-grade inflammation and inflammatory cytokines and 2) oxidative stress due to increased ambient ROS generation (Fig. 1).

**Inflammatory Cytokines and Skeletal Muscle Insulin Resistance**

A close relationship between chronic inflammation and skeletal muscle insulin resistance has recently been established. This is supported by 1) infiltration of inflammatory cells into skeletal muscle, as evidenced by increased macrophages and CD154 (T-cell marker) levels in muscle biopsies from T2DM patients (97); 2) increased inflammatory molecule levels, including TNF-α, IL-6, inducible nitric oxide synthase, fibrinogen, C-reactive protein (CRP), plasminogen activator inhibitor-1, and sialic acid in skeletal muscle are associated with insulin resistance and increase of T2DM (62); 3) increased circulating inflammatory cytokines originating from adipose tissue such as TNF-α, IL-6, IL-1β; 4) skeletal muscles, per se, generate and secrete several inflammatory cytokines (12); 5) skeletal muscle possesses many of the components of the innate immune system, including cytokine receptors and toll-like receptors (TLRs) (41) (Fig. 1). Cytokines or other molecules produced by skeletal muscle fibers that exert autocrine, paracrine, or endocrine effects have been termed “myokines” (60). The list of myokines is growing; to date, these myokines include TNF-α, IL-6, IL-1β, IL-1Ra, IL-8, IL-10, IL-15, and monocyte chemotactic protein (MCP)-1 (60).

TNF-α, TNF-α is a pleiotropic cytokine that induces various cellular responses such as apoptosis, proliferation, and production of inflammatory molecules. TNF-α is mainly produced by macrophages but also by many other cells, including skeletal muscle cells. TNF-α is the first cytokine recognized to have a
direct role in promoting insulin resistance (31). TNF-α is expressed in skeletal muscle from humans, rats, and in cultured myocytes (72). Increased levels of TNF-α have been noted in skeletal muscle tissue and cultured skeletal muscle cells from humans and animals with insulin resistance and/or diabetes (29, 42, 72). There is a significant inverse linear relationship between maximal glucose disposal rate and muscle TNF-α levels (72). High fructose diet-induced insulin resistance and hypertension are associated with increased skeletal muscle TNF-α levels but not adipose TNF-α in experimental rats (85, 99). Mice lacking TNF-α or its receptor are protected from obesity-induced insulin resistance (81, 91), while suppression of TNF-α by anti-TNF-α antibodies or TNF-α-converting enzyme inhibitors improves insulin sensitivity in obese or nonobese insulin-resistant models (31, 86). Because skeletal muscle accounts for the preponderance of in vivo glucose disposal, muscle is the most important target tissue for anti-TNF-α treatment (30).

TNF-α exerts its cellular effects via binding to specific receptors, namely TNFR1 and TNFR2. TNF-α promotes a complex array of postreceptor signaling events, primarily through three major pathways: 1) an apoptotic signaling pathway, 2) activation of JNK and MAPK pathway, and 3) activating NF-κB pathway. Both TNFR1 and TNFR2 are expressed by skeletal muscle (91, 100). TNF-α decreases tyrosine phosphorylation of IRS-1 (19, 30) and increases IRS-1 serine phosphorylation (9). This relative increase in serine to tyrosine phosphorylation may lead to increased ubiquitination/proteosomal degradation of IRS-1, or decreased ability of IRS-1 to engage the p85 subunit of PI3K leading to decreased insulin metabolic signaling. Alternatively, anti-TNF-α antibody infusion results in an improvement in insulin receptor phosphorylation in muscle (8, 30). TNF-α also has been shown to reduce signal transduction at the level of PKB (Akt) and the AS160, as well as insulin-stimulated glucose uptake in skeletal muscle tissue (9). Furthermore, TNF-α diminishes skeletal muscle IRS tyrosine phosphorylation and Akt activation in a p38 MAP kinase-dependent manner (18). AMPK also appears to be an important TNF-α signaling target (81). TNF-α signaling through TNFR1 suppresses AMPK activity via transcriptional upregulation of protein phosphatase 2C. Activation of this phosphatase, in turn, reduces skeletal muscle acetyl CoA carboxylase phosphorylation, suppresses fatty-acid oxidation, and increases intramuscular diacylglycerol accumulation, effects that are associated with insulin resistance both in vitro and in vivo. MAPK isozyme 4 (MAPK4) is another upstream kinase linking ERK1/2 and JNK signaling pathways to TNF-α in human skeletal muscle cells (9). Interestingly, TNF-α infusion increases phosphorylation of p70 S6 kinase, ERK1/2, and JNK, concomitant with increased serine and reduced tyrosine phosphorylation of IRS-1. These effects are, in turn, associated with impaired PI3-K activation and phosphorylation of AS160 (63), a key convergence site for PI3-kinase and AMPK pathways for stimulating glucose transport (Fig. 1).

IL-6. This cytokine is an important cytokine that modulates immune response and has both proinflammatory and anti-inflammatory effects. IL-6 is produced by various cell types, including skeletal muscle (1, 25, 44, 61). Accumulating evidence also indicates that IL-6 is involved in glucose metabolism and insulin action. However, the nature of this role remains controversial. IL-6 may exert an insulin-sensitizing effect and enhance insulin-stimulated glucose disposal in muscle (16, 59, 69). Exercise has been proved as powerful therapy to improve insulin sensitivity and reduce metabolic related diseases. Studies have shown that exercise releases large quantities of IL-6 from muscle, suggesting that IL-6 may play a crucial role in maintaining glucose homeostasis during and after exercise (44, 61). Transgenic mice that overexpress IL-6 are protected from a high-fat diet-induced obesity and insulin resistance compared with control wild-type mice (69). Furthermore, acute IL-6 administration does not impair muscle glucose uptake or whole body glucose disposal in healthy humans (79). On the other hand, studies have also shown that IL-6 could exert deleterious effects in insulin action and glucose homeostasis. For example, the circulating level of IL-6 is elevated in various insulin-resistant states, including T2DM and obesity. In vivo, acute IL-6 treatment in mice reduces insulin-stimulated skeletal muscle glucose uptake associated with defects in IRS-1/PI 3-kinase activity and increases in fatty acyl-CoA levels in skeletal muscle (39). IL-6 has inhibitory effects on the gene transcription of IRS-1, GLUT-4, and peroxisome proliferator-activated receptor-γ under these conditions (14, 68). Moreover, IL-6 induces a rapid recruitment of IRS-1 to the IL-6 receptor complex in cultured skeletal muscle cells and induces a rapid and transient IRS-1 serine phosphorylation and resultant increased IRS-1 ubiquitination in skeletal muscle tissue (96).

What factors may account for the apparent contradictory effects (52) of IL-6 on glucose homeostasis? These factors may include: 1) distinct effects of IL-6 on different tissues; 2) discrepancies between acute and long-term effects; 3) differences between species, i.e., human vs. mouse models; and 4) the complexity of IL-6 interactions with other proinflammatory and anti-inflammatory substances to modulate immune and metabolic function. A better understanding of this intricate cytokine milieu may lead to a better treatment strategy to improve insulin sensitivity.

IL-10. IL-10 is a classical anti-inflammatory cytokine. Recent studies have shown that IL-10 plays a role in modulating glucose metabolism and is expressed in skeletal muscle (25). IL-10 is also overexpressed in adipose tissue macrophages from lean mice, which protect adipocytes from TNF-α-induced insulin resistance (45). Indeed, endogenous IL-10 protects against high-fat diet-induced hepatic steatosis in mice (20). Cotreatment with IL-10 protects skeletal muscle from IL-6 and lipid-induced defects in insulin action. Under these conditions, IL-10 also prevents IL-6-induced defects in hepatic insulin metabolic signaling (39). Moreover, exercise has been shown to increases plasma IL-10 levels (60, 61). Collectively, these data suggest that IL-10 may exert anti-inflammatory benefits and reduce insulin resistance in both hepatic and skeletal muscle tissue.

IL-1. IL-1β, a proinflammatory cytokine, is implicated in pancreatic β-cell destruction leading to type 1 DM (5, 22, 51). IL-1β is also increased in β-cells from patients with T2DM and mediates high glucose-induced β-cell dysfunction and apoptosis (48–50). The IL-1 receptor antagonist (IL-1Ra), an endogenous anti-inflammatory cytokine, counters the actions of IL-1 via inhibiting IL-1 binding to the type II IL-1 receptor (21, 22). The type II IL-1 receptor (IL-1RII) acts as a decoy receptor, inhibiting IL-1 signaling (56). Studies have shown that IL-1Ra improves glycemia (43, 48). The expression of IL-1Ra is
Chemokines, a group of cytokines with small molecular weight, have an important role in inflammation and the pathogenesis of vascular disease via regulating leukocyte trafficking, infiltrating, and activation. Recent studies have indicated that chemokines play a role in glucose metabolism and insulin actions.

Overexpression of MCP-1 in adipose tissues causes insulin resistance (36, 37, 58). Skeletal muscle cells produce several chemokines, such as MCP-1 (10) and IL-8, and express chemokine receptors CXCR1 and 2 and CCR1, 2, 4, 5, and 10 (73). MCP-1 may lead to the infiltration of macrophages into skeletal muscle and adipose tissue, thereby contributing to the low-grade inflammation. Macrophage infiltration is markedly increased in human skeletal muscle from T2DM patients (87). MCP-1 exerts direct inhibitory effects on insulin signaling and reduces glucose uptake in skeletal muscle cells at concentrations even below that found in the circulation. In contrast, macrophage inflammatory protein-1β only impairs insulin metabolic signaling at very high concentrations. MCP-1 may represent the critical molecular link in the cross talk between adipose tissue and skeletal muscle, leading to insulin resistance (73). IL-8 is expressed in human skeletal muscle and increased in response to exercise (2). However, the physiological function of IL-8 in skeletal muscle is still unclear. The roles of chemokines and their receptors in metabolic disease certainly deserve further investigation.

Toll-like receptors. Mammalian TLRs consist of at least 12 membrane proteins that play a crucial role in the innate immune response against bacterial pathogens, mediated by recognizing conserved microbe molecules. After binding to their ligand, TLRs activate downstream signal transduction pathways, such as the MAPK pathway, which eventually results in the activation of transcription factors, including NF-κB, AP-1, and interferon regulatory factor, which, in turn, leads to the transcription of multiple proinflammatory cytokines (3, 40, 88). Skeletal muscle cells and intact whole muscles express multiple TLRs, including TLR1–7 and TLR9 (10, 23, 74). It was recently shown that TLR2 is essential for the development of palmitate-induced insulin resistance in C2C12 myotubes via inhibition of tyrosine phosphorylation of the insulin receptor and the phosphorylation of Akt (74). TLR4 may also be an important link between diet-induced obesity, inflammation, insulin resistance, and diabetes (89). Stimulation with ligands for TLR2 or TLR4 elicits robust increases in MCP-1 expression, whereas gamma interferon priming to induce similar effects with TLR5 (10). Both TLR2 and TLR4 ligands activate the NF-κB pathway. TLRs may also provide therapeutic targets for the treatment of obesity and high-fat-diet induced insulin resistance (40, 74, 89). The precise role of TLRs in skeletal muscle insulin resistance requires further investigation.

Suppressor of cytokine signaling. Members of the suppressor of cytokine signaling (SOCS) family are important negative regulators of cytokine signal transduction. SOCS signaling inhibits the cytokine-activated JAK/STAT signaling pathways. SOCS, especially SOCS1, 3, and 6, have been implicated in cytokine-mediated inhibition of insulin signaling in adipose tissue, liver, and brain (34, 34, 53, 93). Further, in skeletal muscle, SOCS3 is up-regulated after high-fat feeding or by IL-6 stimulation (67, 80, 80, 93). Overexpression of SOCS3 via adenovirus-mediated infection was shown to prevent leptin activation of AMPK signaling (80). Thus, elevated expression of SOCS3 in the skeletal muscle may impair AMPK modulation of insulin-mediated glucose uptake (67, 80). Although IL-6 induces SOCS3 production, SOCS-3 expression in human skeletal muscle in vivo is not related to insulin resistance in the presence of elevated IL-6 concentrations (67). Furthermore, SOCS-3 expression in skeletal muscle may contribute to the exercise-induced increase in IL-6 expression through NF-κB activation (78). SOCS-1 and SOCS-3 can bind directly to the insulin receptor and inhibit tyrosine phosphorylation of IRS-1 and -2. IL-6 also up-regulates SOCS-3 via activation of STAT3 (40). Certainly, the actions of SOCS-3 in skeletal muscle are complex and will require further elucidation before its definitive role is known.

NF-κB. Activation of transcription factor NF-κB, a major regulator of inflammatory responses, depends largely on the function of the inhibitor of NF-κB kinase complex (IKK). IKK is composed of two catalytic subunits, IKK1 and IKK2 (also known as IKKα and IKKβ), and a regulatory subunit, IKKγ (also known as NEMO). Activation of NF-κB involves the phosphorylation and subsequent proteolytic degradation of the inhibitory protein IκB by specific IκB kinases. The free NF-κB (a heterodimer of p50 and p65) then passes into the nucleus where it binds to κB sites in the promoter regions of genes for inflammatory proteins such as cytokines. Many stimuli activate NF-κB, including cytokines, activators of protein kinase C, viruses, and oxidants. Products of the genes that are regulated by NF-κB may also cause further activation of NF-κB. Intralipid infusion activates PKC-θ and IKKβ, promoting insulin resistance in mouse muscle, and the associated insulin resistance is inhibited by salicylate administration or IKKβ depletion (76). Decreased IκBβ content and enhanced IκB/NF-κB signaling are noted in skeletal muscle from patients with
T2DM. The mechanism responsible for the apparent increase in IkB/NF-κB signaling in skeletal muscle in T2DM is not clear. Lipid induces activation of IkB/NF-κB signaling (76). Moreover, skeletal muscle of insulin-resistant subjects is characterized by increases in fatty acyl CoA and ceramides. Recently, it was shown that lipid-induced insulin resistance in L6 myotubes and muscle from rodents and humans is associated with activation of the IkB/NF-κB pathway (76). Evidence of this pathway mediating insulin resistance is further strengthened by the findings that inhibition of IkB/NF-κB signaling improves insulin sensitivity. In support of this concept, it was recently reported that diet-induced obesity in rats leads to a decrease in muscle IkB content (6). However, metabolites of triglycerides and fatty acids (i.e., fatty acyl CoAs, diacylglycerol, and ceramides), and not triglycerides per se, are believed to be responsible for this diet-induced insulin resistance (6). These suggest that activation of IkB/NF-κB pathway and subsequent low-grade inflammation impair insulin action (Fig. 1).

Oxidative Stress and Insulin Resistance

There are several prominent ROS, including superoxide (O$_2^-$), hydrogen peroxide (H$_2$O$_2$) and peroxynitrite (ONOO$^-$. ROS can be generated by various cell organelles and enzymes, such as mitochondria, NAD(P)H oxidases, xanthine oxidoreductase, nitric oxide synthases, and MPO. Normally, ROS play important physiological roles in many organs/tissues (83). However, excess ROS overwhelms antioxidant defenses, leading to oxidative stress, and this, in turn, plays an important role in the pathogenesis and progression of many disorders, including hyperlipidemia, T2DM, hypertension, NAFLD, CKD, and CVD. Several lines of evidence support the important role of oxidative stress in development of insulin resistance. 1) There is an extensive association of oxidative stress with obesity and diabetes (24, 90). ROS are elevated and are inversely correlated with the degree of glycemic control of patients with T2DM (57). Increased O$_2^-$ content is also detected in skeletal muscle from insulin resistant animal models, e.g., KK-Ay mice (75), and transgenic Ren2 rats (7). Further, treatment of insulin-resistant animals with antioxidants $\alpha$-lipoic acid (27) or tempol (7) improves whole body glucose tolerance and insulin-stimulated glucose transport in isolated skeletal muscle. 2) Treatment with hydrogen peroxide in insulin-sensitive cell lines, such as 3T3-L1 adipocytes and L6 myocytes induces insulin resistance, while the addition of antioxidants, such as $\alpha$-lipoic acid and apocynin to the cells abrogates this effect (32, 46, 70, 71, 84, 95). Collectively, these data suggest that oxidative stress play a causal role in insulin resistance.

These findings also raise questions that require further investigation. What downstream pathways translate elevated ROS levels into insulin resistance? ROS have been shown to affect various signaling pathways involving Foxo, MAPK, JAK/STAT, p53, phospholipase C, and PI3K, which depend on the magnitude and type of ROS, the cell type, the duration of exposure, and other factors. ROS activate transcription factors (e.g., NF-κB and AP-1), and upregulate expression of proinflammatory genes such as TNF-α, IL-6, MCP-1, and CRP (11, 26, 54, 55), which are involved in the pathogenesis of inflammation, obesity, and insulin resistance (92, 98). ROS simulate the IkB/NFκB pathway, and hyperglycemia-induced ROS generation could contribute to the lower IkB seen in the T2DM patients. ROS induce JNK activation, which, in turn, may result in insulin resistance (28, 35, 38).

Oxidative stress and inflammation in the renin angiotensin aldosterone system-induced skeletal muscle insulin resistance. The renin angiotensin aldosterone system (RAAS) plays a pivotal role in cardiovascular and renal salt-fluid homeostasis (17). Further, elevated RAAS activity and ANG II levels may contribute to skeletal muscle and systemic insulin resistance (7, 17, 82), for example, systemic or local infusion of ANG II has been shown to cause insulin resistance in skeletal muscle independent of hemodynamic influences, which supports the idea that ANG II can directly and negatively modulate the muscle glucose transport system (66). Data from our group further suggest that ANG II-induced skeletal muscle insulin resistance is mediated by oxidative stress (7, 17). For example, ANG II causes ROS generation in skeletal muscle and impairs insulin-mediated IRS-1 tyrosine phosphorylation, Akt activation, GLUT4 plasma membrane translocation, and skeletal muscle glucose uptake, all of which is significantly attenuated by AT$_1$R blockade or antioxidant treatment (7, 95). Furthermore, we have found that there is a significant linear relationship between oxidative stress and NF-κB activity, e.g., ANG II increases ROS generation and subsequently mediates ANG II-induced increases of NF-κB activation and TNF-α expression in the soleus muscles from insulin-resistant transgenic (mRen2)27/Ren2) rats and the L6 myotubes treated with ANG II, consequently contributing to impaired insulin-stimulated Akt activation, GLUT4 plasma membrane translocation, and glucose uptake (94). High-fructose diets induce skeletal muscle insulin resistance with increased TNF-α expression, and AT$_1$R antagonist treatment improves insulin sensitivity with reduced TNF-α expression in skeletal muscle (99). Accumulating data have also shown that excess aldosterone impairs insulin signaling, contributing to insulin resistance in many tissues from human and animal studies, which is mediated by oxidative stress and inflammation (17). Inhibiting aldosterone with the receptor antagonist, spironolactone, substantially improves insulin-mediated glucose uptake in skeletal muscle from a hypertensive and insulin resistant Ren2 rat model that links to attenuation of ROS generation and NAD(P)H oxidase activity (unpublished data). These suggest that oxidative stress and inflammatory cytokine may also represent critical mediators in RAAS-induced insulin resistance in skeletal muscle. However, the precise mechanisms that link RAAS and skeletal muscle insulin resistance need to be further investigated (Fig. 1).

Summary

The cardiometabolic syndrome is emerging as a global public health issue. Insulin resistance is key factor of pathogenesis of this syndrome. However, the processes by which insulin resistance develops are very complex and remain incompletely understood. Skeletal muscle is the major tissue in glucose metabolism, and impaired insulin metabolic signaling in this tissue is crucial for development of systemic insulin resistance. Oxidative stress, low-grade inflammation, and inflammatory cytokines in skeletal muscle triggered by physical inactivity and excessive caloric intake may represent important
breakthroughs for intervention. Therefore, understanding the precise mechanisms of insulin resistance in skeletal muscle may help to design novel therapy to correct the metabolic and cardiovascular consequences.

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