

Obesity-induced Insulin Resistance and Hyperglycemia

Etiologic Factors and Molecular Mechanisms

J. A. Jeevendra Martyn, M.D., F.R.C.A., F.C.C.M.,* Masao Kaneki, M.D., Ph.D.,† Shingo Yasuhara, M.D., Ph.D.‡

Obesity is a major cause of type 2 diabetes, clinically evidenced as hyperglycemia. The altered glucose homeostasis is caused by faulty signal transduction *via* the insulin signaling proteins, which results in decreased glucose uptake by the muscle, altered lipogenesis, and increased glucose output by the liver. The etiology of this derangement in insulin signaling is related to a chronic inflammatory state, leading to the induction of inducible nitric oxide synthase and release of high levels of nitric oxide and reactive nitrogen species, which together cause posttranslational modifications in the signaling proteins. There are substantial differences in the molecular mechanisms of insulin resistance in muscle *versus* liver. Hormones and cytokines from adipocytes can enhance or inhibit both glycemic sensing and insulin signaling. The role of the central nervous system in glucose homeostasis also has been established. Multipronged therapies aimed at rectifying obesity-induced anomalies in both central nervous system and peripheral tissues may prove to be beneficial.

TYPE-2 diabetes is a polygenic disease. Obesity has been identified as a major causative factor for the insulin resistance and hyperglycemia associated with diabetes.¹ Developed and developing countries alike are experiencing a sharp rise in the incidence of obesity-linked type-2 diabetes.² Consequently, obesity-induced diabetes is emerging as a global health-care problem threatening to reach pandemic levels by 2030, when the incidence is projected to more than double in a period of only 30

years (from 171 million in 2000 to 366 million in 2030).³ The problem is not limited to adults. There has also been a marked increase in obesity (defined as a body mass index of greater than 30 kg/m²) among children.⁴ In the early stages of type-2 diabetes, insulin resistance is countered by a state of hyperinsulinemia brought about by stepped-up insulin production in the pancreas. Euglycemia is therefore maintained. Overt hyperglycemia does not develop until later stages, when pancreatic β cells can no longer compensate for the high levels of insulin resistance in peripheral tissues. Along with diabetes, there has been a concomitant increase of the incidence of metabolic syndrome, an obesity-linked condition characterized by clinical features of insulin resistance, dyslipidemia, and hypertension.^{5,6} Ultimately, it is the compounding effects of these cardiovascular, renal, cerebral, and thrombogenic anomalies that give rise to the increased morbidity and mortality associated with obesity, type-2 diabetes, and metabolic syndrome.⁶

Malfunctions in energy homeostasis resulting from genetic predisposition can lead to obesity. However, the recent increase in obesity is not thought to be due to specific congenital or hereditary defects in lipid metabolism, but to the inability of the body to cope with high-energy food intake, along with a sedentary life style and lack of exercise and/or mechanized work playing a contributing role.²⁻⁴ Adipocyte tissue, previously considered to be no more than an energy-storing depot, also has become a focus of intense scientific interest and is now thought to integrate a wide array of pathophysiologic processes, including nutrient homeostasis, immune response, blood pressure control, hemostasis, bone mass, and thyroid and reproductive function, in both physiologic and pathophysiologic states.^{7,8} Some of these effects are brought about by adipogenic hormones including leptin, adiponectin, and other adipokines (cytokines from fat). This review begins with a brief presentation of the molecular aspects of normal signal transduction *via* the insulin signaling network, followed by in-depth discussion of the molecular mechanisms specific to obesity that induce derangements in insulin signaling (insulin resistance) and hyperglycemia. Metabolic syndrome and its effects on perioperative care have been reviewed recently in ANESTHESIOLOGY⁹ and will not be discussed.

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* Professor, Harvard Medical School; Director, Clinical & Biochemical Pharmacology Laboratory, Massachusetts General Hospital, Boston, Massachusetts; and Anesthesiologist-in-Chief, Shriners Hospital for Children, Boston, Massachusetts. † Assistant Professor, Harvard Medical School; Associate Biochemist, Massachusetts General Hospital; and Shriners Hospital for Children. ‡ Instructor, Harvard Medical School; Assistant Biochemist, Massachusetts General Hospital; and Shriners Hospital for Children.

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Address correspondence to Dr. Martyn: Professor of Anaesthesiology, Harvard Medical School, Director, Clinical and Biochemical Pharmacology Laboratory, Massachusetts General Hospital, Anaesthetist-in-Chief, Shriners Hospitals for Children, Boston, 51 Blossom Street, Room 206, Boston, Massachusetts 02114. jmartyn@etherdome.mgh.harvard.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

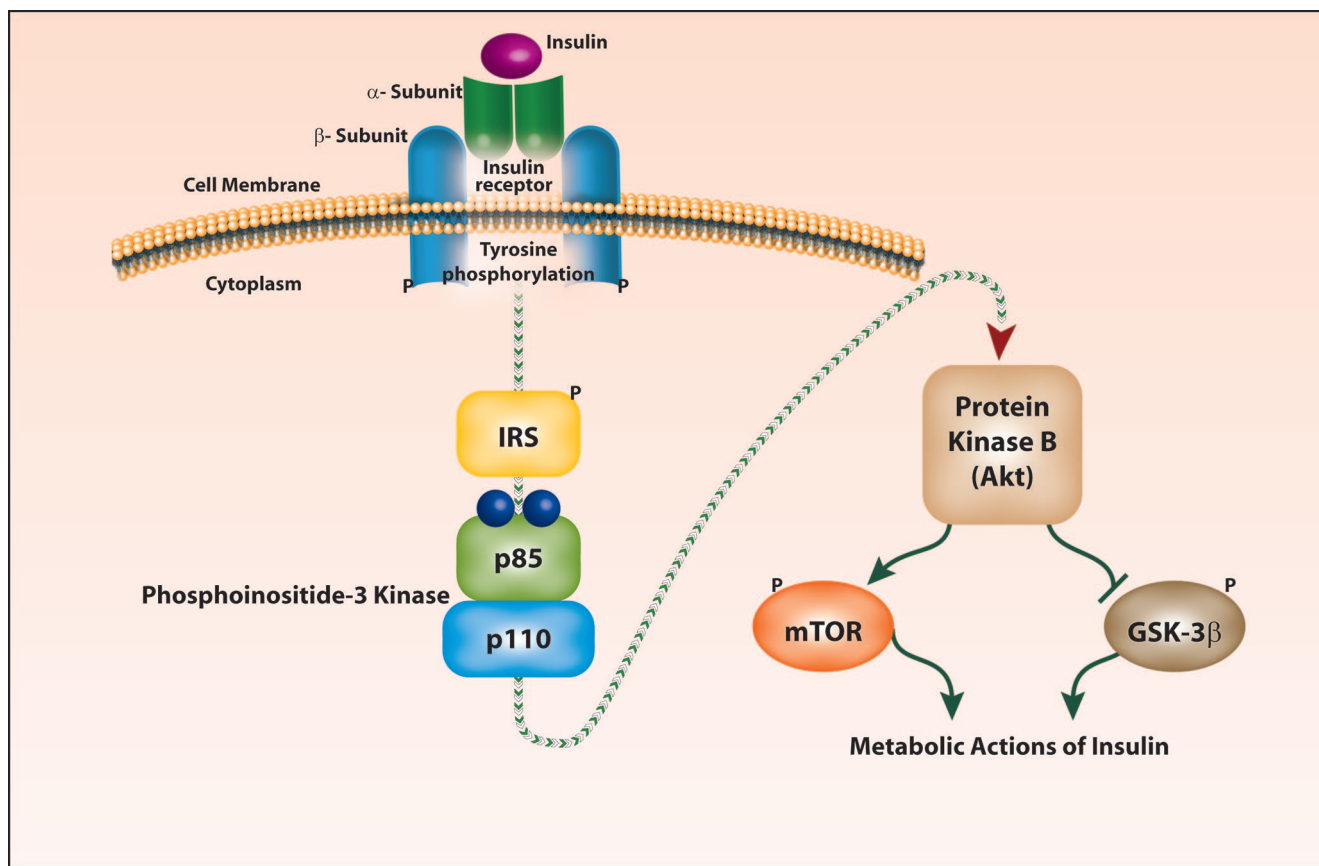


Fig. 1. Signal transduction *via* insulin receptor and its downstream signaling proteins. The insulin receptor is a kinase, an enzyme that catalyzes the transfer of phosphate from adenosine triphosphate to another substrate. When insulin binds to the insulin receptor it undergoes autophosphorylation and catalyzes the tyrosine phosphorylation of insulin receptor substrates (IRS)-1 and -2. These IRS proteins interact with diverse signaling molecules, including phosphoinositide-3 kinase, which in turn activate protein kinase B. The downstream proteins controlled by protein kinase B include mammalian target of rapamycin (mTOR) and glycogen synthase kinase-3 β (GSK-3 β). The metabolic and potent anabolic actions of insulin include glucose metabolism, glycogen–lipid–protein synthesis, cell growth and survival, and antiinflammation. These pleiotropic effects of insulin are mediated by specific gene expression, translation of proteins, and enhanced mitochondrial function.

Physiologic Actions of Insulin and the Insulin-Signaling Network

Insulin is the principal hormone of glucose homeostasis; it stimulates glucose influx into muscle, glycogen synthesis in the liver and muscle, and fat deposition in adipocytes.¹⁰ Other important actions of insulin include the enhancement of protein synthesis, cell survival and growth, prevention of protein catabolism, and antiinflammatory effects.^{11–14} Insulin-like growth factor-1 can behave like insulin, producing the same beneficial effects.^{13,14} Obesity-associated type 2 diabetes is evidenced by increased glucose levels in the blood, which result from elevated glucose production in the liver (gluconeogenesis and glycogenolysis) and decreased glucose uptake by muscle.^{1,10} In obesity-induced diabetes, or any pathologic condition associated with decreased insulin function, hyperglycemia together with the attenuated anabolic and antiinflammatory effects leads to muscle protein loss (muscle wasting), increased tendency to infection, and enhanced inflammatory response.

Similar to the G-protein coupled adrenoceptor, which is the paradigm of eukaryotic signal transduction,¹⁵ insulin also relies on a series of intracellular downstream signals to produce its physiologic effects.¹⁰ The binding of insulin to the α -subunit of the insulin receptor (IR) molecule induces rapid autophosphorylation (addition of a PO_4^- group from adenosine triphosphate) of the β -subunit, which turns on its tyrosine kinase activity (fig. 1).¹⁰ This gives IR the ability to phosphorylate various tyrosine residues of other cytosolic moieties, including insulin receptor substrates (IRS)-1 and -2. Phosphorylation of the tyrosine residues that reside on these substrates is pivotal for the biologic actions of insulin.^{16,17} The tyrosine phosphorylation of IRS proteins leads to the second intracellular step of insulin action, the association of phosphorylated IRS-1 or IRS-2 with the enzyme phosphoinositide-3-kinase (PI3K). The association of IRS-1 with PI3K occurs through the phosphorylation of Tyr-Met-X-Met or Tyr-X-X-Met motifs on IRS-1 and Src homology 2 domains on the 85-kDa subunit of PI3K.¹⁸ Absence of PI3K function due to disease or treatment

with wortmannin (a potent PI3K inhibitor) or with dominant negative p85, which inactivates endogenous PI3K activity, abolishes glucose uptake in muscle and adipose tissue.^{18,19}

The IRS-activated PI3K in turn affects several downstream signaling pathways through the generation of a lipid second messenger, phosphatidylinositol-3, 4, 5-triphosphate. A critical target for PI3K is protein kinase B (Akt/PKB).^{20,21} A serine-threonine kinase, Akt/PKB is the major effector of the IR-IRS-1-PI3K pathway and is activated by the phosphorylation of its threonine 308 and serine 473 residues. Akt/PKB drives the metabolic actions of insulin, including glucose transport, glycogen synthesis, fat deposition, and protein synthesis. It also drives cell growth and cell survival *via* pathways both dependent and independent of activation of the rapamycin-sensitive kinase known as mammalian target of rapamycin, with the downstream targets p70 S6 kinase and 4E-BP1.^{13,14,22} For example, loss of trophic signaling *via* Akt/PKB and downstream proteins not only leads to loss of glucose homeostasis,¹⁹ but also to loss of muscle mass and increased cellular loss by apoptosis.^{23–25} Some of the cell survival or cell growth effects of Akt/PKB are mediated by its actions on the mitochondria. Parenthetically, because the Akt/PKB-PI3K-mammalian target of rapamycin pathway plays a pivotal role in cell growth and survival, these proteins have become the target of novel signal-transduction inhibitors that are used to produce cell death in the area of cancer research.

Another target of Akt/PKB is glycogen synthase kinase-3 β (GSK-3 β), which is a negative regulator of glycogen synthase, the enzyme that catalyzes the synthesis of glycogen. When the serine 9 on GSK-3 β is phosphorylated and inactivated by Akt/PKB, glycogen and protein synthesis are enhanced.^{26,27} It also has been proposed that the Akt/PKB-GSK-3 β pathway mediates some of the antiinflammatory effects of insulin.^{26,27} In addition, GSK-3 β operates not only as a downstream component of insulin signaling, but also as a negative regulator of upstream insulin signaling. GSK-3 β phosphorylates IRS-1 at serine 332, which in turn attenuates the insulin response by inhibiting IR-mediated tyrosine phosphorylation of IRS-1.²⁸ Thus, whether occurring dependently or independently of Akt/PKB activity, increased GSK-3 β activity decreases glycogen synthesis and can lead to impaired upstream insulin signaling as well as enhanced inflammation.^{26,27}

Pathogenesis of Insulin Resistance and Hyperglycemia in Obesity

Despite several years of intense investigation, the pathogenesis of obesity-induced insulin resistance has not been fully elucidated. Recently, however, some of the derangements in insulin signaling have been clarified, along with the etiologic factors that lead to obesity-associated hyperglycemia.

Adipocytes decrease glucose uptake in peripheral tissues by the release of free fatty acids.²⁹ In humans, even brief periods of lipid infusion (e.g., 4 h) will decrease insulin-stimulated glucose uptake in muscle as well as PI3K activity.³⁰ Although the classic features of acute inflammation—*i.e.*, swelling, redness, pain, and fever (tumor, rubor, dolor, calor)—are absent, signs of chronic inflammation are observed with the release of inflammatory cytokines including tumor necrosis factor- α , interleukin-6 (IL-6), and interleukin-1 β (IL-1 β). These cytokines have been implicated in the pathogenesis of insulin resistance.^{28,31} In a published report, however, when antibodies to tumor necrosis factor- α were infused to diabetics, they did not consistently effect an improvement in insulin signaling.³² Nevertheless, contradictory evidence has been observed in rheumatoid arthritis; patients treated with anti-tumor necrosis factor- α antibody experienced a secondary benefit of enhanced insulin sensitivity.³³ Similarly, IL-1 β antagonist, a suppressor of IL-1 β cytokine, has been shown to improve glycemia and β -cell secretory function in obese humans.³⁴

Obesity-associated adipocyte apoptosis (cell death) appears to be the primary event underlying insulin insensitivity. The subsequent cell death-associated infiltration of macrophages appears to explain the presence of chronic inflammation.³⁵ The release of macrophage chemoattractant protein-1 by the adipocyte plays a role in the recruitment of macrophages.⁷ The infiltrating macrophages are implicated in cytokine production (fig. 2). These adipogenic cytokines appear to function in a paracrine fashion, because circulating cytokines are not consistently elevated. The concomitant release of reactive oxygen species exaggerate or play a causal role in cytokine-related insulin resistance.^{36,37} The intracellular mediators of this inflammatory response include nuclear factor (NF)- κ B, c-Jun amino-terminal kinase-stress-activated protein kinase (JNK/SAPK), and induction of the suppressor of cytokine signaling-3.^{5,28,38–40} Macrophage infiltration occurs not only in the adipocyte, but also in the liver.²⁸ The associated activation of the JNK/SAPK pathway also promotes the development of hepatic inflammation leading to hepatic steatosis (fat deposition), lipid peroxidation, and hepatic apoptosis, all of which are seen with obesity-induced diabetes.³⁸ It has been suggested that these inflammatory mediators also lead to serine phosphorylation of IRS-1.^{39,40} Serine phosphorylation, as opposed to tyrosine phosphorylation, inhibits insulin signaling.²⁸ Thus, high-dose aspirin or salicylate has been used as an antiinflammatory agent to treat fat-induced insulin resistance in humans with good success.⁴¹ The antiinflammatory effect of salicylates has been attributed to the inhibition of inhibitor of nuclear factor kappa (IKK) β kinase and NF κ B, which has lead to speculation that the glucose lowering and insulin sensitization may be due to NF κ B inhibition.

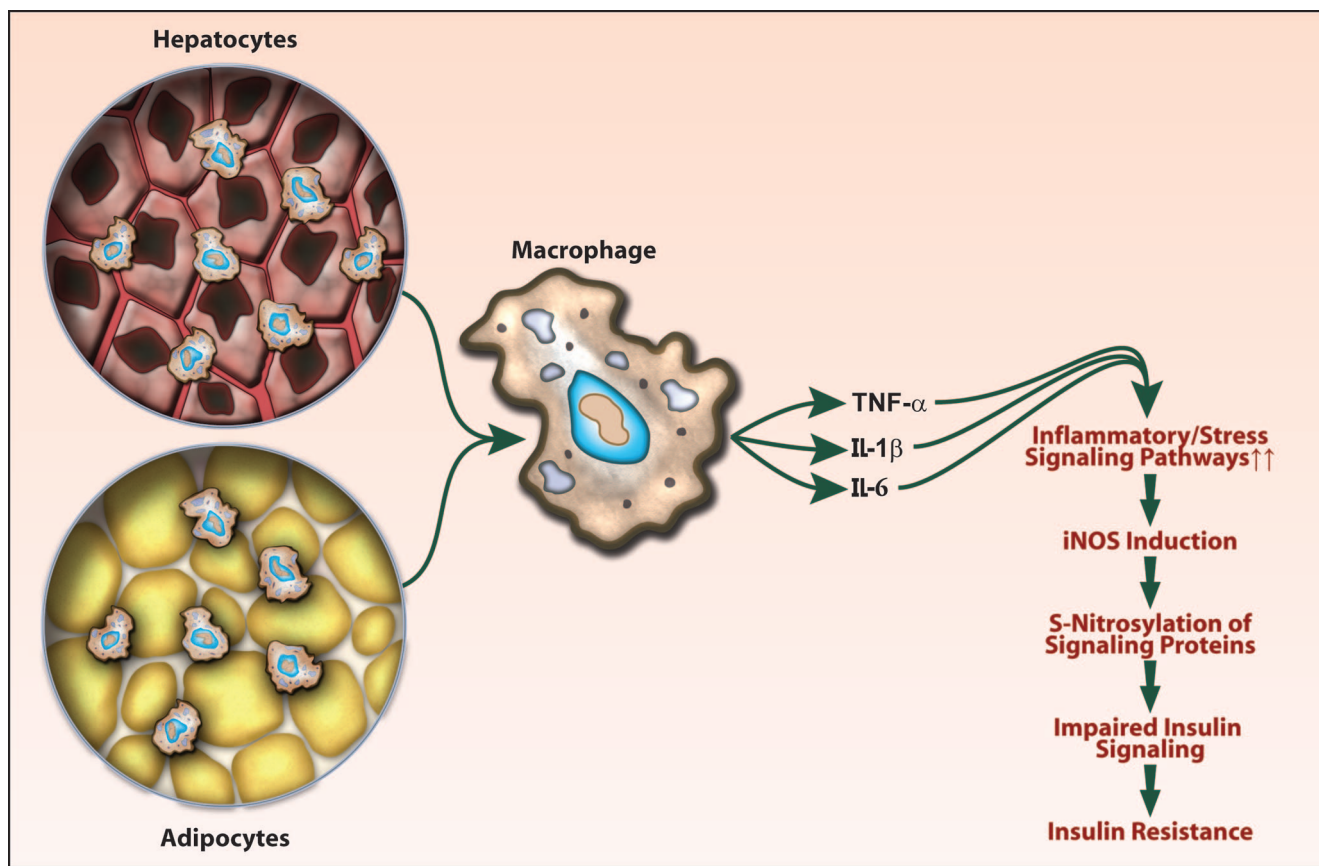


Fig. 2. Obesity leads to an inflammatory response in the liver and in adipose tissues. Obesity-induced inflammation results in infiltration of macrophages and release of cytokines, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β). The downstream effector of cytokine-induced inflammation is induction of inducible nitric oxide synthase (iNOS). The extremely high levels of nitric oxide that are released, together with reactive oxygen species, generate reactive nitrogen species including peroxynitrite, which leads to S-nitrosylation and tyrosine nitration (posttranslational modifications) of proteins. This calcium-independent process alters the function of many proteins, including those involved in insulin signaling. Gene manipulation of iNOS or treatment with iNOS inhibitors ameliorates the deranged insulin signaling as shown in figure 3.

Other etiologic factors have been proposed in the pathogenesis of obesity-induced insulin resistance. These factors include oxidative stress, mitochondrial dysfunction, intracellular lipid accumulation in skeletal muscle and liver, and decreased β -oxidation. Importantly, however, it remains unclear how these factors induce and/or exacerbate insulin resistance, as well as how they interrelate and by what specific mechanisms. Recent studies have begun to answer some of these questions, by elucidating that these pathologic and etiologic factors converge to activate inflammatory or stress signaling pathways.

Obesity-induced Insulin Resistance in Skeletal Muscle

Skeletal muscle is the major site of glucose disposition in the body. The glucose that is transported into muscle is used or stored as glycogen. In skeletal muscle, lipid accumulation has been implicated in the induction of obesity-related insulin resistance. In humans, intramyocellular lipid content correlates quite well with insulin resistance.⁴² Increased lipid accumulation results in activation of protein

kinase C θ and the JNK/SAPK pathway, in part through the elevated production of ceramide, which mediates impaired insulin signal transduction in muscle.^{43,44} JNK2 deficiency ameliorated impaired insulin signaling in skeletal muscle of obese, diabetic (leptin-deficient) mice.⁴⁵ In contrast, unlike the liver, inhibition of the IKK-NF- κ B pathway⁴⁶ or attenuation of endoplasmic reticulum (ER) stress (see Endoplasmic Reticulum Stress)⁴⁷ did not improve insulin resistance in skeletal muscle in mice. These observations indicate that, in skeletal muscle, the JNK/SAPK pathway plays an important role in obesity-induced insulin resistance, whereas the IKK-NF- κ B pathway and ER stress are not involved. However, the molecular bases that would explain these differences in obesity-induced insulin resistance in skeletal muscle *versus* the liver remain largely unknown.

Insulin Resistance and Glucose Homeostasis in the Liver with Obesity

Circulating glucose levels reflect a balance between glucose production by the liver and glucose uptake by the muscle.¹⁰ The liver plays a key role in obesity-in-

duced hyperglycemia and affects multiple pathways.^{5,48} Insulin promotes the synthesis of glycogen, while repressing glucose release in the liver. This effect is enhanced and coordinated through multiple genes that control glycolysis, fatty acid synthesis, gluconeogenesis (synthesis of glucose from proteins), and glycogenolysis (breakdown of glycogen).¹⁰ Insulin inhibits transcription of the gene encoding for phosphoenolpyruvate carboxykinase, the rate-limiting enzyme that controls gluconeogenesis.⁴⁹ Insulin also increases transcription of glycolytic enzymes (glucokinase and pyruvate kinase) and lipogenic enzymes (fatty acid synthase, acetyl-CoA carboxylase). These effects may be mediated by a host of transcription factors and cofactors including forkhead and peroxisome proliferators that activate receptors α and γ and their coactivators.^{50,51} Akt/PKB modulates these transcription factors and coactivators.^{10,13,17} Recent studies indicate that the effect of insulin on lipid metabolism in the liver also is mediated by changes in sterol regulatory element-binding protein-1c (SREBP-1C). Increase in sterol regulatory element-binding protein expression can increase expression of gluconeogenic and lipogenic genes and *vice versa*.^{52,53} Human studies confirm the importance of sterol regulatory element-binding protein in hepatic insulin resistance and hepatic steatosis, particularly in obesity.^{54,55} The presence of inflammation (macrophage infiltration), hepatocellular swelling, and steatosis constitute an operative risk, particularly in the liver, and increase the perioperative morbidity and mortality.^{56,57}

Evidence for the Role of Inducible Nitric Oxide in Obesity-induced Insulin Resistance

Although inflammation leading to activation of the JNK/SAPK and IKK-NF κ B pathways has been implicated in the pathogenesis of obesity-related insulin resistance, little has been published about the downstream effectors of these pathways. Our recent studies in rodents indicate that inducible nitric oxide synthase (iNOS) is a pivotal downstream effector of insulin resistance in many pathologic states, including obesity. Three isoforms of nitric oxide synthase are expressed in mammalian tissues. Endothelial and neuronal nitric oxide are constitutively expressed and generate small amounts of nitric oxide, which produces physiologic action by elevating cyclic guanosine monophosphate in a calcium-dependent manner.⁵⁸ In contrast, inflammation results in sustained high output of nitric oxide (up to 1,000-fold).⁵⁹ These extremely high concentrations of nitric oxide, particularly in the presence of reactive oxygen species, form highly reactive nitric oxide-related species, including peroxynitrite, which lead to cyclic guanosine monophosphate- and calcium-independent posttranslational modifications of proteins such as thiol nitrosylation (S-nitrosylation of cysteine residues) and tyrosine nitration.⁶⁰

Initially, we tested the beneficial effects of iNOS inhibition on inflammation and hyperglycemia induced by lipopolysaccharide.⁶¹ In these studies, using the euglycemic insulin clamp, we documented that lipopolysaccharide-induced hyperglycemia and hepatic glucose output can be completely suppressed by the iNOS inhibitor aminoguanidine.⁶¹ Subsequent studies from our laboratory have demonstrated more clearly the molecular mechanisms by which iNOS induces insulin resistance.⁶²⁻⁶⁴ Diabetic mice had increased expression of S-nitrosylated proteins. S-nitrosylation of tyrosine residues leads to decreased signaling *via* these proteins.⁶²⁻⁶⁴ Increased levels of nitric oxide inactivated insulin-signaling proteins including IRS and Akt/PKB in a concentration-dependent manner.⁶²⁻⁶⁴ The concomitant presence of oxidative stress accelerated the S-nitrosylation and inactivation and/or breakdown of insulin-signaling proteins.^{63,64} Denitrosylation with a reducing agent reactivated the nitrosylation-mediated inactivation of Akt/PKB.⁶²

In the liver, obese (leptin-deficient) mice have a 2.5-fold increase in iNOS protein expression compared with wild type mice (fig. 3A). The immunoreactivity for nitrotyrosine, a marker for nitrosative stress, is elevated in the liver of these obese mice. Treatment with the iNOS inhibitor L-N⁶-(1-Iminoethyl)lysine, better known as L-NIL, reverses elevated nitrotyrosine immunoreactivity in the liver (fig. 3B). In hepatic insulin resistance, there is decreased expression of IRS proteins.¹⁶ The treatment of obese mice with L-NIL increased protein expression of IRS-1 in a proteasome-dependent manner, while IRS-2 expression was increased by L-NIL at the mRNA level.⁶⁴ The increased expression of IRS proteins in the liver was associated with improved insulin signaling *via* IRSs-PI3K together with better glycemic control and insulin sensitivity. The improved insulin sensitivity was evidenced as lower fasting insulin and glucose levels in L-NIL-treated animals (fig. 3C and D).⁶³ All of these effects with iNOS inhibitor were not associated with changes in cyclic guanosine monophosphate in the liver, indicating that endothelial or neuronal NOS does not play a role in insulin resistance. It is also interesting to note that the expression of sterol regulatory element-binding protein, which is usually increased in hepatic insulin resistance, also was reduced after treatment with L-NIL.⁶³ In addition, inhibition of iNOS by gene disruption also reversed the decreased IRS-1 expression and thereby improved IRS-1-mediated insulin signaling in skeletal muscle of obese, diabetic (leptin-deficient) mice.⁶⁴ Some of these findings are consistent with studies by others, which have shown that iNOS expression, S-nitrosylated proteins, and tyrosine nitration are elevated in patients with type-2 diabetes,⁶⁵⁻⁶⁷ and that genetic disruption of iNOS improves insulin signaling in obese mice.⁶⁸ On the basis of these observations, iNOS

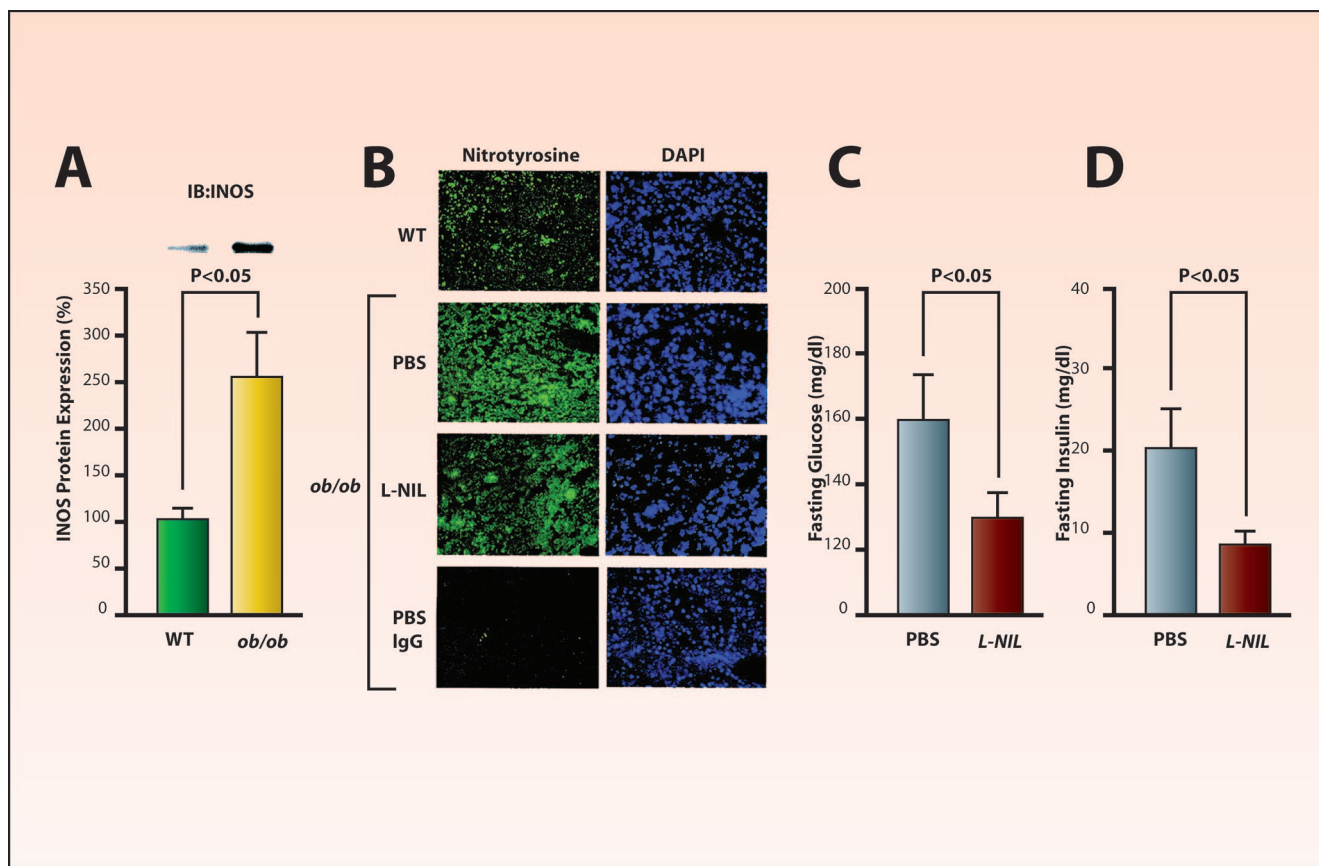


Fig. 3. Expression of inducible nitric oxide synthase (iNOS) and tyrosine nitration in leptin-deficient (*ob/ob*) mice and its reversal with iNOS inhibitor L-N6-(1-Iminoethyl)lysine (L-NIL). (**A**) Immunoblot analyses (IB) revealed that iNOS expression was increased in the liver of *ob/ob* mice compared with wild-type (WT) mice. (**B**) Nitrotyrosine immunoreactivity was elevated in the liver of *ob/ob* mice treated with phosphate buffered saline (PBS) compared with WT mice. L-NIL reduced nitrotyrosine immunoreactivity in *ob/ob* mice. Magnification: $\times 400$. (**C** and **D**) The decrease in nitrotyrosine immunoreactivity observed during treatment of *ob/ob* mice with L-NIL was associated with improved glycemic control, evidenced as normalization of fasting blood glucose level with reduced plasma insulin concentration. Nuclei are stained with diamidino-2-phenylindole. Adapted from Fujimoto *et al.*⁶³

inhibitors may prove to be a useful tool for treating obesity-induced diabetes.

Endoplasmic Reticulum Stress, Hyperglycemia, and Insulin Resistance

As indicated previously, chronic low-grade inflammation with activation of the IKK-NF κ B and JNK/SAPK pathways has been implicated as a causative factor in hepatic insulin resistance.^{38–40} In fact, obesity-related insulin resistance is associated with elevated circulating levels of C-reactive protein, a clinically measurable indicator and marker of acute-phase-protein response to inflammation by the liver.^{69,70} An alternative explanation has been proposed implicating ER stress as a key factor in obesity-linked chronic inflammation and the associated insulin resistance in liver.^{28,47,71}

From an evolutionary standpoint, the ER stress response is a cellular mechanism that evolved in eukaryotes as a coping mechanism for glucose or nutrition deprivation. The ER stress response in mammals was first characterized as the transcriptional activation of glucose-

regulated proteins (e.g., glucose-regulated protein 78) in response to glucose deprivation.⁷² Of note, absence of this ER stress response to glucose deprivation in genetically mutated mice leads to hypoglycemia and death shortly after birth,⁷³ and further supports the notion that ER stress response plays a critical role in glucose homeostasis, particularly in the liver. A critical role for ER stress in obesity-induced hepatic insulin resistance has been demonstrated by the following observations:^{28,47,71} Expression of glucose-regulated protein 78 and RNA-dependent protein kinase-like endoplasmic reticulum kinase (PERK), both indicators of ER stress response, was increased in the liver of leptin-deficient mice and in mice fed a high-fat diet.^{47,71} Mice deficient in X-box protein developed insulin resistance concomitant with elevated ER stress response.⁴⁷ Increased expression in the liver of oxygen-regulated protein 150, which is a resident ER chaperone, protects cells from ER stress^{73,74} and attenuates obesity-induced diabetes in rodents.⁷¹ Conversely, decreased expression of oxygen-regulated protein 150 causes ER stress and insulin resistance in the liver.⁷¹ ER stress mediates activation of IKK-NF- κ B and JNK/SAPK

in cells^{75,76} in association with derangements in lipid metabolism.^{77,78} Induction of iNOS and/or high levels of nitric oxide also can induce IKK-NF- κ B and JNK/SAPK with induction of ER stress.^{79–81} The interaction between iNOS and the IKK-NF- κ B-JNK/SAPK pathway, along with the potentiation of effects caused by this interaction, leads to a vicious cycle of insulin resistance. The clinical significance of ER stress in obesity, steatosis, and insulin resistance in humans is unclear, but pharmacologic agents are being developed to counteract these effects and have proved successful in rodents.⁷⁵

Recently, inflammatory or stress signaling pathways have been highlighted as a major culprit in obesity-induced insulin resistance,²⁸ and iNOS has been proposed as an important component of feed-forward mechanisms that lead to insulin resistance, in which it functions as both a downstream effector and an upstream enhancer of inflammation. Contrary to findings in liver, however, published studies do not find increased ER stress in skeletal muscle of obese, diabetic mice,^{71,75} and although it is conceivable that ER stress may con-

tribute to apoptosis in adipocytes, this has not been investigated.

Central Nervous System Control of Glucose Homeostasis

A close connection between output from the central nervous system (CNS) and glucose homeostasis is now well established.⁸² Adipose tissue, previously thought to be just an energy storage site, controls many physiologic functions by the release of adipokines.⁵ Leptin (based on the Greek *leptos*, or thin) was the first adipokine released by adipocytes to be identified. In addition to exerting insulin-enhancing effects in peripheral tissues, leptin also affects the CNS by controlling food intake through its actions on the mediobasal hypothalamic area (arcuate nucleus), which contains high concentrations of leptin receptor (fig. 4).⁸³ Mutations in the leptin receptor (which cause decreased sensitivity to leptin) or low levels of leptin can lead to increased appetite and obesity in rodents and humans.^{83,84} Some obese subjects

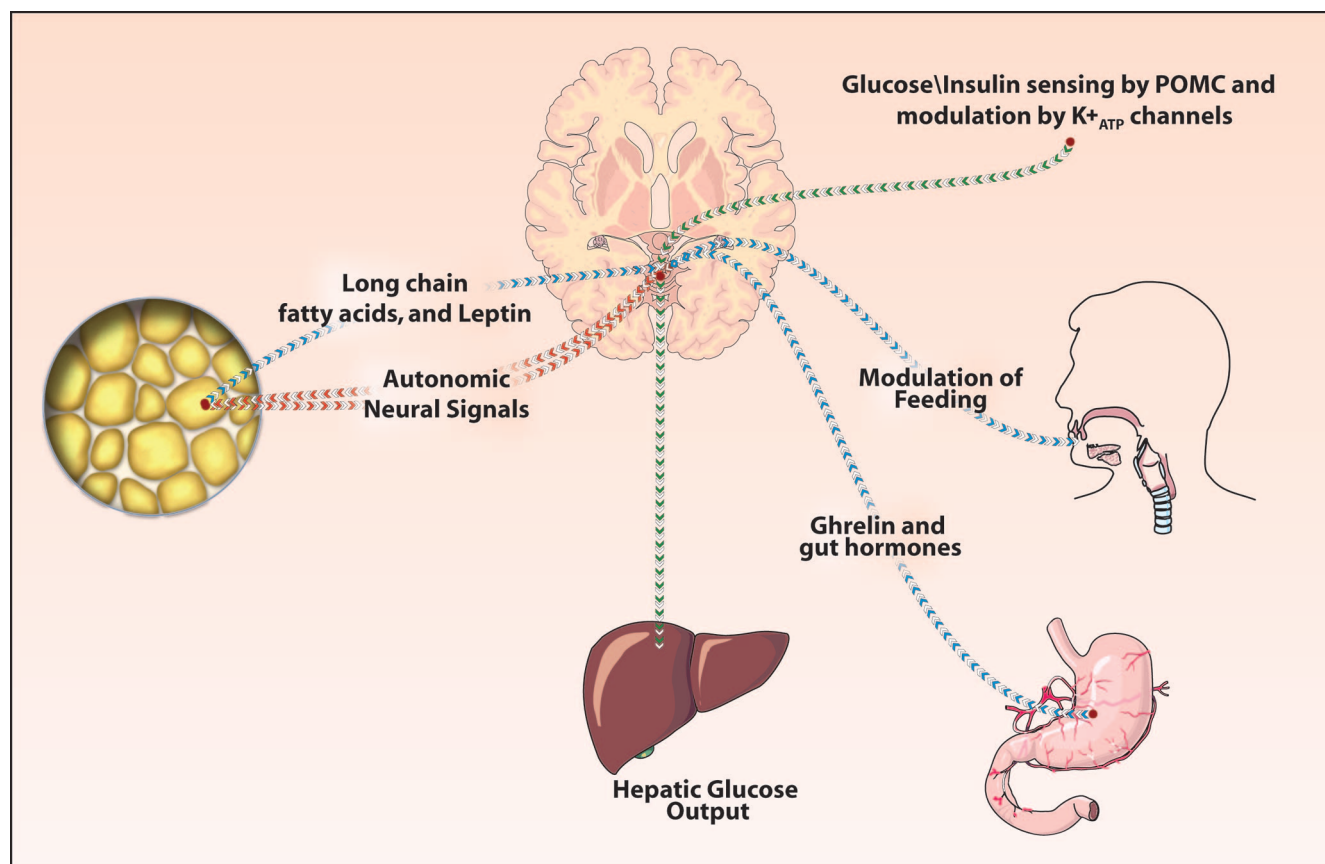


Fig. 4. Central nervous system control of glucose homeostasis. Leptin and long-chain fatty acids released from adipocytes influence food intake *via* the hypothalamus (depicted in blue). Ghrelin and other hormones from the gut also influence food intake and satiety (blue). Afferent and efferent autonomic signals from and to the fat pad, *via* the sympathetic and parasympathetic nerves to and from the hypothalamus, influence fat synthesis and breakdown of fat (depicted in red). Insulin and glucose levels influence potassium adenosine triphosphate (K^{+}_{ATP}) channels in the medial proopiomelanocortin (POMC) neurons on the arcuate nucleus and control neural output to modulate hepatic glucose output (depicted in green). In obesity, the ability to sense these afferent inputs to the hypothalamus is impaired, resulting in increased or orexigenic signals (decreased satiety) and increased nerve-mediated glucose output by the liver.

have an increase in appetite despite high levels of leptin, which may be related to an obesity-induced attenuated response to leptin. Thus, the actions of leptin on energy and food intake are independent of its peripheral (endocrine) effects, in which, among other physiologic functions, it also enhances insulin sensitivity and bone density.^{83,84} The dysregulation of this sensing pathway may lead to obesity and diabetes.

Afferent nerve fibers from fat modulate sensitivity of the CNS to leptin and this effect can be abrogated by denervation.⁸⁵ Long-chain fatty acids (released from the adipocyte) have been added to the growing list of metabolic signals that exert physiologic actions on the hypothalamus.^{83,84} Gut hormones, notably ghrelin, can activate circuits in the hypothalamus; for example, increased levels of ghrelin augment feeding. Several other gut hormones also control food intake, and these humoral circuits from fat and gut are dysfunctional in obesity.⁸³⁻⁸⁶ In particular, it has been suggested that evolutionally conserved fuel sensors, such as adenosine monophosphate-activated protein kinase and mammalian target of rapamycin, may integrate sensory input from nutrients, including those derived from food intake and adipose tissue. These sensors then may use this input to regulate efferent pathways responsible for fuel intake and utilization.⁸⁷

Centrally mediated neural autonomic (sympathetic and parasympathetic) actions can modulate adipocyte functions. It is well known that fat pads are well innervated by the sympathetic nervous system, and sympathetic nerve-mediated lipolysis *via* the adrenoceptor can lead to alterations in lipolysis.^{5,88} There is also evidence that parasympathetic innervation is involved in the control of glucose homeostasis, particularly with respect to abdominal fat tissue.⁸⁹ Using microsurgery, transneuronal retrograde tracing, and hyperinsulinemic euglycemic clamp, Kreier *et al.*⁹⁰ demonstrated that parasympathetic innervation of fat tissue stimulates fat growth. They also substantiated preexisting evidence that the brain controls fat growth by a selective group of neurons. These investigators, in fact, hypothesize that obesity and metabolic syndrome are diseases more of the brain than of any other organ or system.⁹¹ Other investigators have questioned the validity of the role of the parasympathetic nervous system.^{92,93} It is of interest to note that the autonomic nervous system and the immune system (*e.g.*, macrophages) cross-talk during inflammation *via* the sympathetic and parasympathetic pathways.^{94,95} Details of these interactions and cross-talk and how these mechanisms are modified in obesity are unknown.

Insulin and blood glucose levels, known to target liver glucose output *via* glycogenolysis and gluconeogenesis, have now been shown to act on the CNS to control glucose output by the liver. The studies of Pocai *et al.*⁹⁶ show that over and above its direct effects on the liver,

insulin also acts on specialized ion channels called potassium adenosine triphosphate channels located in the proopiomelanocortin neuron on the arcuate nucleus of the hypothalamus to control hepatic glucose production. By opening and closing these potassium adenosine triphosphate channels, the hypothalamus controls output to the liver *via* the vagus, because isolating the hepatic branches of the vagus obviates this response. The physiologic significance of this finding is that increases in insulin concentration in response to feeding in turn decrease the hepatic glucose output. It is also noteworthy that the ability to sense increased concentrations of glucose or insulin (*e.g.*, due to feeding) by the proopiomelanocortin neurons in the hypothalamus is defective in obesity.⁹⁷ The CNS-mediated hepatic glucose output continues in obese subjects despite high glucose and high insulin levels, and for this reason may have a pathogenic role in maintaining the hyperglycemia of obesity.⁹⁷ The mechanism for obesity-induced loss of glucose sensing by proopiomelanocortin involves uncoupling protein-2, because pharmacologic inhibition of uncoupling protein-2 by genipin reverses the loss of glucose sensing. Sulfonyleureas acting on the potassium adenosine triphosphate channels in the hypothalamus decrease neural signal output from the hypothalamus and decrease hepatic glucose output.⁸² The physiologic significance in humans of CNS control of glucose homeostasis in the liver has not been ascertained.

Therapeutic Choices for Treatment of Obesity-induced Insulin Resistance

It is now clear that aggressive control of hyperglycemia in patients with diabetes can attenuate the long-term cardiovascular and renal complications of this disease.^{98,99} Exercise, life style modification, and weight reduction should go *pari passu* with pharmacotherapy.¹⁰⁰ Exercise seems to increase glucose transport in cells independent of Akt/PKB, most likely through the adenosine monophosphate kinase pathway.¹⁰¹ Although weight reduction by liposuction in obesity has no effect on insulin action or risk factors for coronary artery disease,¹⁰² reduction in body weight with gastric bypass surgery not only improves the diabetes but also morbidity and mortality.¹⁰³⁻¹⁰⁵ The complications related to gastric bypass surgery, however, are high in this population.^{103,104}

Metformin is a biguanide. It has a well established, beneficial effect on peripheral tissues and mitochondrial function, in which it enhances the oxidation of fat and glucose presumably by activating adenosine monophosphate kinase.¹⁰⁶ The thiazolidinediones are a newer class of insulin-sensitizing drugs that not only increase peripheral utilization of glucose and suppress glucose production, but also exert pleiotropic effects on fat and inflamma-

tion.^{5,107} The thiazolidinediones function as peroxisome proliferator-activated receptor- γ agonists. In severe obesity, the adipose tissue macrophage is switched from its alternative activated form to its proinflammatory form.¹⁰⁸ The peroxisome proliferator-activated receptor- γ agonists prime the adipose tissue, and the macrophages revert to the alternative activated form,¹⁰⁹ with improvement of insulin resistance.¹¹⁰ These new findings are consistent with the theory that obesity-induced adipose tissue inflammation is a pivotal mediator of insulin resistance (fig. 2) and provide additional scientific basis for therapy with peroxisome proliferator-activated receptor- γ agonists. Thiazolidinediones, however, are associated with a high incidence of adverse cardiovascular events, including congestive heart failure and myocardial infarction, and therefore caution should be exercised when using these drugs.¹¹¹ Additional approaches that could be used to treat obesity and its effects on hyperglycemia include drugs that attenuate appetite and enhance energy expenditure. There are several reports of success with such approaches.^{7,97,112}

GSK-3 β inhibitors, which have multipronged effects on insulin signaling and inflammation as well as glycogen synthesis, could also prove beneficial. Experimental evidence on GSK-3 β inhibitors exists,^{26,27} but clinical studies in obesity are lacking. Although salicylates have proved useful,⁴¹ the use of these derivatives in surgical patients needs careful evaluation. Complications associated with salicylates, particularly in the high doses recommended for treatment of diabetes, include gastric ulceration, increased bleeding, and renal dysfunction. Future therapeutic regimens probably will include the use of iNOS inhibitors, which are currently in development for human use. The rationale for this line of treatment already has been discussed.

Potential Hyperglycemia-independent Impact of Insulin Resistance in Critical Illness

Obesity is associated with worse prognosis in patients with trauma,¹¹³ although conflicting results also have been reported. The deleterious impact of obesity has been postulated to be attributable, at least in part, to derangements in metabolic function. Insulin resistance is a major denominator and a central player of obesity-related metabolic derangements. Attenuated actions of insulin result in hyperglycemia, decreased protein synthesis, increased protein degradation, increased susceptibility to infection, and reduced antiapoptotic (prosurvival) and antiinflammatory actions of insulin,¹⁰⁻¹⁴ all of which contribute to exacerbation of critical illness. For critically ill patients with hyperglycemia, therefore, intensive insulin therapy has been employed in intensive care units to achieve tight glycemic control.⁹ Although

most of the detrimental effects of insulin resistance may be substantially reversed by exogenous insulin administration, it remains an open question whether intensive insulin therapy can fully reverse the detrimental effects of insulin resistance in critical illness, even if tight glycemic control is achieved. Hyperinsulinemia is an independent risk factor for the development of atherosclerosis, a major complication in type 2 diabetes. It is conceivable, therefore, that even if tight glycemic control without hypoglycemia is achieved by insulin therapy, the combination of hyperinsulinemia and insulin resistance may elicit some deleterious outcomes in critically ill patients.

Hyperglycemia is usually a good indicator of insulin insufficiency. However, there are some exceptions in the intensive care unit. Rarely, some patients may exhibit euglycemia or even hypoglycemia despite serious insulin resistance with normal or decreased plasma insulin concentration. Critical illness, such as sepsis and trauma, induces impaired hepatic glucose production independent of insulin action, leading to hypoglycemia,^{114,115} despite the coexisting attenuation of insulin action caused by insulin resistance. In these cases, although hyperglycemia is not observed, other beneficial actions of insulin—including anabolic, antiinflammatory, and antiapoptotic functions—are impaired owing to insulin resistance.

Control of excessive inflammation and subsequent apoptotic cell death has been proposed to be of essential importance to prevent and/or reverse tissue organ failure. Improvement in insulin sensitivity is accompanied by decreased inflammation and *vice versa*. This suggests that insulin-sensitizing drugs may be candidates for reducing the mortality of critically ill patients by their ability to improve insulin sensitivity and reverse excessive inflammation. Unfortunately, thiazolidinediones and metformin, the two clinically approved insulin sensitizers, cannot always be used for critically ill patients because of adverse side effects (e.g., edema and heart failure for thiazolidinediones,¹¹⁶ lactic acidosis for metformin¹¹⁷). Therefore, novel types of insulin-sensitizing drugs, which do not elicit such adverse side effects, would need to be developed to help improve the mortality of critically ill patients by reversal of inflammation and insulin resistance.

As discussed in this review, obesity-induced insulin resistance is closely linked to the inflammatory response and stress signaling pathways. The implication of hyperglycemia in critical illness has been an intense area of investigation for a number of years.¹¹⁸⁻¹²⁰ In contrast, the glycemic control-independent influence of insulin resistance in morbidity and mortality of critically ill patients is poorly understood, although previous studies have documented the glucose level-independent beneficial effects of insulin in rodent models of critical illness. Of interest, a recent study¹²¹ showed that the severity of

insulin resistance is associated with the severity of critical illness and body mass index, although no significant association was found between insulin resistance and basal blood glucose level. Thus, a potential hyperglycemia-independent impact of insulin resistance on prognosis during and after critical illness is worthy of further investigation.

Conclusion

For individuals born in the United States in 2000, the lifetime probability of being diagnosed with obesity and diabetes is substantial.¹²² Obesity is an independent risk factor for cardiovascular disease,¹⁻³ which increases the risk of perioperative complications. Interventions to reduce body weight have beneficial effects on decreasing cardiac complications in the perioperative period. Hyperglycemia and/or insulin resistance are associated with increased morbidity. Correction of hyperglycemia in critically ill patients decreases intensive care unit stay and improves hospital mortality, an effect particularly evident in surgical patients.^{122,123} This beneficial effect is probably related to the pleiotropic effects of insulin on glucose, protein, and inflammation.¹⁰⁻¹⁴ Thus, insulin resistance in the absence of obesity is also a major risk factor for surgical patients.¹¹⁹⁻¹²⁵ The compounding effect of obesity further aggravates perioperative morbidity and leads to systemic diseases that affect vital organs including the brain, kidney, heart, and liver.^{1,6,12}

Obesity-induced diabetes is related to decreased insulin-signaling *via* IR and its downstream proteins. A chronic inflammatory state seems to play a pivotal role in the insulin resistance. Differences do exist in the mechanisms of insulin resistance between liver, muscle, and adipocyte. The role of the CNS in insulin sensors sensing and glucose homeostasis is now well established. Understanding the impairments of insulin-signaling related to obesity-induced diabetes may lead to better pharmacologic methods, not only to treat but also to prevent obesity and type-2 diabetes. In this regard, in addition to behavior modifications that modify food (calorie) intake or alter the composition of foods ingested, development of drugs to decrease appetite and increase metabolism also may prove useful. Recent studies do confirm that multimodal, multifactorial interventions including behavior modifications and surgery have sustained beneficial effects on insulin sensitivity, cardiovascular complications, and mortality.^{9,99,100}

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