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Major causes of insuline resistance

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INTRODUCTION

The metabolic syndrome is also called insulin resistance syndrome.[1] This term was used for the first time in 1922 to describe the few cases of patients with diabetes who required increasing doses of insulin to maintain normoglycemia. Most of these patients developed insulin resistance secondary to the production of antibodies directed against exogenous insulin, which was not sufficiently purified at the time, and what is more, it was obtained from other animal species.[2]
Insulin resistance is currently defined as the body's insufficient response to specific insulin levels. The clinical spectrum of insulin resistance is broad and includes both diabetic patients who require insulin therapy and experience hyperglycemia despite high doses of exogenous insulin, as well as patients with severe insulin resistance who maintain almost normal blood glucose levels due to significantly higher endogenous insulin secretion.[3]
Causes of insulin resistance can be divided into innate and secondary.[3] There are many reasons for insulin resistance, including genetic mutations like insulin receptor mutations, hormonal and pharmacological or immunological. However, insulin resistance is most commonly associated with obesity.[4]

INHERITABLE CAUSES OF INSULINE RESISTANCE

Defects intrinsic to target cells could be divided into mutations of the insulin-receptor genes and defects in other genes important for insulin action like glucose transporters, substrates for insulin-receptor kinase or signaling intermediates and cellular inhibitors of insulin-receptor kinase.[3]

Insulin resistance most commonly coexists with obesity but may also occur in an unusually severe form in rare patients with monogenic defects. Such patients may loosely be grouped into those with primary disorders of insulin signaling and those with defects in adipose tissue development or function (lipodystrophy).[4] Examples of inheritable diseases that coexist with IR, apart from lipodystrophies are: Leprechaunism, Rabson-Mendenhall Syndrome and Type A syndrome of insulin resistance.

SECONDARY INSULIN RESISTANCE

Secondary IR causes involve those connected to normal and abnormal physiologic states, specific hormonal and metabolic factors and immune mediated states (tab).[3,4]

SECONDARY INSULINE RESISTANCE CAUSES			
ABNORMAL PHYSIOLOGIC STATES	NORMAL PHYSIOLOGIC STATES	SPECIFIC HORMONAL OR METABOLIC FACTORS	IMMUNE MEDIATED STATES
stress	puberty	glucocorticoids (e.g., Cushing's syndrome)	anti-insulin antibodies
fasting/starvation	advanced age	growth hormone (acromegaly)	anti-insulin receptor antibodies in type B syndrome
uremia	pregnancy	catecholamines (e.g., pheochromocytoma)	
cirrhosis		glucagon (e.g., glucagonoma)	
ketoacidosis		thyroid hormone (thyrotoxicosis)	
obesity		hyperinsulinemia (e.g.,insulinoma)	
diabetes/hyperglycemia		hyperglycemia (diabetes)	
		free fatty acids (nonesterified fatty acids)	
		adenosine	
		islet amyloid polypeptide	

OBESITY AND INSULIN RESISTANCE

Obesity, particularly abdominal obesity, is most frequent risk factor associated with resistance to the effects of insulin on peripheral glucose utilization, often leading to type 2 diabetes mellitus. Obesity is associated with a low-grade inflammation of white adipose tissue (WAT) resulting from chronic activation of the innate immune system and which can subsequently lead to insulin resistance, impaired glucose tolerance and diabetes. WAT is the physiological site of energy storage as lipids. In addition, it has been recognized as an active participant in numerous physiological and pathophysiological processes. Adipocytes share with immune cells certain properties such as complement activation and pro-inflammatory cytokine production. Fat cells precursors also share features with macrophages. Preadipocytes have the capacity for phagocytosis in response to several stimuli.

In obesity, WAT is characterized by an increased production and secretion of a wide range of inflammatory molecules including TNF-alpha and interleukin-6 (IL-6), which may have both local and systemic effects. Recent data indicate that obese WAT is infiltrated by macrophages, which may be a major source of locally-produced pro-inflammatory cytokines. Interestingly, weight loss is associated with a reduction in the macrophage infiltration of WAT and an improvement of the inflammatory profile of gene expression.

Several factors derived from adipocytes as well as from infiltrated macrophages probably contribute to the pathogenesis of insulin resistance. Most of them are overproduced during obesity, including leptin, TNF-alpha, IL-6 and resistin.[5]

Contrary, adiponectin is down-regulated in obesity.[6] Decreased expression of adiponectin correlates with insulin resistance. Adiponectin decreases insulin resistance by decreasing triglyceride content in muscle and liver in obese mice.[7] In addition, adiponectin counteracts the pro-inflammatory effects of TNF-alpha on the arterial wall and probably protects against the development of arteriosclerosis.[5]

Studies in genetically obese animals suggest that increased release of TNF-alpha from adipose tissue may play a major role in the impairment in insulin action.[8–11] The applicability of these findings to humans is controversial. In a study of a homogeneous Native Canadian population, plasma TNF-alpha concentrations were positively correlated with insulin resistance.[12]

Leptin could modulate TNF-alpha production and macrophage activation. Both TNF-alpha and IL-6 can alter insulin sensitivity by triggering different key steps in the insulin signaling pathway. Activation of TNF receptors (as well as for IL-6) activates the NF-κB and Janus kinase (JNK) signaling pathways that lead to phosphorylation of the 307 serine residue in IRS-1 proteins. Inactive IRS-1 is not able to participate in further insulin signaling mechanisms i.e.

in the binding and activation of PI-3K. A further effect of attenuated IRS-1 and PI-3K binding under TNF is inhibition of GLUT4 translocation and reduction of insulin-dependent glucose transport into the cell.[13] IL-6 may induce hepatic CRP synthesis and may promote the onset of cardiovascular complications.[5]

In rodents, resistin expression is limited to adipose tissue, while in humans, it appears to be an inflammatory molecule made mainly in macrophages. In rodents resistine impairs insulin sensitivity. Circulating levels of resistin are increased in obesity, and an increase in serum resistin levels has been shown to induce insulin resistance in several rat and mouse models.

However, role of resistine in humans is uncertain. Proinflammatory cytokines whose levels are increased in obesity and diabetes, such as TNFα an in d IL-6, dramatically induce resistin in human macrophages.[14–16] Moreover, resistin itself markedly stimulates the expression of proinflammatory cytokines in human mononuclear cells. Given the emerging interrelationship between inflammation and metabolic disease, hyperresistinemia may be a biomarker, and/or a mediator, of metabolic and inflammatory diseases in humans as well as in rodents.[16]

CONCLUSIONS

Insulin resistance can be caused by multiple factors. Although it can affect slim patients, most commonly IR is associated with obesity. Since western countries deal with obesity epidemic, we have to be prepared for insulin resistance epidemic as well. To do so, we need to get acquainted with pathophysiology of IR and obesity and get to know relationship between them profoundly.

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