34. NEW APPROACHES OF THE BIOCHEMICAL MECHANISMS OF INSULIN RESISTANCE

Author: Condrea Cătălin

Scientific adviser: Veronica Sardari, MD, Department of Biochemistry and Clinical Biochemistry, *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova.

Introduction. Insulin resistance (IR) is a complex metabolic syndrome that leads to diabetes mellitus type 2 (DM2) in about 90% of cases. There are various biochemical mechanisms behind IR, the majority being the interruption of signaling pathways such as insulin receptor substrate 1 and 2 (IRS 1 and IRS2) or serine/threonine protein kinase (AKT), leading to the blockage of the main proteins. The disruption of the insulin signaling pathway is the common cause of IR, especially with the decrease of the protein glucose transporter 4 (GLUT-4) that leads to a decrease in the insulin mediated glucose import to cells.

Aim of study. Aim of the study is to elucidate and describe the biochemical mechanisms of insulin resistance (IR) underlying the development of effective treatment for type 2 diabetes

Methods and materials. To achieve the proposed goal, a bibliographic search was performed using the following platforms: Medscape, PubMed, and American Physiological Society Journal. Articles that were published between 2010 and 2020 were selected.

Results. One of the main factors leading to IR is hyperlipidemia, which is present in obesity. Hyperlipidemia leads to the excessive formation of secondary mediators, such as diacylglycerol (DAG) and ceramides that disrupt the insulin signaling pathway in the cell. DAG activates protein kinase C theta (PKCθ), which, in the muscle, inhibits IRS 1 and IRS 2, and, in the liver, activates protein kinase C epsilon (PKCε). Ceramides, in turn, will block serine/threonine protein kinase (Akt) by altering its binding to protein kinase C zeta (PKCζ). Obesity creates a chronic low-intensity inflammation in the adipose tissue with the synthesis of proinflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukins 6, 18 and 1 β. These proinflammatory cytokines will cause systemic IR by activating inhibitory kinase of nuclear factor κ-B (IKK) and c-jun 1-terminal kinase (JNK), which will block IRS1 and IRS2 substrates. Smoking has also been shown to contribute to the development of IR. This occurs because the nicotine inside cigarettes binds with the nicotinic receptor α1 and with acetylcholine (NAchR), activating it. Once activated, NAchR increases the mammalian target of rapamycin (mTOR) with increased IRS-1 Ser636 phosphorylation and reduced insulin-stimulated glucose uptake.

Conclusion. IR is mostly caused by factors such as obesity, overnutrition, chronic inflammation and smoking. These factors lead to the interruption of the insulin signaling pathway at the level of the Akt kinase and the insulin receptor substrates IRS1 and IRS2, so these are the best places of action for newly developed medications.