Obesity and insulin resistance: molecular basis for clinical appraisal

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Abstrak

Many persons have a constellation of major risk/actors, life-habit risk factors, and emerging risk factors that constitute a condition called the Metabolic Syndrome. Eight components characteristic of the Metabolic Syndrome are: I. insulin resistance (with or without glucose intolerance), 2. hyperinsulinemia, 3. abdominal obesity, 4. raised blood pressure, 5. atherogenic dyslipidemia (T Triglyceride, T Postprandial lipemia, Small dense LDL or Type B pattern), 6. procoagulant state (t Fibrinogen, T PAI-1), 7. hyperuricemia, 8. endothelial dysfunction ft Albumin excretion rate, etc).

Among the single etiologic factors being considered are: 1. a genetic defect in one or more components of the insulin action cascade leading to insulin resistance, 2. malnutrition during fetal development, and 3. abdominal obesity. It is possible that these three factors could be in some way interrelated. Several mechanisms implicated in the development of insulin resistance in obesity can be shortly postulated below. TNF-a oversecreted by the enlarged fat cells impairs insulin action by inhibiting insulin receptor signaling, possibly by increasing IRS-l serine phosphorylation GLUT-4 expression and translocation to the cell surface will be impaired by TNF-a.

Leptin released from visceral adipocytes may inhibit insulin action in the liver by impairing insulin receptor signaling, leading to reduced down-regulation of PEPCK, the rate-limiting enzyme in gluconeogenesis. Glucose-stimulated insulin released from pancreatic fi-cell is also impaired by leptin through STAT-3 production stimulated by leptin via leptin receptor on the surface membrane of fl-cell, and then STAT-3 stimulates the opening of K+Arp-channels, and consequently insulin release will be inhibited.

Resistin, as well as TNF-a and leptin released by adipocytes, decrease insulin sensitivity and to be suggested to inhibit adipogenesis; insulin administration rapidly increases resistin levels to normal in adipose tissue. Potential therapeutic beneficial effects of metformin for obesity and insulin resistance may be selectively categorized into 3 groups. In carbohydrate metabolism, metformin prevents pancreatic j3-cellfrom gluco-and lipotoxicity, increases insulin receptor binding, and increases insulin receptor tyrosine kinase (IRTK) activity.

Metformin increases oral glucose-induced GLP-l amide levels in obese non-diabetic subjects; metformin is able to inhibit GLP-l degradation induced by dipeptidyl-peptidase IV. GLP-l is a gastrointestinal hormone, which stimulates insulin secretion and promotes satiety, and hence GLP-l and dipeptyl-peptidase IV-inhibitor can be proposed as therapeutic goals for the treatment of patients with Type 2-DM (T2DM) and obesity.

In lipid metabolism, metformin may improve lipid profile. Several vasoprotective effects also belong to

Metformin, f.e. 4. Hyperinsulinemia, J- Fibrinogen, -I PAl-I, -I FactorXHIa which functions to stabilize fibrin, 4- Platelet aggregation, i Capillary permeability, -I SMC-Fibroblast activity, and i Carbonyl stress (pathway to AGE formation).

Conclusion: Obesity and insulin resistance are two major components of the metabolic syndrome, which predispose individuals to the development of T2DM and coronary heart disease. TNF-a and leptin, which are oversecreted by enlarged fat cells, play pivotal roles in the molecular defects of insulin action in obesity-linked insulin resistance. Pleio-tropic properties (vasoprotective effects) of metformin beyond carbohydrate and lipid effects may contribute to the beneficial therapeutic tools for obesity-linked insulin resistance.