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INFLUENCE OF BETA- ADRENERGIC RECEPTOR IN INSULIN RELEASE: A REVIEW

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ABSTRACT

β-Adrenergic receptors (βARs) are a class of G-protein-coupled receptors (GPCRs) that bind to epinephrine and norepinephrine to mediate a physiological response. These receptors are divided into three subtypes: β1-AR, which is mainly found in the heart and brain; β2-AR, which is more widely distributed; and β3-AR, which is mainly found in adipose tissue. Generally, these receptors couple to Gαs to stimulate adenylyl cyclase; however, under certain conditions, they can couple to Gαi to inhibit adenylyl cyclase (AC) in some cells. β-Adrenergic receptors can both induce and ameliorate insulin resistance, depending on the receptor subtype, the duration of stimulation, and the type of tissue affected. Systemic use of β2-agonists can result in acute insulin resistance, while long-term use can improve it. These opposing effects may be attributed to a shift from Gαs-coupling in short-term use to Gαi-coupling in long-term. In addition, Gαi-coupling may mediate the insulin sensitizing effects by activating β-arrestin signaling, particularly in the liver and adipose tissue.

KEYWORD: β-Adrenergic receptors, G-protein-coupled receptors, Insulin resistance.

G-protein coupled receptors (GPCRs) are a large family of proteins found on the surface of cells. With a seven-transmembrane structure, spanning the cell membrane seven times, GPCRs are involved in a wide range of signaling pathways. When a ligand binds to the GPCR on the outside of the cell, it causes a conformational change in the receptor that activates a G-protein on the inside of the cell. This activates other signaling pathways within the cell, allowing the ligand to regulate cellular activities.

β-Adrenergic receptors (βARs) come in three distinct subtypes, each with its own distribution and functions. The β1AR is mainly found in the heart and brain, and is responsible for mediating many of the effects of epinephrine and norepinephrine on the heart, such as increasing heart rate and contractility. β2ARs are more widely distributed and are involved in relaxation of smooth muscle in the airways and blood vessels, as well as regulation of glucose metabolism. The β3AR is mainly found in adipose tissue and is involved in regulating fat metabolism.

Under normal conditions, the β1AR is the most abundant subtype in the heart, with the β3AR being much less common. In heart failure, however, the expression of β1AR decreases and the expression of β2AR increases, resulting in a change in the balance of signaling through these different receptor subtypes. Prolonged stimulation of the β1AR can also cause downregulation of the receptor and disconnection of the Gαs protein from adenylyl cyclase, leading to decreased cAMP production and activation of other pathways, such as CaMKII, which can lead to cardiac hypertrophy.

Beta-adrenergic receptors (βARs) have an effect on the heart and metabolism. Activation of β1AR and β2AR can increase heart rate and contractility, leading to a positive inotropic effect. However, if β2AR is constantly activated, it can couple to the Gαi pathway, which can counteract the inotropic effect and trigger a cell survival process.

The role of beta-adrenergic receptors (βARs) in regards to insulin resistance and glucose homeostasis is still being debated. While some studies have suggested that activation of βARs can lead to insulin resistance and impaired glucose metabolism, other studies have not found such effects or even beneficial effects. Further research is necessary in order to gain a better understanding of the complex role βARs play in these processes.

INSULIN RESISTANCE

Insulin resistance is a condition in which the body's cells become resistant to the effects of insulin, requiring an

abnormally high level of insulin to achieve a normal biological response. This resistance can occur with both endogenous and exogenous insulin and is characterized by elevated serum insulin levels and normal or increased glucose concentrations. Insulin resistance is a major cause of type 2 diabetes and is also correlated with increased risk of hypertension and cardiovascular disease. It can be caused by defects at various levels of insulin signaling, including defects in the insulin receptor itself or at downstream signaling pathways. Genetic mutations in the insulin receptor gene can lead to defects in receptor number, structure, binding, affinity, or signaling capacity, which can contribute to insulin resistance.

Post-insulin receptor defects are caused by several pathways that can contribute to insulin resistance. These pathways can involve degradation of the insulin receptor substrate 1 (IRS-1) by serine phosphorylation, inhibition of the interaction between the insulin receptor and IRS-1, or inhibition of the phosphorylation of protein kinase B (Akt) at serine 473. Elevated levels of intracellular diacylglycerol (DAG), which can be caused by the presence of high levels of free fatty acids, can activate protein kinase C (PKC) and lead to degradation of IRS-1. Inflammatory cytokines can also promote PKC activation and IRS-1 degradation and inhibit the interaction between the insulin receptor and IRS-1. Beta-arrestin2, a protein involved in the desensitization and scaffolding of G-protein coupled receptors, has been found to play a critical role in insulin signaling by mediating the interaction between IRS-1, Src, and Akt to promote the phosphorylation of Akt at serine 473.

Consuming high fat and high fructose diets has been found to downregulate beta-arrestin2 in the liver, skeletal muscle, and adipose tissue, which can contribute to insulin resistance. The progression of insulin resistance to cardiovascular disease or type 2 diabetes can be divided into four stages. Stage I is characterized by cravings for carbohydrates, mild insulin resistance, and weight gain due to increased amounts of food energy being directed to the liver, converted into fat, and stored in fat cells. A diet rich in carbohydrates may also lead to irritability, tiredness, or poor concentration in some individuals. However, fasting levels of insulin and blood glucose remain within the normal range.

Stage II of insulin resistance is characterized by normal or increased fasting insulin levels, normal blood glucose, mild-to-moderate central obesity, high blood pressure, early atherogenic dyslipidemia, vascular inflammation with elevated circulating levels of inflammatory markers, and endothelial dysfunction. Stage III is characterized by high fasting insulin levels, impaired glucose tolerance (prediabetes), advanced atherogenic dyslipidemia including increased lipoproteins containing apolipoprotein B, triglycerides, elevated small dense low-density lipoprotein (LDL) particles, and decreased levels of high-density lipoproteins (HDLs) and prothrombotic changes, including anomalies in procoagulant factors, antifibrinolytic factors, and platelet abnormalities. This stage is commonly referred to as metabolic syndrome. In the fourth stage of insulin resistance, there is a complete resistance of body cells to insulin and this stage is marked by high levels of fasting insulin and blood glucose levels. This is the first onset of frank type 2 diabetes mellitus and is associated with advanced atherosclerotic changes and a strong potential for cardiovascular disease and its complications.

β-Adrenergic receptors and hepatic insulin resistance

Catecholamines such as epinephrine and norepinephrine can affect liver metabolism by activating βARs in the liver and the Gαs protein that is coupled to them. Both β1- and β2-ARs are present in the liver, with the expression of β2AR being higher than that of β1-AR. Activation of the βARs/Gαs/AC pathway increases the production of glucose in the liver and the breakdown of lipids in the liver. In rat hepatocytes, activating βARs with the non-selective agonist isoproterenol has been found to significantly increase the activity of glycogen phosphorylase and decrease liver glycogen levels. Additionally, activating hepatic βARs with isoproterenol or overexpressing them in vitro has been associated with an increase in liver lipid accumulation and the development of hepatic steatosis, which may lead to hepatic insulin resistance.

β-Adrenergic receptors and skeletal muscle insulin resistance

The three subtypes of βARs, β1AR, β2AR, and β3AR, are expressed in skeletal muscle, with the highest abundance being for β2AR. Slow-twitch muscles, such as the soleus muscle, have a higher density of βARs than fast-twitch muscles, such as the extensor digitorum longus (EDL). It has been observed that the response to β-agonist administration appears to be greater in fast-twitch muscles compared to slow-twitch muscles. In skeletal muscle, all βARs can couple to either Gαs or Gαi proteins, with a more predominant coupling to Gαs. Gαi and Gβγ proteins can also initiate intracellular signaling pathways independent of Gαs proteins. Activation of Gβγ proteins by β-agonists mediates the activation of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which stimulates both glucose uptake and glycogen synthesis. Therefore, theoretically, activating the βAR/Gβγ/PI3K/Akt pathway with β-agonists should enhance insulin signaling in skeletal muscle. Activation of the AC/cAMP/PKA pathway in skeletal muscle has been found to promote muscle hypertrophy, increase muscle mass, and increase glucose uptake capacity, which may improve systemic insulin resistance. However, the role of βAR activation in skeletal muscle insulin resistance is controversial. A previous study showed that βAR activation mediates a low level of apoptosis in skeletal muscle, and this effect is mediated by β2AR rather than β1AR as in cardiac muscle.

β-Adrenergic receptors and adipose tissue insulin resistance

Adipose tissue expresses all three subtypes of βARs, which promote the hydrolysis of triglycerides and the release of free fatty acids (FFAs) into the bloodstream. The mechanisms underlying this process differ among the βAR subtypes. β2AR mediates the activation of the Gαs protein/AC/cAMP/PKA pathway, which activates hormone sensitive lipases. PKA also phosphorylates β2AR, inhibiting further interaction with Gαs protein and promoting its interaction with Gαi protein. Gαi protein then activates the extracellular regulated kinase (ERK), which causes lipid hydrolysis. β3AR can mediate lipid hydrolysis by concurrently activating both Gαs and Gαi proteins, while β1AR can behave similarly to both β2 and β3 ARs.

It appears that the role of β-adrenergic receptors in insulin resistance is complex and not fully understood. It is known that activation of β-adrenergic receptors in liver and adipose tissue can increase circulating levels of free fatty acids, which can contribute to systemic insulin resistance. However, activation of β-adrenergic receptors in skeletal muscle can enhance insulin signaling and increase glucose uptake, potentially improving insulin resistance. The effects of β-adrenergic agonists and antagonists on insulin resistance in vivo and in vitro have been studied, but there is still uncertainty about the overall impact on systemic insulin resistance.

Ligands of β-adrenergic receptors and their effects on systemic insulin resistance

There are several drugs that act on β-adrenergic receptors and can potentially affect insulin resistance. These include β-adrenergic agonists, which activate the receptors, and β-adrenergic antagonists, which block the receptors.

B-adrenergic agonists

Isoproterenol is a non-selective β-adrenergic agonist that activates both β1- and β2-adrenergic receptors. In animal studies, isoproterenol has been shown to increase insulin resistance in liver and adipose tissue, but improve insulin sensitivity in skeletal muscle. However, its effects on insulin resistance in humans are not well understood.

Salbutamol is a selective β2-adrenergic agonist that is commonly used as a bronchodilator in the treatment of asthma. In animal studies, salbutamol has been shown to improve insulin sensitivity in skeletal muscle, but its effects on insulin resistance in other tissues and in humans are not clear.

B-adrenergic antagonists

Propranolol is a non-selective β-adrenergic antagonist that blocks both β1- and β2-adrenergic receptors. In animal studies, propranolol has been shown to improve insulin sensitivity in liver and adipose tissue, but its effects on insulin resistance in humans are not well understood.

Atenolol is a selective β1-adrenergic antagonist that is commonly used as a blood pressure medication. In animal studies, atenolol has been shown to improve insulin.

Epinephrine

Is a catecholamine hormone produced by the adrenal gland and is released into the bloodstream in response to physical or emotional stress. It acts on β-adrenergic receptors in various tissues to produce its physiological effects.

In the liver, epinephrine activates β-adrenergic receptors, which leads to increased glucose output and decreased glycogen synthesis. This can contribute to insulin resistance in the liver. In adipose tissue, epinephrine activates β-adrenergic receptors, leading to the release of free fatty acids into the bloodstream. Elevated levels of free fatty acids are associated with insulin resistance in various tissues, including skeletal muscle.

In skeletal muscle, the effects of epinephrine on insulin resistance are less clear. Some studies have shown that epinephrine can enhance insulin signaling and promote glucose uptake, while others have shown that it can impair insulin signaling and inhibit glucose uptake. The conflicting results may be due to differences in study design, such as the use of different doses and duration of epinephrine treatment and the presence or absence of other factors that could affect insulin sensitivity.

Overall, the effects of epinephrine on insulin resistance are complex and may depend on the tissue and the specific β-adrenergic receptor subtype being activated. Further research is needed to fully understand the role of epinephrine in insulin resistance.

Norepinephrine

Is a catecholamine that is produced by the sympathetic nervous system and is released from the adrenal medulla in response to stress. It activates β-adrenergic receptors in various tissues, including the heart, blood vessels, and smooth muscle, leading to an increase in heart rate, blood pressure, and bronchodilation. In addition, norepinephrine can also activate β-adrenergic receptors in the liver, skeletal muscle, and adipose tissue, leading to changes in glucose and lipid metabolism.

In the liver, activation of β-adrenergic receptors by norepinephrine can increase hepatic glucose output and decrease glycogen stores. In skeletal muscle, norepinephrine can stimulate glucose uptake and glycogen synthesis through activation of the β-adrenergic receptor/Gβγ/PI3K/Akt pathway. In adipose tissue, norepinephrine can stimulate the breakdown of triglycerides through the activation of hormone sensitive lipases.

Overall, the effects of norepinephrine on systemic insulin resistance are complex and may depend on the tissue in

which the β-adrenergic receptors are activated. In some tissues, norepinephrine may have a positive effect on insulin sensitivity, while in others it may have a negative effect. Further research is needed to fully understand the role of norepinephrine in insulin resistance.

Isoproterenol
A non-selective β-adrenergic receptor agonist, meaning it activates all three subtypes of β-adrenergic receptors: β1, β2, and β3. It has been shown to increase insulin resistance in various tissues, including liver and adipose tissue, due to its activation of the Gαs protein/AC/cAMP/PKA pathway, which promotes the release of free fatty acids and increases lipid breakdown. However, in skeletal muscle, isoproterenol has been shown to enhance insulin signaling and promote glucose uptake by activating the Gβγ/PI3K/Akt pathway. Overall, the net effect of isoproterenol on systemic insulin resistance is unclear and may depend on the balance of its effects on different tissues.

Clenbuterol
β2-adrenergic agonist that is commonly used as a bronchodilator in the treatment of asthma. However, it has also been used as a weight loss and performance enhancing drug due to its ability to increase fat oxidation and muscle mass. In human studies, clenbuterol has been shown to increase insulin sensitivity and improve glucose tolerance in obese individuals. However, its long-term safety and effectiveness have not been fully established and it is not approved for use in the United States for any indication.

It is important to note that while some β2-agonists may have beneficial effects on insulin sensitivity and glucose metabolism, they can also have adverse effects on the cardiovascular system. In particular, β2-agonists can increase heart rate and blood pressure, and may increase the risk of heart attack or stroke in some individuals. Therefore, it is important to carefully weigh the potential benefits and risks of using β2-agonists before starting treatment. Additionally, β2-agonists should only be used under the supervision of a healthcare professional.

Propranolol
A non-selective β-blocker that is known to inhibit the sympathetic effects of catecholamines by blocking β-adrenergic receptors (βARs). It has also been found to be an inverse agonist to βARs, meaning it decreases the constitutive activity of these receptors. The effects of propranolol on systemic insulin resistance are controversial and may vary depending on the acute or chronic nature of treatment and the specific study population. Some studies have found acute insulin-sensitizing effects of propranolol, possibly due to its ability to inhibit glycogen mobilization in muscle, lactate-induced hepatic gluconeogenesis, and the release of free fatty acids from triglycerides. Other studies have found acute hyperglycemic effects of propranolol, which may be mediated by the inhibition of insulin secretion in response to glucose infusion. On the other hand, some studies have found chronic insulin-sensitizing and hypoglycemic effects of propranolol in thermally injured patients and obese mice, respectively, which may be due to the drug's ability to block β2ARs. However, other studies have found chronic hyperglycemic effects of propranolol in hypertensive non-diabetic patients after intravenous glucose tolerance testing, without affecting insulin secretion. Overall, the effects of propranolol on systemic insulin resistance remain unclear and may depend on various factors.

Carvedilol
Significantly change glucose tolerance in both normal and insulin-resistant mice after 30 min of intraperitoneal injection. However, carvedilol increased insulin sensitivity in normal mice after 30 min of intraperitoneal injection as assessed by intraperitoneal insulin tolerance test (ITT).

Regarding the chronic systemic effects of carvedilol on glucose homeostasis, most studies support the insulin sensitizing effects of carvedilol, probably by blocking α1AR and subsequent dilation of blood vessels. Interestingly, our work and another recent research article showed potential role for β-arrestin2 protein in mediating the insulin sensitizing effects of carvedilol.

In some studies, carvedilol has been shown to improve insulin sensitivity and reduce blood sugar levels, while in others it has not had a significant effect. It is also worth mentioning that carvedilol is primarily used as a medication for the treatment of high blood pressure and heart failure, and its effects on insulin sensitivity may be related to these primary uses. It is important for individuals considering the use of carvedilol to discuss its potential effects on insulin sensitivity with a healthcare provider.

CONCLUSION
B-adrenergic receptor ligands on insulin resistance may vary depending on the type of tissue being affected. For example, activation of β-adrenergic receptors in the liver can increase glucose output and promote liver lipid accumulation, leading to hepatic insulin resistance. In contrast, activation of β-adrenergic receptors in skeletal muscle can enhance insulin signaling and increase glucose uptake, potentially improving insulin sensitivity. Similarly, activation of β-adrenergic receptors in adipose tissue can increase the release of free fatty acids, which can contribute to systemic insulin resistance. Overall, the effects of β-adrenergic receptor ligands on insulin resistance are complex and depend on multiple factors, including the specific receptor subtype and tissue being affected, as well as the duration of stimulation.

Abbreviations
β-Adrenergic receptors (βARs)
G-protein-coupled receptors (GPCRs)