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Short Communication

Pathophysiology of Insulin Resistance: from Metabolic Syndrome to type 2 Diabetes

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Abstract

Pseudoneurological disorders are conditions in which psychological or depressive experiences manifest as physical, seemingly neurological, symptoms. Patients complain of pain, dizziness, or other bodily ailments, while objective examinations reveal no organic abnormalities. These symptoms are often mistakenly considered exaggerated or imaginary, leading patients to miss out on the help they need. These symptoms often stem from underlying forms of anxiety and depression, disguised as somatic complaints. Understanding the psychogenic nature of such conditions allows for appropriate treatment and restoration of the patient's emotional and physical well-being.

Keywords: pseudoneurological disorders; depression; anxiety; somatization

Introduction

The reduction of peripheral tissue sensitivity to the hormone insulin is a fundamental disorder underlying the development of a number of endocrine-metabolic pathologies. In the conditions of modern civilization, characterized by physical inactivity and excess calorie intake, this problem becomes especially relevant. Epidemiological studies in recent decades clearly demonstrate the close relationship between insulin resistance, obesity and carbohydrate disorders.

WHO statistics show a rapid increase in the prevalence of diabetes: if in the 1980s the number of patients was about 108 million people, then by 2025 this figure exceeded 600 million. The vast majority of cases (about 95%) are type 2 diabetes, the pathogenesis of which is inextricably linked with peripheral insulin resistance. The purpose of this study is to comprehensively analyze the pathophysiological aspects of the formation of insulin resistance and its transformation into clinically manifest diabetes mellitus.

Insulin resistance: definition and mechanisms

Insulin resistance refers to a pathological condition in which the cellular structures of skeletal muscle, adipose tissue and hepatocytes demonstrate a subnormal response to physiological concentrations of circulating insulin. In response to the development of this situation, the body turns on compensatory mechanisms in the form of enhanced production of the hormone by the β-cells of the islet apparatus of the pancreas, which leads to the development of hyperinsulinemia. This pathophysiological phenomenon serves as a unifying link between various manifestations of metabolic syndrome.

Molecular mechanisms

At the cellular signaling level, insulin resistance is formed due to disruption of the normal functioning of insulin-dependent transduction pathways. Initiation of the signaling cascade occurs when a hormone molecule interacts with the external

domain of a receptor belonging to the receptor tyrosine kinase family. This interaction triggers the process of autophosphorylation of the cytoplasmic domains of the receptor with subsequent activation of insulin receptor substrates of the first and second types.

Key pathological changes include: dysregulation of expression and decreased functional activity of insulin receptors; defects in post-translational modification of IRS proteins; activation of negative insulin signaling regulators (SOCS family proteins, PTEN phosphatases); disruption of the mechanisms of translocation of type 4 glucose transporter to the plasma membrane. The combination of these changes causes a decrease in peripheral glucose utilization and an increase in hepatic gluconeogenesis activity.

Mechanism	Description of the violation
Receptor level	Decreased insulin receptor expression and affinity

Mechanism	Description of the violation
Postreceptor level	Irs-1/2 phosphorylation disorder SOCS activation
Signal paths	PI3 K/AKT activity decreased, JNK/IKK enhanced
GLUT4	Impaired translocation to the membrane

Table 1. Molecular mechanisms of insulin resistance

The role of inflammation and adipokinov

Adipose tissue has a central function in the pathogenesis of insulin resistance. With the development of fat body weight, there is a predominant accumulation of visceral fat, which is accompanied by a chronic low-intensity inflammatory process. Under these conditions, adipocytes begin to intensively secrete proinflammatory cytokines (tumor necrosis factor alpha, interleukins 6 and 1-beta), as well as chemotactic factors that recruit macrophage cells into the fat depot.

Disruption of the adipokine balance plays a significant role in the formation of metabolic disorders. The concentration of leptin in the blood increases significantly (leptin resistance develops), while the production of adiponectin, which has pronounced insulin-sensitizing properties, significantly decreases. In contrast, adipokines such as visfatin and resistin contribute to the development and progression of peripheral insulin resistance.

Metabolic syndrome

Metabolic syndrome (insulin resistance syndrome) is a complex condition characterized by a combination of several mutually reinforcing metabolic disorders: central type obesity, arterial hypertension, dyslipidemia (hypertriglyceridemia combined with decreased levels of high-density lipoproteins) and carbohydrate metabolism disorders. Insulin resistance is the pathophysiological foundation of this syndrome.

Diagnostic criteria for metabolic syndrome according to IDF recommendations (2005) suggest the presence of abdominal obesity (waist circumference of at least 94 cm in Caucasian males and at least 80 cm in females) plus at least two of the following components: increased serum triglycerides (≥ 1.7 mmol/L), decreased HDL-C concentration (< 1.03 mmol/L in males, < 1.29 mmol/L in females, blood pressure ≥ 130/85 mm Hg fasting glycaemia ≥ 5.6 mmol/L.

Component	Criteria	Pathophysiology
Abdominal obesity	OT ≥ 94 cm (M), ≥ 80 cm (F)	Visceral fat, inflammation
Hypertriglyceridemia	≥ 1.7 mmol/l	Increased VLDL yield
Low HDL-C	< 1.03 (M), < 1.29 (F)	Violation of reverse transport of HS
Arterial hypertension	≥ 130/85 mmHg.	Activation of SNA, RAAS
Hyperglycemia	≥ 5.6 mmol/L	Liver resistance to insulin

Table 2. Components of metabolic syndrome and their pathophysiological foundations

From Type 2 Diabetes Resistance

The evolution from the compensated stage of insulin resistance to decompensation of carbohydrate metabolism and clinically verified type 2 diabetes mellitus is due to a progressive decrease in the functional activity of β-cells of the islets of Langerhans. In the initial stages, compensatory hyperinsulinemia ensures the maintenance of normoglycemia, however, as the pathological process develops, β cells lose the ability to adequately respond secretory.

Key factors determining disease progression include: glucotoxicity (cytotoxic effects of chronic hyperglycemia on β cells), lipotoxicity (excessive intake of free fatty acids), endoplasmic reticulum stress, oxidative stress and amyloid deposition fibrils in the parenchyma of the islets. These pathological processes lead to apoptosis of β cells and a decrease in the functioning mass of the islet apparatus.

Stage	Glycemia	State of β cells
I. Compensation	Normal	Hyperplasia, hyperfunction
II. Transition	Tolerance is impaired	Initial dysfunction
III. Decompensation	DM2 (HbA1c ≥ 6.5%)	The mass of β cells is reduced by 50%
IV. Severe DM2	Poor control	The mass of β cells is reduced by 70%

Table 3: Steps in the progression of insulin resistance to type 2 diabetes mellitus

Conclusion

Insulin resistance is a polyetiological pathological condition that is the pathophysiological basis of metabolic syndrome and type 2 diabetes mellitus. The pathogenesis of this condition includes a complex of molecular disorders of insulin-dependent signal transduction, chronic inflammation of visceral adipose tissue, imbalance of the adipokine system, as well as progressive dysfunction and death of pancreatic β-cells.

An in-depth understanding of these mechanisms is of fundamental clinical importance for the implementation of programs for early diagnosis, prevention and development of targeted therapeutic approaches. The current treatment strategy aims to improve peripheral insulin sensitivity (use of biguanides, thiazolidinediones, SGLT2 inhibitors), as well as to protect the functional competence of β cells and slow down the progression of the pathological process.

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