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Pathophysiological Processes of Type 2 Diabetes Mellitus

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Review Article

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ABSTRACT

Diabetes mellitus (DM) is complex metabolic disorder which increases continuously worldwide. Type 2 diabetes mellitus is one of the most prevalence diseases. The mechanisms behind this disease are complicated and interfere with each other. The main defects in type 2 diabetes are an insulin resistant, decrease insulin secretion and increased hepatic glucose production. Each defect has many possible mechanisms. The purpose of this article is to review the possible mechanisms lead to development of type 2 diabetes.

INTRODUCTION

Diabetes mellitus (DM) is an endocrinological and metabolic disorder which increases continuously worldwide ^[1]. DM is generally classified into type 1 (T1DM) and type 2 (T2DM) diabetes mellitus. T2DM is a chronic metabolic disorder that results from defects in insulin secretion and/or insulin action ^[2]. Almost 85 - 95% of all diabetes in high income countries is of type 2 accounting for an even higher dominance in developing countries ^[1]. T2DM is a complex heterogeneous group of metabolic disorders characterized by hyperglycemia ^[3]. The mechanisms of T2DM development are complicated, but there are three key physiological defects in the onset of hyperglycemia in T2DM include insulin resistant, diminished insulin secretion and increased hepatic glucose production ^[4,5]. The purpose of this article is to collect all possible mechanisms lead to development of type 2 diabetes (**Figure 1**).

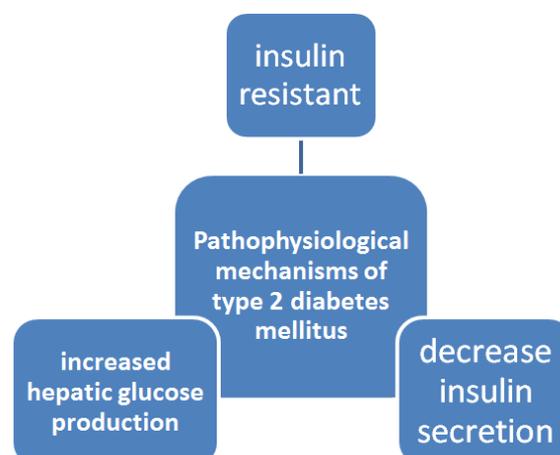


Figure 1: Pathophysiological mechanisms of type 2 diabetes mellitus.

MECHANISMS OF INSULIN RESISTANCE

Insulin resistant is complex process include many mechanisms such as, lipids accumulation, endocrine role of adipose tissues, oxidative stress, mitochondria dysfunction and inflammatory mediators (**Figure 2**).

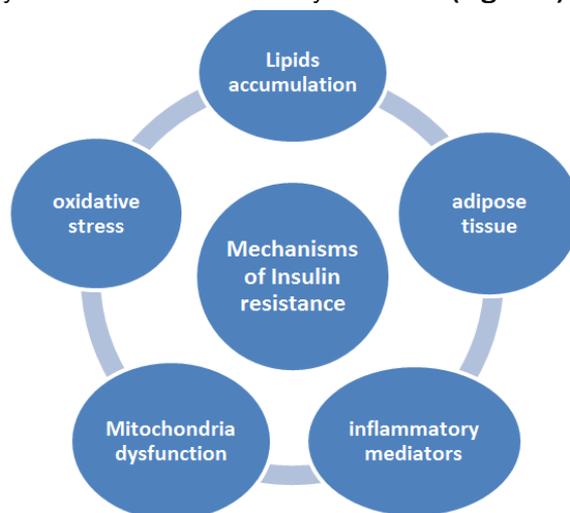


Figure 2: Mechanisms of Insulin resistance.

Lipids accumulation

T2DM patients are characterized by a decreased fat oxidative rate and increase the circulating free fatty acids (FFAs) ^[6,7]. Lipid species accumulate as a result of the impairment of fatty acid oxidation, resulting in the redirection of long-chain acyl CoAs into endoplasmic reticulum-localized and cytosolic lipid species, such as ceramides, diacylglycerols (DAG), and triglyceride ^[8]. These lipid species known to cause insulin resistance by reducing insulin-stimulated glucose uptake ^[9]. Many studies support this mechanism through suppression of mitochondrial glycerol-3-phosphate acyltransferase-1 (GPAT1, the first enzyme in TG synthesis) or acetyl CoA carboxylase-2 (ACC 2) activity results in increased fatty acid oxidation, lowered DAG levels and reversal of hepatic insulin resistance ^[10].

Role of adipose tissue

Adipocytes have a regulatory role in the development of insulin resistance, where it acts as an endocrine organ producing adipokines which modulate glucose homeostasis ^[11]. Visceral and peripheral adipocytes secrete a many factors, which may alter systemic insulin action and hepatic glucose production, including adiponectin, leptin, resistin, tumour necrosis factor- α (TNF α) and retinol-binding protein-4 (RBP4) ^[12]. Adiponectin and Leptin have been considered as anti-diabetogenic factors because their common capacity to decrease triglyceride (TG) synthesis, stimulate β -oxidation and induce insulin action in both skeletal muscle and liver ^[8]. These effects related to their common ability to activate 5'-AMP which activate protein kinase (AMPK) ^[13]. AMPK enzyme responds to a fall in ATP and a rise in AMP levels by activating both glucose and fatty acid oxidation ^[8]. In addition, leptin has direct effects on insulin sensitivity and may also reverse insulin resistance in mice with congenital lipodystrophy ^[14]. Many studies revealed that leptin levels are increased and adiponectin levels are decreased in insulin-resistant obese humans and animals, which suggests that obesity leads to a state of leptin resistance and adiponectin deficiency ^[8]. Other study confirmed that adiponectin expression is decreased in obese humans and mice. Role of resistin can explain by its ability to decreases insulin-dependent glucose transport *in vitro* ^[15]. In addition it increases fasting blood glucose concentrations and hepatic glucose production *in vivo* ^[15]. At a molecular level, TNF- α increases serine phosphorylation of insulin receptor substrate (IRS-1) and downregulates glucose transporter GLUT4 expression ^[16], thereby contributing to insulin resistance ^[17]. Increased serum retinol-binding protein-4 (RBP4) protein levels induced hepatic expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase and impaired insulin signaling in muscle ^[3]. RBP4 protein levels were elevated in insulin-resistant mice and obese and diabetic humans ^[3].

Role of oxidative stress

There is considerable evidence that hyperglycemia results in the production of reactive oxygen species (ROS), leading to increased oxidative stress in a variety of tissues ^[18]. Oxidative stress causes a complex dysregulation of cell metabolism and plays a key role in the pathogenesis of insulin resistance ^[19].

Mitochondria and NADPH oxidase are considered the main sources of ROS overproduction, provided that mitochondrial superoxide production is a common feature in insulin resistance models. Oxidative stress condition accompanied with decrease mRNA levels of the antioxidant enzymes include superoxide dismutase, glutathione peroxidase and catalase. Eventually all these changes contribute in development diabetes ^[19]. Increased lipid peroxidation markers have thus been observed in the liver of animal models of diabetes and obesity ^[20]. In addition, several clinical trials have revealed improved insulin sensitivity in diabetic patients treated with the antioxidants ^[21].

Mitochondria dysfunction

There are many evidences that mitochondrial dysfunction is associated with T2DM and insulin resistance. Multiple factors include: genetic factors, oxidative stress, mitochondrial biogenesis, and aging may disturb mitochondrial function, resulting in insulin resistance [22]. In humans, several studies have also demonstrated insulin infusions leading to increased expression of mitochondrial proteins, higher oxidative enzyme activity and elevated ATP synthesis in muscle [23]. However, direct effect of insulin on mitochondrial function is diminished in patients with insulin resistance [23]. These results suggesting that insulin is able to activate mitochondrial biogenesis and oxidative capacity, and insulin resistance could in part contribute to mitochondrial dysfunction [24].

Role of inflammatory mediators

Inter organ communication leading to insulin resistance may also involve an inflammatory component [12]. The transcription factor nuclear factor (NF)- κ B is example of such a common regulator. Depending on the kinetics and mode of induction (NF)- κ B may induce apoptosis or promote survival in the β -cells [25]. Obesity results in activation of the transcription factor NF- κ B and its targets in the liver. Overexpression of a constitutively active version of the NF- κ B-activating kinase, I κ B kinase catalytic subunit- β (IKK β), in the liver of normal rodents results in liver and muscle insulin resistance [8]. Further, this signaling node may influence peripheral insulin resistance via actions in myeloid cells [26].

REDUCTION OF INSULIN SECRETION

The decreased β -cell mass and β -cell dysfunction contribute to the defective insulin secretion typical in T2DM. Several mechanisms may be explained this diminished in insulin secretion (**Figure 3**).

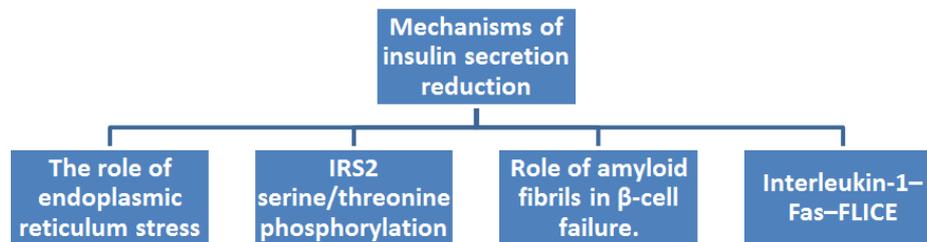


Figure 3: Mechanisms of insulin secretion reduction.

The role of endoplasmic reticulum stress

Endoplasmic reticulum (ER) plays important role in the regulation of cellular responses of insulin [27]. If the capacity of ER is exceeded, ER stress is produced. Insulin receptor-substrate 1(IRS-1) is a substrate for insulin receptor tyrosine kinase, and serine phosphorylation which mediated by Jun N-terminal kinase (JNK), reduces insulin receptor signaling [28]. ER stress led to a significant increase in JNK-mediated serine phosphorylation of (IRS-1) and thereby inhibited insulin action [27].

IRS2 serine/threonine phosphorylation

Decreased insulin receptor substrate (IRS2) expression may lead to spontaneous β -cell apoptosis [29]. Because of several mechanisms relevant to pathogenesis of T2DM may increase IRS2 serine/threonine phosphorylation [30] with resultant IRS2 ubiquitination poor insulin.

Role of amyloid fibrils in β -cell failure

Amylin is synthesized and secreted from islet β - and δ -cells which has a propensity to form amyloid fibrils [8]. Deposition of toxic amyloid fibrils may be additional mechanism that links overnutrition and hyperstimulation of the islet β -cell to eventual β -cell decompensating [8]. Several studies represent that, human amylin overexpression increase rates of β -cell apoptosis, diminished insulin secretion and reduced β -cell mass, finally resulting in the onset of glucose intolerance and then diabetes [31].

Interleukin-1-Fas-FLICE

Cytokines are central in the development of diabetes. Fas is death receptor present on the surface of pancreatic β -cells contributes to cytokine-induced apoptosis [32]. Fas engagement can be switched from death signal to induction of proliferation when the caspase 8 inhibitor, FLICE-inhibitory protein (FLIP), is active [33]. Short-term exposure to hyperglycemia will induce low levels of IL-1 β , inducing IL-1Ra, Fas, and FLIP, leading to decreased apoptosis and enhanced proliferation and function [33]. However, prolonged hyperglycemia will decrease FLIP, switching this adaptive pathway toward deleterious signals and eventually to diabetes [34].

Hepatic glucose production

Many evidences suggested that hepatic glucose production increase in T2DM, which may due to enhanced gluconeogenesis [35]. Insulin receptor substrate IRS -1 and -2 are complementary key players in the regulation of hepatic insulin signaling and expression of genes involved in gluconeogenesis, glycogen synthesis, and lipid metabolism [36]. Dysfunction of IRS proteins initially

leads to postprandial hyperglycemia, increased hepatic glucose production, and dysregulated lipid synthesis [37]. Other potential factors may be responsible for the increased hepatic gluconeogenesis [38]. These include hepatic insulin resistance and diminished insulin secretion, particularly in the postprandial state [39].

CONCLUSIONS

The Pathophysiological processes of type 2 diabetes mellitus include 3 pathological defects: insulin resistant, diminished insulin secretion and increased hepatic glucose production. Insulin resistant is the most feature of T2DM which progress through multiple possible mechanisms includes; lipid accumulation, endocrine role of adipose tissues, oxidative stress, mitochondria dysfunction and inflammatory mediators. Understanding of these mechanisms open the way to discover suitable drugs for control development this disease and its complications in the future.

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