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Forum Editorial

Redox Regulation of Insulin Action and Signaling

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INSULIN is the major hormone contributing to glucose homeostasis. Aberrant secretion or action of this hormone has been implicated in the pathogenesis of diabetes mellitus (26). Insulin action on its target cells is initiated by insulin-induced activation of intrinsic protein tyrosine kinase (PTK) activity of the β subunit by the insulin receptor (IR) (27). Once activated, IR-PTK can phosphorylate several cytosolic IR substrates (IRSs and Shc), which serve as docking sites for Src homology 2 domain-containing signaling molecules (25). Among these signaling molecules, phosphatidylinositol 3-kinase (PI3-K) activation has emerged as a key player mediating the metabolic effects of insulin (22). PI3-K phosphorylates phosphatidylinositol (PI) lipids at position 3 of the inositol ring, and generates 3-phosphorylated forms of PI, such as phosphatidylinositol 3,4,5-trisphosphate, which are implicated in the activation of phospholipid-dependent kinases and related serine/threonine protein kinases responsible for the phosphorylation and stimulation of several downstream signaling protein kinases, such as protein kinase B (PKB) (also known as Akt), glycogen synthase kinase 3, $p70^{s6k}$, and protein kinase C-ζ (22). Activation of these protein serine/threonine kinases has been demonstrated to play a key role in insulin-induced glucose transport, glucose transporter-4 (GLUT-4) translocation, glycogen, and protein synthesis.

In recent years, considerable evidence has accumulated to suggest the involvement of reactive oxygen and nitrogen species (ROS/RNS) in modulating insulin signaling and action. Exogenous hydrogen peroxide (H_2O_2) has been reported to mimic several physiological responses of insulin, such as glucose transport (9), glycogen synthesis (11), lipogenesis (14), lipolysis (12), and phosphoenolpyruvate carboxykinase gene expression (23), although the H_2O_2 concentrations required for these effects were in the millimolar range (9, 11, 12, 14, 23). Furthermore, stimulation of cells with insulin was found to generate small amounts of H_2O_2 (13) via a NADPH oxidase-dependent system (14). This insulin-induced, endogenously produced H_2O_2 appears to be essential for initial tyrosine phosphorylation of IR and IRS protein, and is achieved by oxidative inhibition of protein tyrosine phosphatase (13, 14, 16). On the other hand, several studies have indicated that long-term exposure of various cell types to H_2O_2 exerts an inhibitory effect on insulin action. For example, in L6 myotubes as well as in 3T3-L-1 adipocytes, H_2O_2 treatment decreased insulin-induced glucose transport and membrane translocation of GLUT-4 (20). This effect was associated with attenuation of PI3-K/PKB signaling events and an increase in serine phosphorylation and degradation of IRS-1 (19). Phosphorylation of IRS-1 in specific serine residues has been implicated in dysregulated PI3-K/PKB activation and appears to be among the potential molecular mechanisms of insulin resistance (24, 26).

In vascular smooth muscle cells (VSMC) also, H_2O_2 induced a decrease of PKB phosphorylation that was associated with a decline of IR autophosphorylation (6). In these studies, the total amount of IRS-1 remained unchanged by H_2O_2 treatment (6), which is in contrast with reports on 3T3-L1 adipocytes or FAO rat hepatoma cells (19). However, these investigators did not examine if H_2O_2 caused an increase in serine phosphorylation or a decrease in tyrosine phosphorylation of IRS-1 (6). Interestingly, pretreatment of VSMC with H_2O_2 resulted in partial inhibition of insulin-binding activity in these cells (6). However, other studies, which have demonstrated an attenuation of insulin-induced responses by H_2O_2 or other agents, have not reported a similar decrease of insulin-binding activity (8, 19, 20, 24). It thus appears that low levels of endogenously generated H_2O_2 function as an initiator (13, 14) or "primer" of IR phosphorylation (21) and subsequent downstream signaling, whereas higher concentrations and longer exposure to exogenous H_2O_2 serve as an attenuator of the insulin response (6, 8, 19, 20).

Another free radical, nitric oxide (NO), has also emerged as a modulator of insulin action. Enhanced NO production due to heightened inducible NO synthase (iNOS) activity has been suggested to contribute to insulin resistance in genetic and diet-induced rodent models of insulin resistance (18). NO

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has the ability to react to superoxide anion and to generate highly reactive peroxynitrite radicals that, by catalyzing the nitration of proteins, can impair their functions (1). In this regard, the peroxynitrite-induced nitration of several key tyrosine residues in IRS-1 was recently shown to reduce insulin stimulation of glucose uptake and the PI3-K/PKB signaling pathway (17). Further support for a potential role of iNOS as a negative modifier of insulin signaling and action is provided by studies in which iNOS-deficient mice were protected from diet-induced insulin resistance (18).

These developments implicating redox molecules as regulators of insulin signaling and action prompted this *Forum* issue of *Antioxidants & Redox Signaling.* The aim of this *Forum* is to highlight some important studies relating to the role of ROS and RNS in various aspects of insulin signaling and action. The issue contains one original contribution and six reviews in the field. The original article by Mehdi *et al*. explores the upstream components involved in H_2O_2-induced signaling events (15). The six reviews are written by experts in this important area of research, and summarize the work done in their own and other laboratories. Dröge discusses the mechanism and potential contribution of oxidative enhancement of IR autophosphorylation (3). Goldstein *et al*. describe the mechanism and targets of insulin-induced H_2O_2 generation in initiating the insulin signaling cascade (7). The work presented by Konrad highlights the role of the antioxidant molecule α-lipoic acid as a stimulator/potentiator of the insulin signaling cascade and as a potential antidiabetic agent (10). Evans *et al*. summarize the mechanisms by which ROS/RNS contribute to insulin resistance (4). Frank *et al*. provide an up-to-date summary on the modulation of insulin signaling by redox in vascular and endothelial cells (5). Finally, Christon *et al*. discuss the recent progress made on the contribution of NO synthase in promoting insulin resistance and endothelial dysfunction (2).

I hope that this *Forum* issue will serve as a good source of information on redox modulation of insulin signaling and action. I wish to thank the authors for their excellent contributions, full cooperation, and sustained interest in putting this *Forum* issue together. I also appreciate the support from the Editors-in-Chief of *Antioxidants & Redox Signaling* for organizing this focused *Forum* issue.

ABBREVIATIONS

GLUT-4, glucose transporter-4; H_2O_2, hydrogen peroxide; iNOS, inducible nitric oxide synthase; IR, insulin receptor; IRS, insulin receptor substrate; NO, nitric oxide; PI, phosphatidylinositol; PI3-K, phosphatidylinositol 3-kinase; PKB, protein kinase B; PTK, protein tyrosine kinase; RNS, reactive nitrogen species; ROS, reactive oxygen species; VSMC, vascular smooth muscle cells.

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