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Forum Review

The Molecular Basis for Oxidative Stress-Induced Insulin Resistance

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ABSTRACT

Reactive oxygen and nitrogen molecules have been typically viewed as the toxic by-products of metabolism. However, accumulating evidence has revealed that reactive species, including hydrogen peroxide, serve as signaling molecules that are involved in the regulation of cellular function. The chronic and/or increased production of these reactive molecules or a reduced capacity for their elimination, termed oxidative stress, can lead to abnormal changes in intracellular signaling and result in chronic inflammation and insulin resistance. Inflammation and oxidative stress have been linked to insulin resistance *in vivo.* Recent studies have found that this association is not restricted to insulin resistance in type 2 diabetes, but is also evident in obese, nondiabetic individuals, and in those patients with the metabolic syndrome. An increased concentration of reactive molecules triggers the activation of serine/threonine kinase cascades such as c-Jun N-terminal kinase, nuclear factor-κB, and others that in turn phosphorylate multiple targets, including the insulin receptor and the insulin receptor substrate (IRS) proteins. Increased serine phosphorylation of IRS reduces its ability to undergo tyrosine phosphorylation and may accelerate the degradation of IRS-1, offering an attractive explanation for the molecular basis of oxidative stress-induced insulin resistance. Consistent with this idea, studies with antioxidants such as vitamin E, α-lipoic acid, and *N*-acetylcysteine indicate a beneficial impact on insulin sensitivity, and offer the possibility for new treatment approaches for insulin resistance. *Antioxid. Redox Signal.* 7, 1040–1052.

INTRODUCTION

Oxidative stress, defined as a persistent imbalance between the production of highly reactive molecular species (chiefly oxygen and nitrogen; Table 1) and antioxidant defenses (Fig. 1), is associated with a wide variety of pathologies, including diabetes, cardiovascular disease, cancer, and neurodegenerative diseases (47, 108, 121). The detrimental impact of reactive molecules on biological function was first brought to light almost 50 years ago by Harman, who proposed a causative role of free radicals in the aging process (48). The interest in free radicals continues to attract widespread experimental attention (7, 49). Although not proven, evidence to support the idea that oxidative stress likely plays a causative role in the tissue and cellular damage in these diseases is accumulating (7, 10, 47, 121).

In particular, diabetes mellitus is strongly associated with oxidative stress, which could be a consequence of either increased production of free radicals, reduced antioxidant defenses (121, 144), or both. There is considerable evidence that hyperglycemia results in the generation of reactive oxygen species (ROS), ultimately leading to oxidative stress in a variety of tissues. Another major source of reactive molecules, including superoxide and hydrogen peroxide (H_2O_2), is the enzyme NAD(P)H oxidase, which is activated by a variety of inflammatory cytokines (23, 155). In the absence of an appropriate compensatory response from the endogenous antioxidant network, the system becomes overwhelmed (redox

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TABLE 1. SELECTED EXAMPLES OF BIOLOGICALLY IMPORTANT REACTIVE SPECIES

Type	*Free radicals*	*Nonradicals*
Reactive oxygen species (ROS)	Superoxide, $^{\bullet}O_2^-$ Hydroxyl, $^{\bullet}OH$ Peroxyl, $^{\bullet}RO_2^-$ Hydroperoxyl, $^{\bullet}HO_2^-$	Hydrogen peroxide, H_2O_2 Hypochlorous acid, HOCl
Reactive nitrogen species (RNS)	Nitric oxide, $^{\bullet}NO$ Nitrogen dioxide, $^{\bullet}NO_2^-$	Peroxynitrite, $OONO^-$ Nitrous oxide, HNO_2

Reactive oxygen and nitrogen species (ROS and RNS) are defined as highly reactive molecules, including charged species such as superoxide, hydroxyl radical, and nitric oxide and uncharged species such as hydrogen peroxide. Table adapted from Rösen *et al.* (121).

imbalance), leading to the activation of stress-sensitive (*i.e.*, inflammatory) intracellular signaling pathways (25, 79). One major consequence is the production of gene products that cause cellular damage and are ultimately responsible for the late complications of diabetes.

In addition to playing a key role in the etiology of diabetic complications, chronic activation of stress-sensitive signaling pathways by reactive molecules induces insulin resistance and impairs insulin secretion *in vitro* (27). Oxidative stress has been linked to insulin resistance *in vivo* (11, 14, 105, 107, 144, 146). More recent studies have found that this association is not restricted to insulin resistance in the context of diabetes, but is also evident in obese, nondiabetic individuals

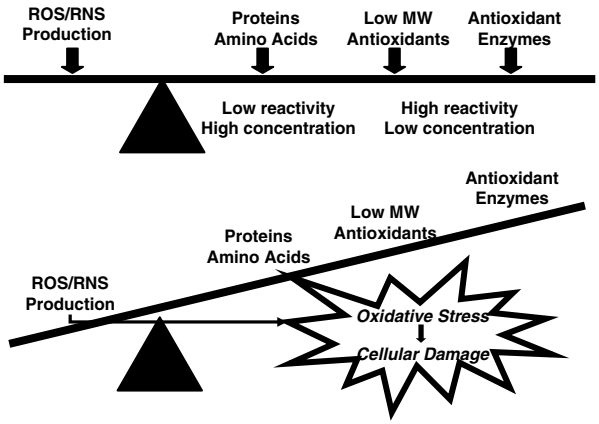

FIG. 1. Redox balance and oxidative stress. The steady-state level of reactive molecules is determined by the rate of their production and their ability to be cleared (inactivated) by endogenous antioxidants (shown) or antioxidant supplementation. Components of the endogenous antioxidant system include various proteins (*e.g.*, thioredoxin, metallothionein) and amino acids (*e.g.*, taurine, L-arginine), low molecular weight (MW) antioxidants (*e.g.*, α-lipoic acid, glutathione, vitamin C, vitamin E), and antioxidant enzymes (*e.g.*, superoxide dismutase, catalase, glutathione peroxidase). Under physiological conditions, a redox balance exists; when the production of reactive molecules exceeds the capacity for their clearance, a redox imbalance occurs. When the imbalance persists, oxidative stress ensues. Figure adapted from Dröge (23).

(31, 132, 142), and in those with the metabolic syndrome (32, 58, 85, 130). These latter findings are an important advance in this field for several reasons. First, they are consistent with the idea that oxidative stress could be an early event in the pathology of diabetes, and not simply a consequence of chronic hyperglycemia. If confirmed, therapeutic approaches that target oxidative stress could provide symptomatic relief, delay the onset, or prevent disease progression. Second, these findings suggest that the production of reactive molecules and the ensuing oxidative stress could originate from a source other than hyperglycemia, including increased free fatty acids (FFA) (27, 61, 140) or hyperinsulinemia (29). Third, they are also consistent with the idea that the detrimental effects of oxidative stress are not confined to the tissues in which diabetic complications occur, but likely extend to skeletal muscle and perhaps other target tissues of insulin. Skeletal muscle is the major site for insulin-stimulated whole body glucose disposal, and a major target for insulin resistance (21, 113).

If oxidative stress is casually linked to insulin resistance, then it is reasonable to expect that treatment with antioxidants would have a beneficial impact on insulin sensitivity. There is evidence to support this idea *in vitro*, in animal models, and in small clinical trials (25, 28). In brief, *in vivo* studies in animal models of diabetes indicate that antioxidants, especially α-lipoic acid (LA), improve insulin sensitivity (53, 54). Several clinical trials have also demonstrated improved insulin sensitivity in insulin-resistant and/or diabetic patients treated with the antioxidants vitamin C, LA, vitamin E, glutathione, and *N*-acetylcysteine (13, 15, 28, 33, 55, 56, 65, 106). In patients with type 2 diabetes, both acute and chronic administration of LA improves insulin resistance as measured by both the euglycemic–hyperinsulinemic clamp and the Bergman minimal model (63–65, 75). For LA, the magnitude of this increased insulin sensitivity compares favorably with currently available medications, metformin and rosiglitazone. These insulin sensitizers produced an approximate 25% and 20% improvement in insulin-stimulated glucose metabolism (62, 97). In addition, the short-term (6-week) oral administration of a novel controlled release formulation of LA lowered plasma fructosamine levels in patients with type 2 diabetes (26). The ability of antioxidants to protect against the detrimental effects of hyperglycemia and FFA, major contributors to insulin

resistance (98, 123), along with the clinical benefits often reported following antioxidant therapy, supports a causative role of oxidative stress in mediating and/or worsening insulin resistance (27). The focus of this article will be to discuss a possible molecular mechanism linking oxidative stress to insulin resistance.

REDOX REGULATION OF INSULIN ACTION: POSITIVE ROLE

Dating back to Harman's original proposal that free radicals are causally involved in the aging process (48, 49), free radicals have been typically viewed as the toxic by-products of metabolism. However, recent work has revealed that reactive species, including H_2O_2, serve as signaling molecules that are involved in the regulation of normal cellular function (23, 34, 80, 103, 117). Reactive molecules mediate the effects of growth factors, cytokines, and other ligands (23). In particular, H_2O_2 clearly functions as a second messenger and is required for the optimal activation of numerous signaling pathways, especially those mediated by receptor tyrosine kinases (for review, see 128). To wit, an elaborate antioxidant enzyme system present in aerobic organisms from bacteria to man apparently has evolved to regulate H_2O_2 signaling (147).

With respect to the role of reactive molecules and insulin action, the ability of H_2O_2 (and other oxidants) to exert insulin-like effects has been known for over 30 years. Czech and colleagues reported that thiols in the presence of Cu^{2+}, a combination that generates H_2O_2, stimulated glucose incorporation into glyceride-glycerol and glyceride-fatty acids in isolated rat epididymal adipocytes (18, 19). Direct evidence for the insulin-like effects of H_2O_2, including the stimulation of hexose monophosphate shunt activity (19, 69), glucose transport (20, 89), glycogen synthesis (82), pyruvate dehydrogenase activity (96, 102), lipid synthesis (96), amino acid transport (133), and antilipolysis (88), was subsequently provided by numerous groups. The similarity of the effects of H_2O_2 *in vitro* to those of insulin suggested that H_2O_2 (or some other oxidant) might actually serve as a "second messenger" of insulin (95, 96).

This hypothesis gained support when it was reported that insulin increased the intracellular production of H_2O_2 in isolated rat epididymal adipocytes (95). Another group observed that NADPH oxidase activity in membranes isolated from rat adipocytes was higher in cells exposed to insulin, and resulted in increased H_2O_2 in the extracellular medium compared with control adipocytes (101). These and other data (20) provided the basis for one of the earlier explanations of the mechanism of insulin action. The hypothesis, put forth by May and de Häen (95), was that insulin increased the production of H_2O_2, which increased membrane sulfhydryl oxidation (20), thereby stimulating glucose transport.

Subsequent work in this area has established that human adipocytes possess a plasma membrane NAD(P)H oxidase that functions as an insulin-sensitive H_2O_2-generating system (76). NAD(P)H oxidases have also been identified in other target tissues of insulin, including liver (6, 99), muscle (150), and vascular cells (61). In adipocytes, there is evidence that the NAD(P)H oxidase is coupled to the insulin receptor via a heterotrimeric $G\alpha_{i2}$ protein (77), and antisense silencing of $G\alpha_{i2}$ results in insulin resistance (100).

Several years after May and de Häen proposed a role for H_2O_2 in insulin action, it was discovered that in both intact cells and cell-free preparations the insulin receptor rapidly underwent phosphorylation following insulin binding (67, 68). In a cell-free system, phosophorylation occurs exclusively on tyrosine (68), whereas in intact cells phosphorylation on serine and threonine residues is also increased (67). Work from multiple groups firmly established that the insulin receptor was a tyrosine kinase, whose activity rapidly increased following insulin binding, leading to autophosphorylation and enhanced tyrosine kinase activity toward exogenous substrates (5, 120, 125, 151, 152). These data led to the now widely held view that insulin receptor tyrosine phosphorylation was an "intermediate" step linking hormone binding to insulin action (73, 119), along with being an obligate event in mediating the varied physiological effects of insulin (16, 38).

Two of the three major hypotheses [the third being nonoxidant insulin mediators (40, 81, 118, 129, 131)] of that era to explain the mechanism of insulin action converged when Hayes and Lockwood determined if the insulin-like effects of H_2O_2 affected the tyrosine kinase activity of the insulin receptor. They found that treatment of isolated rat adipocytes or crude cellular homogenates with 3m*M* H_2O_2, a maximally effective concentration for the stimulation of glucose uptake, increased insulin receptor tyrosine kinase activity and autophosphorylation (51). However, the direct addition of H_2O_2 to partially purified insulin receptors did not result in increased receptor tyrosine kinase activity or autophosphorylation (51). These results suggested that the effect of H_2O_2 to increase receptor tyrosine phosphorylation was indirect, possibly attributable to the activation of non-receptor tyrosine kinases or other factors. An alternative possibility, that the insulin-like effects of H_2O_2 might be mediated via inhibition of protein tyrosine phosphatase (PTPase) activity, was unexplored at this time because an enzyme with PTPase activity had not yet been discovered.

Direct evidence exposing H_2O_2 as a positive mediator in insulin signaling along with identifying a likely mechanistic basis is emerging. In both highly insulin-responsive 3T3-L1 adipocytes and human HepG2 hepatoma cells, Goldstein and colleagues have shown that insulin rapidly and transiently increases H_2O_2 production (92). This effect is concentration-dependent, and associated with significant reductions in overall PTPase activity in cell homogenates, cytosol, and solubilized particulate fractions from HepG2 hepatoma cells. A similar effect was observed in solubilized lysates from 3T3-L1 adipocytes (92) and in adipocytes from obese humans (149). In addition, it was demonstrated in HepG2 hepatoma cells and 3T3-L1 adipocytes [but not in human adipocytes (149)] that insulin treatment caused a significant reduction in the activity of protein tyrosine phosphatase-1B (PTP-1B) (92), a PTPase previously shown to be a negative regulator of insulin action (39, 71, 92). The reduction in PTP-1B activity by insulin in both cell types was prevented by preincubation with catalase, which blocks insulin-stimulated H_2O_2 production. Pretreatment with catalase also led to a reduction in insulin-stimulated tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 (IRS-1), indicative of a more active PTP-1B due to

reduced H_2O_2 production. Using diphenyleneiodonium, a pharmacological inhibitor of NADPH oxidase (and insulin-stimulated H_2O_2 production), Goldstein and colleagues have also shown that H_2O_2, presumably increased as a result of insulin-stimulated NADPH oxidase activity, is also required for insulin-mediated inhibition of PTPase activity and insulin stimulation of phosphatidylinositol 3-kinase (PI 3-kinase), serine/threonine kinase Akt (Akt), and glucose transport (91). Thus, H_2O_2 generated in response to insulin functions as a positive regulator of both the early steps of insulin action and the distal steps.

As revealed by data from the Goldstein laboratory (92) and others (128), PTPases, including PTP-1B, are likely targets for inhibition by H_2O_2. The kinetic mechanisms of PTPases have been extensively characterized (12, 22, 30), indicating that this enzyme class shares a common requirement for the cysteine residue in the catalytic site to be in the reduced state for catalytic activity. This cysteine residue is susceptible to oxidation to sequentially more inert forms. This inactivation can be reversed by biological thiols, including glutathione (143). Thus, the ability of insulin to generate a transient burst of reactive molecules such as H_2O_2 provides a mechanism to propagate the insulin signal by the targeted inactivation of PTPases, including PTP-1B. It is well established that the selective and transient inhibition of PTP-1B, a negative regulator of insulin signaling, improved insulin action and is antidiabetogenic (24, 39, 92–94, 148).

REDOX REGULATION OF INSULIN ACTION: NEGATIVE ROLE

The redox regulation of insulin signaling described in the above studies likely reflects the situation in which reactive molecules such as H_2O_2 are produced and are present at relatively low steady-state levels required for normal cellular function. The chronic and/or increased production of these reactive molecules or a reduced capacity for elimination can lead to abnormal changes in intracellular signaling and gene expression, resulting in a pathological situation (25).

Previously, we and others have used H_2O_2 to cause oxidative stress and inhibit insulin action in L6GLUT4 muscle cells, 3T3-L1 adipocytes, and other cell lines (37, 90, 109, 126, 127, 138, 139). The addition of micromolar concentrations of LA to the incubation medium protected against oxidative stress-induced insulin resistance (90, 127). We have now conducted additional studies in an improved muscle cell line in which to study insulin action. In general, L6 muscle cells have relatively low levels of the insulin receptor. To test the ability of hyperglycemia, a more physiological condition, to induce oxidative stress and insulin resistance in muscle, we have developed a more insulin-responsive muscle cell line, L6GLUT4-IR cells. These cells are doubly transfected to overexpress both glucose transporter 4 (GLUT4) and the human insulin receptor (IR), and thus respond to insulin with a much greater effect on glucos transport. In these new L6 cells, 0.1 n*M* insulin significantly increases glucose transport; a half-maximal effective concentration (EC_{50}) is seen at 1 n*M*. At maximally effective concentrations, insulin increases glucose transport by approximately three- to fourfold over basal. In L6GLUT4-IR, 20 m*M* glucose decreased the basal and insulin-stimulated glucose transport by ~50% (Fig. 2). This effect was blocked by pretreatment with the antioxidant LA.

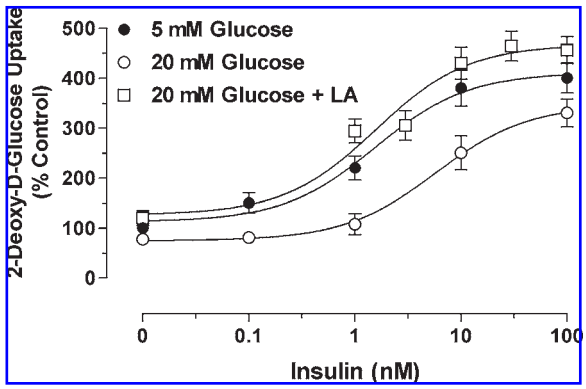

FIG. 2. Insulin-sensitive L6 cells: effect of LA on hyperglycemia-induced suppression of insulin-stimulated glucose transport. L6GLUT4 muscle cells were transfected to express the human insulin receptor (designated as L6GLUT4-IR cells). L6GLUT4-IR cells were cultured for 5 days in DMEM containing 5 m*M* glucose (control), 20 m*M* glucose, and 20 m*M* glucose plus LA (100 μ*M*). Cells were washed, incubated with increasing concentrations of insulin for 30 min, and 2-deoxy-D-glucose uptake measured. Copyright © 2002 The Endocrine Society. Data are from Evans *et al.* (25). Reprinted with permission from the Endocrine Society.

We next determined whether incubation with high glucose activated nuclear factor-κB (NF-κB), a major oxidative stress-sensitive transcription factor, and if activation could be blocked by LA. We incubated L6GLUT4-IR cells, and as a control, human fibroblasts, in a high glucose (20 m*M*) medium for 5 days. In the L6GLUT4-IR cells, but not in control fibroblasts, there was an increase in NF-κB activity (Fig. 3). Concomitant incubation with high glucose plus 100 μ*M*

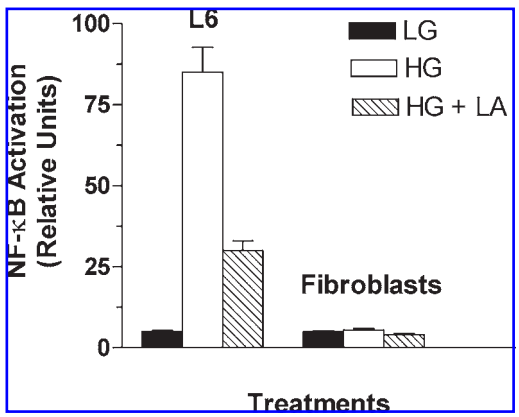

FIG. 3. High glucose incubation increases NF-κB in L6GLUT4-IR muscle cells, but not fibroblast cells: prevention by LA. L6GLUT4-IR and human fibroblast cells were incubated in either 5.5 m*M* (LG) or 20 m*M* (HG) glucose for 5 days in the presence and absence of 100 μ*M* LA. NF-κB activity (p50 subunit) was measured by gel shift analysis. Results are the means (± SEM) of triplicates.

LA prevented this activation. These data, therefore, provide support for the idea that incubation with high glucose leads to oxidative stress, resulting in insulin resistance.

The negative impact of hyperglycemia on insulin-mediated glucose disposal was first proposed almost 20 years ago by Unger and Grundy (141), and subsequently confirmed *in vitro*, *in vivo*, and in clinical studies (46, 83, 84, 122, 123). However, until recently, there have been no published studies to show that the hyperglycemia-induced impairment in insulin action *in vivo* could be attributed to oxidative stress. Recent data from Fantus and colleagues provide direct *in vivo* validation of the hypothesis that hyperglycemia can cause oxidative stress in muscle, resulting in insulin resistance (45). In their study, normal rats were infused with glucose for 6 h to maintain a circulating glucose concentration of 15 m*M*. This procedure induced a significant decrease in insulin-stimulated glucose uptake as measured by euglycemic–hyperinsulinemic clamp (Fig. 4). This resistance was prevented by coinfusion of two different antioxidants (*N*-acetylcysteine and taurine). Further, following the high glucose infusion, a significant (fivefold) increase in soleus muscle protein carbonyl content, a marker of oxidative stress, was observed. Thus, the observation *in vitro* that hyperglycemia can cause oxidative stress in muscle resulting in impaired insulin-stimulated glucose disposal is also evident *in vivo*.

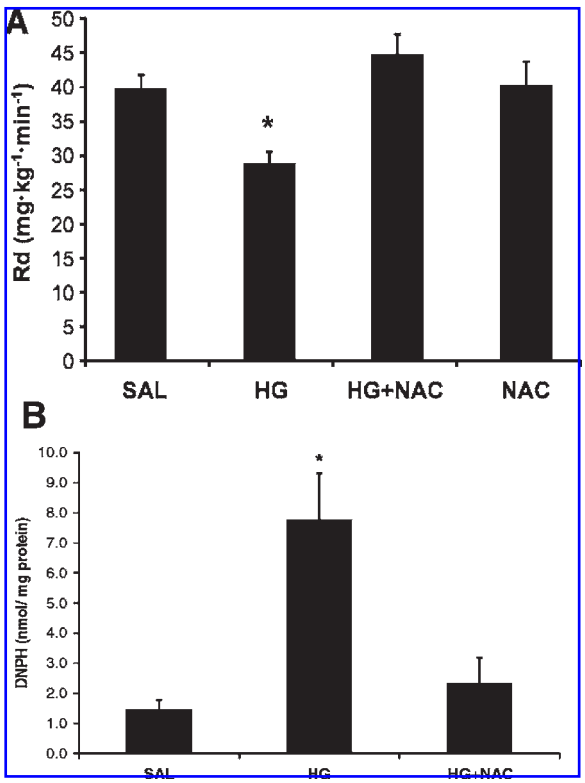

FIG. 4. ***N*-Acetylcysteine (NAC) prevents hyperglycemia-induced insulin resistance in rats. (A)** Rats were infused with saline (SAL), glucose to achieve a concentration of 15 m*M* (HG), HG + NAC, or NAC alone for 6 h (0–360 min) followed by a hyperinsulinemic–euglycemic clamp over 2 h (360–480 min). Values for Rd (peripheral insulin sensitivity) were calculated from measurements taken during the final 30 min of the hyperinsulinemic–euglycemic clamp. HG significantly decreased Rd, an effect that was prevented by NAC. $^{*}p < 0.05$ versus all other groups. **(B)** Rats were infused for 6 h as described above, and soleus muscles were removed (*i.e.*, without the hyperinsulinemic clamp procedure) and processed for assessment of protein carbonyl content using the 2,4-dinitrophenylhydrazine (DNPH) method. HG markedly increased DNPH reactivity, a marker of protein oxidation, which was abolished by NAC. $^{*}p < 0.001$ versus all other groups. Data are from Haber *et al.* (45).

OXIDATIVE STRESS AND INSULIN RESISTANCE: POSSIBLE MECHANISTIC LINK

In vitro, an increase in reactive molecules can lead to the activation of multiple serine kinase cascades (1, 17, 78) or inhibition of PTPases (92, 128, 143). A variety of other redox-sensitive molecules also exist (4, 23). As discussed above, these are normal physiological events designed to mediate signal transduction. Under physiological conditions, the increase in reactive molecules does not necessarily cause oxidative stress, as it is counterbalanced by the endogenous antioxidant network (Fig. 1). However, the chronic and/or increased production of these reactive molecules or a reduced capacity for elimination can cause oxidative stress and dysregulation in intracellular signaling, ultimately resulting in a pathological situation including insulin resistance (25).

The insulin signaling pathway offers a number of potential targets (substrates) of these activated kinases, including the insulin receptor and the family of IRS proteins. For IRS-1 and -2, an increase in serine phosphorylation decreases the extent of tyrosine phosphorylation, and is consistent with the attenuation of insulin action (2, 43, 52, 70, 87, 111, 115, 145, 157) (Fig. 5). The serine/threonine phosphorylated forms of IRS molecules are less able to associate with the insulin receptor and downstream target molecules, especially PI 3-kinase (110, 111), resulting in impaired insulin action, including protein kinase B (PKB) activation, and glucose transport (8, 136, 157). In addition, the serine-threonine phosphorylated forms of IRS molecules are more susceptible to proteasome-mediated degradation (42, 50, 112, 145, 156).

There are several major stress-sensitive kinases that, when activated, are likely involved in attenuating insulin signaling via effects on IRS proteins. In Chinese hamster ovary cells, both the proinflammatory cytokine tumor necrosis factor-α (TNF-α) and anisomycin stimulate IRS-1-associated c-Jun N-terminal kinase (JNK)/stress-activated protein kinase (SAPK) activity, resulting in increased serine phosphorylation of IRS-1 catalyzed by JNK/SAPK (2, 3). Consequently, insulin-stimulated tyrosine phosphorylation of IRS-1 was substantially reduced and insulin action impaired. More recent results have indicated that JNK also functions as a negative regulator during normal insulin stimulation. In mouse embryo fibroblasts, $32D^{IR}$ cells, and 3T3-L1 adipocytes, JNK activity is increased in response to insulin (86). As shown in previous studies using TNF-α and anisomycin (2, 3), insulin-stimulated JNK activity led to increased serine phosphoryla-

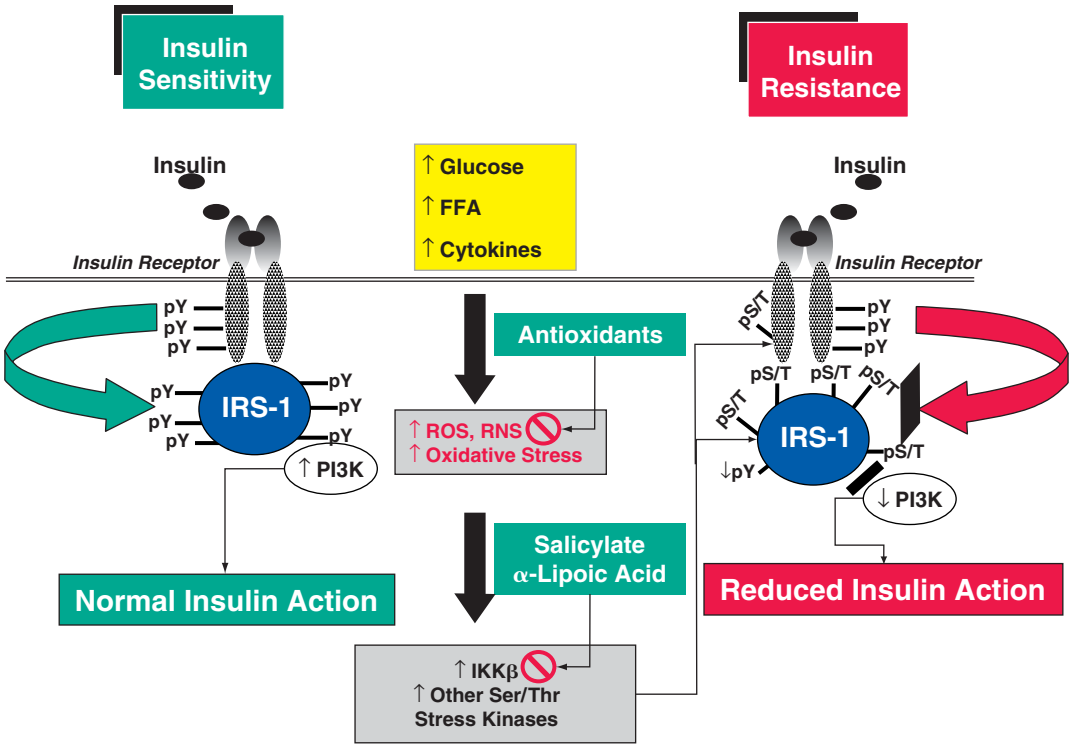

FIG. 5. The role of serine kinase activation in oxidative stress-induced insulin resistance. A variety of stimuli, including hyperglycemia-elevated free fatty acids (FFA), cytokines, and others, increase ROS (and RNS) production and oxidative stress. This results in the activation of multiple stress-sensitive serine/threonine kinase signaling cascades, such as IKKβ and others (see text for details). Once activated, these kinases are able to phosphorylate multiple targets, including the insulin receptor and IRS proteins such as IRS-1 and IRS-2. Increased phosphorylation of the insulin receptor or IRS proteins on discrete serine or threonine sites (pS/T) decreases the extent of insulin-stimulated tyrosine phosphorylation (pY) (8, 111). Consequently, the association and/or activities of downstream signaling molecules [*e.g.*, PI 3-kinase (P13K)] are decreased, resulting in reduced insulin action (insulin resistance). The protective effects of antioxidants (*e.g.*, LA, *N*-acetylcysteine, etc.) on oxidative stress-induced insulin resistance could relate to their ability to preserve the intracellular redox balance (neutralizing ROS) or, analogous to pharmacological agents (*e.g.*, salicylates, p38 MAPK inhibitors), by blocking the activation of stress-sensitive kinases (9, 90, 154). Copyright © 2003 American Diabetes Association. Figure is from Evans *et al.* (27). Reprinted with permission from the American Diabetes Association.

tion of IRS-1 on Ser^{307}, resulting in reduced insulin signaling. Thus, it appears that JNK serves as a heterologous inhibitor of insulin action during acute and chronic inflammation and as a feedback inhibitor during insulin stimulation (86). *In vivo*, JNK activity is increased in insulin target tissues in multiple rodent models of insulin resistance and obesity (57). The absence of JNK1 in mice results in decreased adiposity, increased insulin sensitivity, and enhanced insulin signaling, consistent with its role as stress- and inflammation-induced negative regulator of insulin action.

Iκβ kinase B (IKKβ), another major stress-sensitive kinase, controls the activation of NF-κB and is increased in insulin-resistant muscle from a variety of sources (153). Activation of IKKβ increases IRS-1 serine phosphorylation on Ser^{307} (35) and inhibits insulin action; salicylates and ligands for peroxisome proliferator-activated protein γ, both of which inhibit IKKβ activity (124, 134), restore insulin sensitivity both *in vitro* and *in vivo* (72, 154). Recent work has identified IRS-1 as a direct substrate of IKKβ (35). Treatment with aspirin and salicylates alter the phosphorylation patterns of the IRS proteins, resulting in decreased serine phosphorylation and increased tyrosine phosphorylation and insulin action (36, 66, 72, 154).

Support for the importance of IKKβ in insulin resistance *in vivo* is provided by results of recent gene knockout experiments in mice. IKKβ (+/−) heterozygotes were more insulin-sensitive (as judged by increased glucose infusion rate during hyperinsulinemic–euglycemic clamp) compared with their normal (+/+) littermates (72, 154). This improvement in insulin sensitivity was even more dramatic when IKKβ (+/−) mice were crossbred with insulin-resistant *ob/ob* mice. Preliminary clinical evidence implicating IKKβ in insulin resistance has also been recently provided. Treatment of nine patients with type 2 diabetes for 2 weeks with high-dose aspirin (7 g/day) resulted in reduced hepatic glucose production and fasting hyperglycemia, and increased insulin sensitivity (60).

In L6 muscle cells, activation of p38 mitogen-activated protein kinase (MAPK) by oxidative stress (H_2O_2) is linked to H_2O_2-mediated inhibition of insulin-stimulated glucose transport (9). Inhibition of insulin signaling was reversed by a specific inhibitor of p38 MAPK (9). Interestingly, p38 MAPK has been suggested as an activator of the glucose transporter

(74, 135). Due to the existence of multiple isoforms of this enzyme (104, 137), it is possible that this latter effect is mediated by a different isoform.

Additional stress-sensitive kinases that are reported to be involved in IRS-mediated insulin resistance include the mammalian target of rapamycin (mTOR) (44, 50), several isozymes of protein kinase C (PKC), including PKCθ and PKCδ (for review, see 41), the salt-inducible kinase (SIK2) (59), and a novel IRS serine kinase (116). Clearly, there is compelling evidence that serine/threonine phosphorylation attenuates insulin signaling by reducing the extent of tyrosine phosphorylation of IRS proteins. There is also evidence that increased serine/threonine phosphorylation accelerates the degradation of IRS-1 protein, which also results in insulin resistance (42, 50, 112, 145, 156). In addition, it is well documented that these kinases (*e.g.*, JNK IKKβ, PKC, p38 MAPK) are activated in response to a variety of stress-inducers, including ROS and other reactive molecules (for review, see 25). The acute activation of JNK by insulin and subsequent increased phosphorylation of IRS-1 on Ser^{307} might serve as a signal to terminate the insulin signal under physiological conditions (86). However, chronic activation of JNK and likely other serine/threonine kinases as occurs in response to oxidative stress and inflammation leads to the pathological condition of insulin resistance.

To date, only one published study has directly evaluated the effects of oxidative stress on IRS serine phosphorylation and IRS protein content, in the context of cellular insulin resistance (114). Consistent with the molecular basis of oxidative stress-induced insulin resistance proposed here, these investigators found that oxidative stress (H_2O_2) caused an increase in serine phosphorylation of IRS-1 and IRS-2, decreased content of IRS-1, and insulin resistance in 3T3-L1 adipocytes. However, the following aspects of this study raise questions regarding this proposed mechanism: (a) the prevention of serine phosphorylation and IRS-1 degradation using a pharmacological inhibitor (rapamycin) was not associated with an improved acute response to insulin; (b) protection against oxidative-stress insulin resistance by LA did not prevent IRS serine phosphorylation and IRS-1 degradation; and (c) oxidative stress decreased PKB phosphorylation, an effect that was prevented by LA (as was the decrease in glucose uptake, but not increased serine phosphorylation of IRS). The magnitude of the effect of oxidative stress on PKB was greater than its effect on IRS-1 degradation, suggesting a greater degree of impairment as the insulin signal is propagated downstream (114). These results support the idea that oxidative stress-induced insulin resistance may not be limited to alterations in IRS function or content, and may involve other downstream sites. Additional studies will be required using targeted approaches, such as small interfering ribonucleic acid (siRNA) and transgenic mice, and physiological inducers of oxidative stress, such as hyperglycemia, FFA, and hyperinsulinemia (either alone or in combination), to evaluate this hypothesis more effectively.

CONCLUSIONS AND IMPLICATIONS

Reactive molecules serve an important physiological role as second messengers. However, when their concentration exceeds the capacity for elimination by the endogenous antioxidant network, oxidative stress ensues. The levels of reactive molecules can be increased by hyperglycemia, increased FFA, inflammatory cytokines, increased NAD(P)H oxidase activity, or their combination. This can lead to abnormal changes in intracellular signaling, resulting in chronic inflammation and insulin resistance *in vivo*. From a mechanistic perspective, an increase in reactive molecules can trigger the activation of stress-sensitive serine/threonine kinase signaling pathways such as JNK, NF-κB, p38 MAPK (and others) that in turn phosphorylate multiple targets, including the insulin receptor and IRS proteins. Increased serine phosphorylation of IRS reduces its ability to undergo tyrosine phosphorylation and may accelerate the degradation of IRS-1, offering a plausible explanation for the molecular basis of oxidative stress-induced insulin resistance. For confirmation, targeted approaches (such as siRNA and transgenic mice) that silence the expression of candidate kinases, along with evaluating the effects of physiological inducers of oxidative stress such as hyperglycemia, FFA, and hyperinsulinemia (either alone or in combination), will be required.

There are convincing data to support an important role for the activation of JNK, IKKβ, PKC, and perhaps other stress- and inflammation-activated kinases in the pathogenesis of oxidative stress-induced insulin resistance, and suggest that they might be attractive pharmacological targets to increase insulin sensitivity. The use of antioxidants and pharmacological inhibitors in suppressing the chronic activation of these pathways is consistent with this idea. Moreover, identification of the molecular basis for the protection afforded by a variety of antioxidants against oxidative stress-induced damage might lead to the discovery of additional pharmacological targets for novel therapies to prevent, reverse, or delay the onset of oxidative stress-induced insulin resistance.

ABBREVIATIONS

Akt, serine/threonine kinase Akt; FFA, free fatty acids; GLUT4, glucose transporter 4; H_2O_2, hydrogen peroxide; IKKβ, IκB kinase β; IR, insulin receptor; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; LA, α-lipoic acid; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; PI-3 kinase, phosphatidylinositol 3-kinase; PKB, protein kinase B; PKC, protein kinase C; PTPase, protein tyrosine phosphatase; PTP-1B, protein tyrosine phosphatase-1B; RNS, reactive nitrogen species; ROS, reactive oxygen species; SAPK, stress-activated protein kinase; siRNA, small interfering ribonucleic acid; TNF-α, tumor necrosis factor-α.

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