МЕДИЦИНА

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DEVELOPMENT OF PERIPHERAL INSULIN RESISTANCE AS A CONSEQUENCE OF CENTRAL LEVERS OF INFLUENCE

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The process of regulating intake and consumption to maintain energy balance is called lipostasis. Disruption of this system and metabolism can lead to disorders that may also cause changes in the structure of the gut microbiota. Insulin and leptin are key feedback signals. Their complex interaction with specific receptors in the central nervous system influences human eating behavior (pioglitazone) and leptin resistance (metformin) in patients with type 2 diabetes mellitus, helping to restore normal lipostatic function.

Key words: *insulin resistance, leptin resistance, gut microbiota, type 2 diabetes mellitus, metformin, pioglitazone.*

Recently, many reports have appeared about the involvement of various substances in the development of central insulin resistance. For example, the role of ghrelin has been noted. With chronic intracerebroventricular administration, glucose and triglyceride uptake in adipose tissue improves, fat oxidation is suppressed, and lipogenesis increases [1]. Thyroid hormones also play a key role, as it is known that their receptors are found in nearly all human cells [2].

Insulin is the main factor in the development of insulin resistance. In recent years, it has become clear that insulin's effects on the central nervous system influence a wide range of functions, including eating behavior, peripheral glucose regulation, sympathetic activity, and even reproductive functions [1].

The processes of regulating consumption and expenditure to maintain energy balance are collectively known as the lipostatic mechanism (or lipostat). This complex regulatory system, which involves brain activity, functions through negative feedback and "protects" stable body weight (mainly adipose tissue). Therefore, when the lipostat operates correctly, it is difficult to gain or lose mass [3].

Interesting data have also been obtained on the relationship between insulin resistance, hypothyroidism, and obesity with the intestinal microbiota. In patients, several significant correlations were found between the gut microbiota and the parameters studied. A negative correlation was observed between body mass index and Bifidobacterium spp. and Escherichia coli, and a positive correlation was found between body mass index and some opportunistic pathogens. Thus, there is a weak but reliable direct relationship with Shigella spp. and Staphylococcus aureus, while an inverse, less reliable relationship exists with Helicobacter pylori. Interesting correlations were identified, showing a tendency toward confidence with Salmonella spp. and Bacteroides thetaiotaomicron, and a plausible feedback trend between BMI, Faecalibacterium prausnitzii, and Candida

spp. Therefore, the intestine and the microbiota present there are not only capable of digesting food but also directly involved in the development of insulin resistance and obesity. [4].

There are two main fat feedback signals: insulin and leptin. Both cross the blood-brain barrier and enter the hypothalamus area, which is responsible for the autonomic control of food intake. The arcuate nucleus of the hypothalamus contains two types of neurons: neuropeptide Y (NPY) and proopiomelanocortin (POMC), which secrete the corresponding peptides. However, the NPY neuron also secretes the so-called Agouti-related peptide (AgRP). Leptin and insulin stimulate anorexigenic POMC neurons and inhibit orexigenic neurons (those that stimulate appetite). During weight loss, for example, leptin and insulin levels decrease, the activity of POMC neurons is suppressed, and NPY/AgRP activity is increased. AgRP blocks the melanocortin-4 receptor, leading to increased food intake. Therefore, the neurons of the arcuate nucleus work together through insulin and leptin to ensure energy balance [5].

There is even a cephalic phase of insulin secretion, which occurs in response to barely perceptible taste stimuli [6]. For example, signals received through the olfactory system, taste, and normal awareness create a pleasant sensation of "food reward" [5]. An increase in leptin decreases the enjoyment of "food rewards" and reduces motivation to eat. Conversely, if leptin levels decrease, the desire for "food rewards" increases [5; 7].

Insulin acts in the brain on insulin receptors through the PI3K pathway, converting phosphatidylinositol diphosphate into triphosphate, which, by activating protein kinase B and other mediators, promotes glucose transport, glycogen synthesis, and proteins. It also increases fat storage [5]. It should be noted that factors disrupting the PI3K pathway include TNF-α. Conversely, other authors attribute powerful anorexigenic properties to TNF-α, believing it inhibits the activity of the hunger center and stimulates the satiety center in the hypothalamus [8].

Although the data above describe insulin as an appetite-suppressing factor, clinical practice appears to show the opposite. An overdose of insulin or insulin secretagogues increases appetite in patients with diabetes mellitus (DM), leading to overeating and hyperglycemia [9].

Several experimental studies also support these findings. Chronic intracerebroventricular insulin administration to mice increased fat mass, adipocyte size, and tissue lipoprotein lipase expression, indicating enhanced lipogenesis. It is likely that peripheral effects develop as a result of central insulin resistance (which means insulin does not have an anorexigenic effect) caused by prolonged intracerebroventricular insulin infusion. At the same time, it is believed that insulin acts as a catabolic hormone within the CNS and as an anabolic hormone in the periphery, promoting lipogenesis [10].

Studies in mice that had their insulin receptors completely eliminated and those that retained only central receptors confirmed that the effect of insulin through the central nervous system is essential for regulating peripheral adipose tissue and glucose metabolism. Both mouse groups exhibited severe hyperinsulinemia, hyperglycemia, hyperadiponectinemia, and hyperleptinemia (considering the adipose tissue mass). More significant fat mass loss was observed in fully insulin-resistant mice [1].

An unusual clinical study using euglycemic and hyperglycemic clamps concluded that glucose, not insulin, should be considered an appetite regulator. It was found that euglycemia in patients with type 2 diabetes stimulated appetite and overeating, while hyperglycemia had the opposite effect, and insulin levels did not differ between the experimental groups [9]. Therefore, it was determined that, most likely, it is not insulin but glucose levels that change under its influence, making glucose the main regulator of eating behavior and the state of carbohydrate and fat metabolism in the periphery. At the same time, insulin resistance should not be overlooked when examining this phenomenon.

Other researchers argue that insulin's role in maintaining energy homeostasis diminishes in comparison to leptin's capabilities [1]. Leptin, in particular, can enhance the sensitivity of peripheral tissues to insulin and inhibit its production, both by acting on the hypothalamus (central regulation) and directly on pancreatic β cells (peripheral regulation). Recent findings suggest that leptin's effect on reducing food intake operates through the PI3K pathway, which it shares with insulin in the central nervous system [11]. It is also important to remember that leptin's existence depends on insulin, which stimulates lipogenesis (leptin is produced in adipose tissue). Therefore, leptin is essentially dependent on insulin's "conscientious work".

Recently, the role of insulin in relation to mental activity has been clarified through the use of experimental models [5]. Insulin not only enhances the absorption of glucose by the brain, increases levels of neurotransmitters (dopamine, acetylcholine, norepinephrine), modulates neuronal activity, protects against oxidative stress, but also improves memory.

Clinical studies have confirmed that insulin resistance raises the risk of cognitive impairment, and treating insulin resistance improves mental performance not only in people with insulin resistance but also in patients with type 2 diabetes or Alzheimer's disease. Therapy with pioglitazone (30 mg/day), unlike nateglinide (120 mg three times daily), improved not only glycemia but also memory by 40%. Administration

of rosiglitazone to 500 Alzheimer's patients with insulin resistance but without T2DM for 6 months stabilized their condition, whereas the placebo group experienced disease progression [12].

The study of metformin revealed a significant decrease in leptin content compared to the control group in rats with induced streptozotocin diabetes. In a clinical study of patients with type 2 diabetes mellitus and high leptin levels (suspected leptin resistance), a decrease in this hormone was observed following the use of metformin. Additionally, in such patients, not only was normalization of blood glucose and a reduction in insulin resistance according to the HOMA-IR index noted, but also a decrease in appetite [13]. Clearly, in this context, we are discussing the mitigation of central leptin resistance due to metformin. At the same time, as mentioned, leptin's action is linked to insulin effects, which does not exclude the possibility of a dual effect of metformin in improving sensitivity to these hormones in brain tissues.

Therefore, insulin resistance in the central nervous system is just as important as in the periphery. As a result, new areas of research for drugs that could effectively address these issues are emerging.

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РОЗВИТОК ПЕРИФЕРИЧНОЇ ІНСУЛІНОРЕЗИСТЕНТНОСТІ ЯК НАСЛІДОК ЦЕНТРАЛЬНИХ ВАЖЕЛІВ ВПЛИВУ

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Процес контролю надходження й споживання для підтримки енергетичного гомеостазу називається ліпостатом. Порушення цієї системи та метаболізму здатне призводити до порушень, що можуть проявлятися навіть у зміні структури мікробіоти кишки. Ключовими сигналами зворотного зв'язку є інсулін і лептин. Їх складна взаємодія з певними рецепторами в центральній нервовій системі визначає харчову поведінку людини. Деякі препарати, маючи центральну дію, пом'якшують інсулінорезистентність (піоглітазон) і лептинорезистентність (метформін) у хворих на цукровий діабет 2-го типу, забезпечуючи нормалізацію ліпостатної функції.

Ключові слова: *інсулінорезистентність, лептинорезистентність, мікробіота кишківника, цукровий діабет 2-го типу, метформін, піглітазон.*