

Chapter (8)

Visceral Obesity & Metabolic Syndrome: Insulin resistance

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- Summary
- Aim
- Mechanisms
- Molecular basis:
 - § Alteration in glucose transporters
 - § Defects in signaling pathway
 - § Effects of FFAs
- Links to diabetes, obesity, dyslipidemia and hypertension
 - § Role of adipokines
- Therapeutic targets
- Stimulation of glucose uptake
 - § Agents to counter insulin resistance
 - § Non-insulin mediated stimulation

SUMMARY

- Insulin resistance is associated with compensatory hyperinsulinemia, but individual contributions of either of these two conditions remain incompletely understood and a subject of intense investigation.
- An important mechanism is the reduced strength of insulin signaling via the insulin receptor substrate (IRS)-1/phosphatidylinositol (PI) 3-kinase pathway, resulting in diminished glucose uptake and utilization in insulin target tissues. Fatty acids as well, have an important role in insulin resistance

AIM OF THE CHAPTER

The aim of this chapter is to delineate some aspects of the interrelation of visceral obesity, the metabolic syndrome and insulin resistance; besides, elucidating the molecular mechanisms of their detrimental cardio-metabolic effects.

DEFINITION OF INSULIN RESISTANCE

- The Consensus Development Conference of the American Diabetes Association defined insulin resistance as an impaired response to the physiological effects of insulin, including those on glucose, lipid and protein metabolism, and the effects on vascular endothelial function (1).
- Biologically, insulin resistance has been defined as glucose uptake < lowest quartile for background population under hyperinsulinaemic euglycaemic conditions (2).
- Clinically, the term insulin resistance implies that higher-than-normal concentrations of insulin are required to maintain normoglycemia. On a cellular level, this term defines an inadequate strength of insulin signaling from the insulin receptor downstream to the final substrates of insulin action involved in multiple metabolic and mitogenic aspects of cellular function (3).

MOLECULAR MECHANISMS OF INSULIN RESISTANCE:

- Insulin action is initiated by an interaction of insulin with its cell surface receptor (4)
- The insulin receptor is a heterotetrameric protein that consists of two extracellular α subunits and two transmembrane β subunits connected by disulfide bridges (5).
 - Insulin binding to the extracellular α subunit induces conformational changes of the insulin receptor that activate the tyrosine kinase domain of the intracellular portion of the β subunit. (6, 7)
 - Once the tyrosine kinase of insulin receptors is activated, it promotes autophosphorylation of the β subunit itself, where phosphorylation of three tyrosine residues (Tyr-1158, Tyr-1162, and Tyr-1163) is required for amplification of the kinase activity. (8,9)
 - Activation of the tyrosine kinase of the insulin receptor also leads to a rapid phosphorylation of the so-called "docking proteins," such as insulin receptor substrate (IRS)-1, -2, -3, and -4, and several Shc proteins (52-, 46-, and 64-kDa isoforms) that, in turn, attract multiple intracellular signaling intermediates. (10, 11)
- Initial attempts to unravel the molecular mechanism of insulin resistance have strongly suggested that a defect responsible for insulin resistance in the majority of patients lies at the post-receptor level of insulin signaling.
- Subsequent studies in insulin-resistant animal models and humans have consistently demonstrated a reduced strength of insulin signaling via the insulin receptor substrate (IRS)-1/phosphatidylinositol (PI) 3-kinase pathway, resulting in diminished glucose uptake and utilization in insulin target tissues.
- Serine phosphorylation of IRS proteins can reduce their ability to attract PI 3-kinase, thereby minimizing its activation. A number of serine kinases that phosphorylate serine residues of IRS-1 and weaken insulin signal transduction have been identified. Additionally, mitochondrial dysfunction has been suggested to trigger activation of several serine kinases, leading to a serine phosphorylation of IRS-1.
- The IRS and Shc proteins play an important regulatory role in the insulin signaling cascade, as in their phosphorylated form they become points of anchoring for intracellular proteins containing Src-homology-2 (SH-2) domains (12). Whereas interaction of IRS and Shc proteins with the intracellular domain of the insulin receptor constitutes the first step in dispersing the directions of insulin signaling intracellularly,

their ability to attract multiple signaling intermediates to their own phosphorylated domains further partitions insulin signaling downstream, thus accounting for the multitude of insulin's biological effects (13).

- Most, if not all, of the metabolic and antiapoptotic effects of insulin are mediated by the signaling pathway involving IRS proteins, phosphorylation, and activation of phosphatidylinositol (PI) 3-kinase, and other pathways.

FATTY ACID/LIPID-INDUCED INSULIN RESISTANCE (FIG. 1)

- Elevated free fatty acid levels reduce intracellular glucose-6-phosphate levels.
- An increase in fat oxidation might be responsible for insulin resistance in obese states. According to this proposal, increased fatty acid oxidation would cause an increase in the mitochondrial acetyl coenzyme A (CoA):CoA and NADH:NAD₊ ratios with subsequent inactivation of pyruvate dehydrogenase.
- In turn, this would induce a rise in intracellular citrate levels, leading to inhibition of phosphofructokinase and G6P accumulation. Because G6P inhibits hexokinase activity, this would result in intracellular glucose accumulation and decreased glucose uptake.
- Fatty acid infusion can have direct effects on GLUT4 activity, or can alter insulin-regulated GLUT4 trafficking between intracellular compartments and the cell accumulation in skeletal muscle (14), in both cases, insulin resistance ensues.
- Molecular details of FFAs induced IR are shown in figure

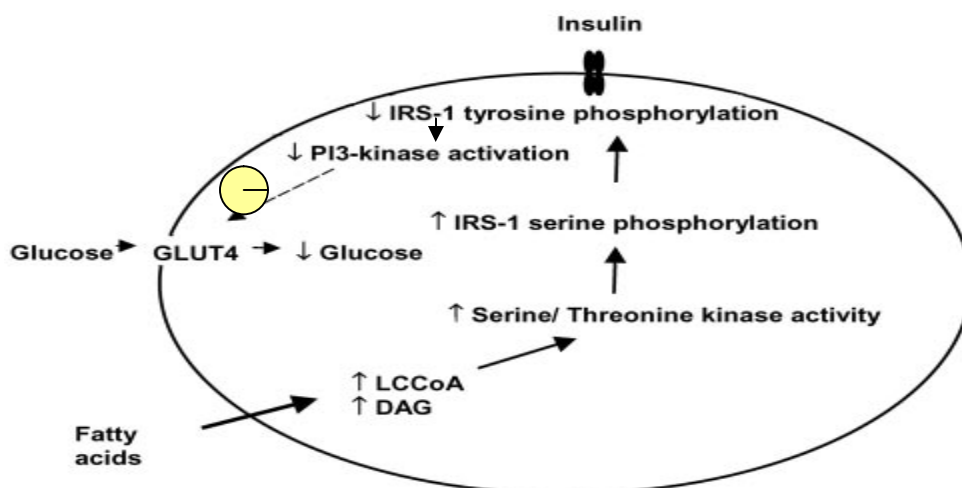


Fig. (1) Mechanism of fatty acid-induced insulin resistance.

GLUCOSE TRANSPORTERS

- Glucose transport in mammalian cells is dependent upon membrane-associated carrier proteins.
- Mammalian cells possess two types of glucose carriers (a) the Na⁺-glucose co-transporter and (b) the facilitative glucose transporter.
- The Na⁺-glucose co-transporter transports glucose against its concentration gradient by coupling its uptake with the uptake of Na⁺.
- GLUT1 is a widely expressed isoform that provides cells with their basal glucose requirements. It plays a unique role in transporting glucose across epithelial and endothelial barrier tissues. GLUT2 is an isoform expressed in hepatocytes, pancreatic b-cells, and the basolateral membranes of intestinal and renal epithelial cells. It acts as a high-capacity transport system to allow the flux of glucose into or out of these cells in a non-rate-limiting manner (15).
- In the liver GLUT2 mediates the bi-directional transport of glucose by hepatocytes.
- GLUT3 is an isoform that is responsible for glucose uptake into neurons.
- The localization of the GLUT4, mainly expressed in insulin sensitive tissues, such as muscle and adipose tissue, changes in response to insulin. It is responsible for increased glucose disposal in these tissues in the postprandial state and is vital in whole-body glucose homeostasis (16).
- The GLUT5, expressed in small intestine is involved in the trans-cellular transport of glucose by absorptive epithelial cells.
- GLUT7 is present in the endoplasmic reticulum (ER) membrane that allows the flux of free glucose out of the lumen of ER following the action of glucose-6-phosphatase on glucose 6-phosphate. GLUT6 and GLUT8 appear to recycle in a dynamic-dependent manner between internal membranes and the plasma membrane in rat adipose cells (17).
- Each glucose transporter operates most efficiently at different levels of blood glucose. For example, GLUT4 can swiftly reduce high levels of glucose in the post-prandial state. Elevated cell surface levels of the GLUT4 facilitate enhanced glucose uptake from the circulation and storage in fat and muscle. GLUT3 operates efficiently at low blood glucose concentrations in order to ensure constant supply of glucose to the brain when blood glucose levels are low. GLUT2, in its regulatory function, has an activity that is

linear across a wide range of blood glucose concentrations and can provide an insulin demand signal to the pancreatic b-cells at various glucose levels (18).

ROLE OF ADIPOKINES IN INSULIN RESISTANCE

- The adipokines or adipocytokines (See chapters 5,6) are a group of cytokines (cell-to-cell signaling proteins) secreted by adipose tissue.
- Their relative roles in modifying appetite, insulin resistance and atherosclerosis are the subjects of intense research, as they may be modifiable causes of morbidity in people with obesity.

Adiponectin (see chapter 6)

- This hormone plays a role in the suppression of the metabolic derangements that may result in type 2 diabetes, obesity, atherosclerosis and non-alcoholic fatty liver disease (NAFLD).
- Metabolic effects of Adiponectin :
 - Glucose flux
 - Gluconeogenesis
 - Glucose uptake
 - Lipid catabolism
 - β -oxidation
 - Triglyceride clearance
 - Protection from endothelial dysfunction insulin sensitivity
 - Weight loss

Leptin (from the Greek word leptos, meaning thin) (see also chapter 5)

- Circulating leptin levels give the brain a reading of energy storage for the purposes of regulating appetite and metabolism. Leptin works by inhibiting the activity of neurons that contain neuropeptide Y (NPY) and agouti-related peptide (AgRP), and by increasing the activity of neurons expressing α -melanocyte-stimulating hormone (α -MSH) (19).

- The NPY neurons are a key element in the regulation of appetite; small doses of NPY injected into the brains of experimental animals stimulates feeding, while selective destruction of the NPY neurons in mice causes them to become anorexic.
- Conversely, α -MSH is an important mediator of satiety, and differences in the gene for the receptor at which α -MSH acts in the brain are linked to obesity in humans.
- In the presence of insulin, melatonin interacts with insulin and upregulates insulin-stimulated leptin expression.
- To date, only leptin and insulin fulfill the criteria of an adiposity signal. It circulates at levels proportional to body fat. It enters the central nervous system (CNS) in proportion to its plasma concentration. Its receptors are found in brain neurons involved in regulating energy intake and expenditure.

Tumor necrosis factor (see also chapter 5)

- TNF- α has a number of actions on various organ systems, generally acting together with IL-1 and Interleukin-6 (IL-6):

§ **On the hypothalamus:**

- Stimulating of the hypothalamic-pituitary-adrenal axis, stimulating the release of corticotropin releasing hormone (CRH).
- Suppressing appetite.
- Fever.

§ **On the liver:**

- Stimulating the acute phase response, leading to an increase in C-reactive protein and a number of other mediators.
 - It also induces insulin resistance by promoting serine-phosphorylation of insulin receptor substrate-1 (IRS-1), which impairs insulin signaling.
- On macrophages: stimulates phagocytosis, and production of IL-1 oxidants and the inflammatory lipid prostaglandin E2 (PGE2).

THERAPEUTIC TARGETS FOR INSULIN RESISTANCE:

Lifestyle Modification

- Lifestyle modifications such as weight loss, exercise, and smoking cessation have been shown to improve insulin sensitivity and lipid profile, to lower blood pressure, to decrease the risk of developing type 2 diabetes, and to reduce the risk of coronary heart disease and stroke (20).
- Lifestyle modification remains the cornerstone of any successful diabetes and cardiovascular prevention program. Invariably, improvement in insulin sensitivity is associated with better insulin signaling along the PI 3-kinase pathway.

Biguanides (metformin)

- Different mechanisms of metformin action in the basal vs. the insulin-stimulated state have been described.
- In the basal, postabsorptive state, the improvement of fasting hyperglycemia is mostly due to a decrease of the accelerated endogenous glucose production. This results from inhibition of both gluconeogenesis and glycogen breakdown.
- The fact that reduction in basal glucose production occurs in the presence of lower or unaltered insulin levels suggests that glucose production in liver and kidney (22,23) is more sensitive to the restrictive action of insulin after treatment with metformin.

Thiazolidinediones (TZDs)

- Thiazolidinediones are synthetic ligands that bind to a family of nuclear receptors known as peroxisome proliferator-activated receptors (PPARs) (24). The TZDs' binding affinity for PPAR- γ appears to correlate with their glucose-lowering ability. For example Rosiglitazone has a greater PPAR- γ binding affinity than does pioglitazone, which translates to a more glucose lowering.
- These drugs are also known as insulin sensitizers because they appear to improve insulin sensitivity (25). In addition to lowering blood glucose, both drugs may improve other cardiovascular risk factors, such as lipids, blood pressure, inflammation, and endothelial function (26).
- These observations suggest that reversal of insulin resistance may be accompanied by an improvement in the cardiovascular risk factors. Because thiazolidinedione

receptors are expressed in all major cells of vasculature (27), the direct action of these drugs on arterial wall may be even more important than their effect on glycemia.

AGENTS TO INHIBIT FATTY ACID OXIDATION

- Inhibitors of carnitine palmitoyltransferase 1 (CPT-1), which is the rate-limiting enzyme for transfer of long-chain fatty acyl-CoA into the mitochondria, like etomoxir, have been shown to have antihyperglycemic activity in type 2 diabetic patients, predominantly due to inhibiting hepatic gluconeogenesis and decreasing plasma TG concentrations (28).
- Furthermore, in the spontaneously hypertensive rat model, acute etomoxir treatment improved glucose tolerance and blood pressure significantly, suggesting an increased insulin sensitivity (29). However etomoxir treatment (100 mg/day) for 3 days in a placebo-controlled, randomized, double-blind study of 12 type 2 diabetic subjects, failed to demonstrate any effect (30).
- Prospectively, the slow reversibility of the antigluconeogenic effect of CPT-1 inhibitors and the resulting interrupted defense against hypoglycemia may limit the clinical usefulness of these compounds (31).
- Thus, based on the currently available data, agents to inhibit fatty acid oxidation do not have a marked antihyperglycemic potency.

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