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Pratheepkumar V., Thanushya R.

MECHANISMS OF INSULIN SIGNALING PATHWAYS IN HYPOTHYROIDISM

Tutor: PhD, associate professor Khotko C.A.
Department of Biological Chemistry
Belarusian State Medical University, Minsk

Insulin signaling is crucial for glucose homeostasis, cell growth, and metabolic regulation. Hypothyroidism, characterized by low thyroid hormone levels, alters insulin action, leading to increased insulin resistance and metabolic disorders. At the cellular level, insulin exerts its effects through the binding of insulin to its receptor (INSR), a transmembrane tyrosine kinase. This interaction triggers a cascade of phosphorylation events, primarily involving insulin receptor substrates (IRS), PI3K (phosphoinositide 3-kinase), and AKT (protein kinase B). Low thyroid hormone levels in hypothyroidism can affect insulin receptor expression, leading to decreased insulin sensitivity, affecting glucose uptake and metabolism.

Thyroid hormones, particularly T3, increase the expression of the INSR gene, promoting insulin binding and signaling. In hypothyroid states, this expression decreases, leading to decreased receptor activity. T3 enhances the phosphorylation of insulin receptor substrate (IRS) proteins primarily by stimulating the activation of protein kinase B (Akt) and other signaling molecules, such as phosphoinositide 3-kinase (PI3K), that facilitate this phosphorylation event. It promotes the recruitment of insulin receptors to the plasma membrane, increasing the receptor's availability for insulin binding and subsequent signaling. which leads to increased tyrosine kinase activity and subsequent phosphorylation of IRS at specific tyrosine residues. This phosphorylation not only activates IRS proteins but also facilitates their binding to signaling molecules like PI3K, thereby amplifying downstream signaling pathways that regulate glucose metabolism and cellular growth.In hypothyroidism, reduced levels of thyroid hormones result in diminished activation of signaling pathways, such as the PI3K/Akt pathway, thereby leading to decreased phosphorylation of IRS-1 at critical tyrosine residues. This impairment hinders IRS-1's ability to effectively propagate insulin signaling, ultimately contributing to insulin resistance and disrupted glucose metabolism.

Hypothyroidism impairs glucose and lipid metabolism, exacerbates insulin resistance. Thyroid hormones enhance the transcription of genes involved in lipolysis, which leads to increased levels of adipose triglyceride lipase (ATGL) while concurrently decreasing hormone-sensitive lipase (HSL) activity through the modulation of related signaling pathways, such as AMP-activated protein kinase (AMPK). Additionally, thyroid hormones can influence the expression of peroxisome proliferator-activated receptors (PPARs), which regulate the transcription of metabolic genes, leading to a reduction in HSL expression and overall lipolytic activity. In hypothyroidism, elevated levels of pro-inflammatory cytokines such as TNF-α and IL-6 promote the activation of stress kinases, like JNK and IKK, which can phosphorylate IRS proteins at serine residues. This serine phosphorylation of IRS proteins inhibits their ability to transmit insulin signals, thereby exacerbating insulin resistance and impairing glucose metabolism. Hypothyroidism management often involves levothyroxine (Medicine) administration, which restores thyroid hormone levels, improving insulin sensitivity and metabolic parameters. Studies show that correction leads to enhanced glycemic control in patients with metabolic syndrome, emphasizing the importance of thyroid hormone levels in insulin resistance-related conditions.

In summary, hypothyroidism significantly disrupts insulin signaling and glucose metabolism due to reduced thyroid hormone levels, which impair the expression and activity of insulin receptors and IRS proteins. This results in increased insulin resistance and exacerbated metabolic disorders, as seen in diminished activation of the PI3K/Akt pathway. Elevated pro-inflammatory cytokines in hypothyroid states can cause serine phosphorylation of IRS proteins, further inhibiting insulin signaling. This highlights the critical role of thyroid hormones in maintaining glucose homeostasis and overall metabolic health.