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Review

Incretin-based therapy and pancreatic beta cells

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Abstract

Type 2 diabetes (T2D) is a complex, progressive disease with life-threatening complications and one of the most serious public-health problems worldwide. The two main mechanisms of T2D pathogenesis are pancreatic beta cell dysfunction and insulin resistance. It is now recognized that pancreatic beta cell dysfunction is a necessary factor for T2D development. Traditional therapies for controlling blood glucose are suboptimal as they fail to meet target goals for many patients. Glucagon-like peptide-1 receptor agonists (GLP1RA) and dipeptidyl peptidase-4 inhibitors (DPP4I) are an attractive class of therapy because they reduce blood glucose by targeting the incretin hormone system and, in particular, have the potential to positively affect pancreatic beta cell biology. This review outlines our current understanding of pancreatic beta cell incretin system dysfunction in T2D and summarizes recent evidence of the effect of incretin-based therapies on beta cell function and mass. Incretin-based therapies have shown strong evidence for beneficial effects on beta cell function and mass in animal studies. In humans, incretin-based therapies are effective glucose-lowering agents, but further study is still required to evaluate their long-term effects on beta cell function and safety as well as beta cell mass expansion.
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1. Introduction

Type 2 diabetes (T2D) is one of our most challenging public-health problems today. It is a complex, progressive multisystemic disease with serious, potentially life-threatening microvascular and macrovascular complications. Over the past decades, considerable efforts have been made to control glycaemia in T2D, focusing on several different pathogenic processes. The primary mechanisms of pathogenesis of T2D are impaired insulin secretion and insulin resistance. Insulin secretory dysfunction is associated with high glucagon production, which contributes to hyperglycaemia in T2D. Therefore, researches into new therapeutic approaches for T2D has targeted these mechanisms [1].

Although insulin resistance is an important factor in T2D, it has become clear that decreased pancreatic beta cell function is a prerequisite for the development of hyperglycaemia and T2D. Two studies—the UKPDS [2] and ADOPT [3]—have suggested a progressive loss of beta cell function, although insulin secretion was not directly measured. This decline is associated with worsening glycaemia and an increasing need for multiple antidiabetic agents, and eventually results in the need for insulin therapy in many patients.

Thus, the therapeutic modalities that benefit beta cell function are increasingly being recognized as important tools for T2D management. Notably, a relatively novel class of antidiabetic agents, incretin-hormone-based therapies—specifically, glucagon-like peptide-1 analogue/receptor agonists (GLP1RAs) and dipeptidyl peptidase-4 inhibitors (DPP4Is)—represent a whole new therapeutic direction for T2D management and offer

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an attractive approach to many aspects of T2D pathophysiology, including beta cell function.

The present review provides an overview of pancreatic beta cell dysfunction as a primary pathogenic feature of T2D and the possible contribution of incretin hormone defect, and summarizes recent experimental and clinical findings for the effects of incretin-based therapies on beta cell function and mass.

2. Insulin secretion defect in type 2 diabetes

Glucose is the dominant factor controlling beta cell function and survival. Glucose entering beta cells via glucose transporters is rapidly phosphorylated to glucose-6-phosphate by glucokinase and then undergoes oxidation in mitochondria, leading to ATP production and subsequent closure of the K_{ATP} channel. This elicits cell membrane depolarization and entry of Ca^{2+} through the opening of L-type voltage-dependent calcium channels. The Ca^{2+} influx induced by glucose increases cytosolic Ca^{2+} levels, which triggers insulin secretion.

In non-diabetic subjects, insulin secretion stimulated by intravenous (IV) glucose infusion is biphasic: a rapid, early peak (first phase) is followed by a second slower and gradually rising peak (second phase) (see Rorsman and Renstrom for a review [4]). First-phase insulin secretion is rapidly stimulated by the increased cytosolic Ca^{2+} and is largely due to the exocytosis of primed (readily releasable) insulin granules. Second-phase insulin secretion is slow, activated by cytosolic Ca^{2+}, ATP and cAMP production, and due to the subsequent supply of new insulin granules for release. Glucose-stimulated insulin secretion (GSIS) can be modulated by amino acids, free fatty-acids and non-nutrient secretagogues, such as incretin hormones, growth factors and neurotransmitters.

2.1. First-phase insulin secretion in type 2 diabetes

In T2D, first-phase insulin secretion is abolished, and the second phase is reduced and delayed [5]. It is known that first-phase insulin secretion is pivotal to the transition from a fasting to a fed state through the following functions: suppression of hepatic glucose production; suppression of lipolysis; and preparation of target cells to the action of insulin by crossing the endothelial barrier. Although hyperglycaemia may play a role in insulin secretory dysfunction, a defective first phase persists in T2D patients after hyperglycaemia reduction [6]; therefore, it has been suggested that patients with T2D have an intrinsic beta cell defect.

Reduction of first-phase insulin secretion has been found not only in patients with T2D, but also in those with prediabetic states such as impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), and first-degree relatives with T2D (see Guillausseau et al. for a review [7]). Thus, beta cell abnormalities can precede the development of overt T2D, and first-phase insulin secretion has been proposed as a predictive marker of T2D in high-risk groups [8].

2.2. Second-phase insulin secretion in type 2 diabetes

In T2D, the slow, gradual second phase of GSIS that follows first-phase secretion is reduced and delayed, but remains partially functional or sometimes exaggerated due to hyperglycaemia evolved from defective first-phase insulin secretion [5]. Second-phase insulin secretion decreases hepatic glucose production just as the first phase does, but to a lesser extent [9]. More important, it increases glucose utilization in peripheral tissues [10]. Thus, second-phase insulin secretion is important for glucose homoeostasis even though its importance has been relatively underestimated compared with the first phase.

2.3. Functional defect vs loss of beta cell mass

Butler et al. [11] reported their findings on beta cell volume for 124 pancreases from the autopsies of well-characterized individuals according to body mass index (BMI) and glucose status. Obese and lean T2D patients had 63% and 41% deficits in relative beta cell volume compared with non-diabetic obese and lean cases, respectively. In addition, obese subjects with IFG had a 40% deficit in beta cell volume compared with non-diabetic obese cases. This study concluded that beta cell mass is decreased in T2D through increased beta cell apoptosis. Subsequently, Yoon et al. [12] reported that the relative beta cell volumes in T2D patients with BMI < 25 kg/m^2 were < 50% of the mean for control groups. Rahier et al. [13] reported that beta cell mass was about 39% lower in T2D patients than in matched controls based on 109 pancreatic autopsy specimens. The decrease in beta cell mass with duration of diabetes, along with further impairment of insulin secretion, could contribute to the progressive deterioration of glucose homoeostasis.

However, overt fasting hyperglycaemia develops only with a > 90% loss of beta cell mass [14]. Furthermore, in spite of the 50% reduction of beta cell mass in T2D patients, maximum insulin secretion in response to IV glucose plus arginine reaches only 15% of that observed in non-diabetic subjects [15]. Thus, the intrinsic defect in secretory machinery is probably more severe than accounted by the reduction of beta cell mass alone in T2D.

2.4. Cellular and molecular pathways involved in beta cell functional defects in type 2 diabetes

Many factors, including glucotoxicity, lipotoxicity, inflammation, cytokines, islet amyloid deposits, autoimmunity, incretin defects and insulin resistance, have been suggested as key pathophysiological features of beta cell defects in T2D (Fig. 1).

2.4.1. Glucotoxicity and lipotoxicity (or glucolipotoxicity)

Glucotoxicity is defined as beta cell failure induced by chronically elevated glucose levels through decreased insulin secretion and insulin gene expression, and is clearly distinct from beta cell exhaustion [16]. Lipotoxicity refers to the negative effect of chronic elevated plasma free fatty-acid (FFA) levels on beta cell function [17]. Although numerous studies have shown the

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