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Abnormalities in insulin secretion in type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus is a multifactorial disease, due to decreased glucose peripheral uptake, and increased hepatic glucose production, due to reduced both insulin secretion and insulin sensitivity. Multiple insulin secretory defects are present, including absence of pulsatility, loss of early phase of insulin secretion after glucose, decreased basal and stimulated plasma insulin concentrations, excess in prohormone secretion, and progressive decrease in insulin secretory capacity with time. β-cell dysfunction is genetically determined and appears early in the course of the disease. The interplay between insulin secretory defect and insulin resistance is now better understood. In subjects with normal β-cell function, increase in insulin is compensated by an increase in insulin secretion and plasma glucose levels remain normal. In subjects genetically predisposed to type 2 diabetes, failure of β-cell to compensate leads to a progressive elevation in plasma glucose levels, then to overt diabetes. When permanent hyperglycaemia is present, progressive severe insulin secretory failure with time ensues, due to glucotoxicity and lipotoxicity, and oxidative stress. A marked reduction in β-cell mass at post-mortem examination of pancreas of patients with type 2 diabetes has been reported, with an increase in β–cell apoptosis non-compensated by neogenesis.

Résumé

Anomalies de l'insulinosécrétion dans le diabète de type 2

Le diabète de type 2 est une maladie multifactorielle, secondaire à une réduction du captage du glucose et à une production glucosée hépatique excessive, liées à une diminution conjointe de l'insulinosécrétion et de l'insulinosensibilité. Les anomalies de l'insulinosécrétion sont multiples: perte du caractère pulsatile de la sécrétion basale, perte du pic précoce induit par l'administration intraveineuse de glucose, insulinopénie basale et stimulée par le glucose, sécrétion excessive de prohormones, et réduction progressive de l'insulinosécrétion avec le temps. Le rôle du déficit de l'insulinosécrétion, ainsi que l'interface entre insulinopénie et insulinorésistance sont actuellement mieux compris. Chez des sujets dont la fonction β-insulaire est normale, l'augmentation des besoins en insuline (obésité, sédentarité, vieillissement, grossesse) est compensée par une insulinosécrétion accrue, ce qui permet de garder une glycémie normale. Chez les sujets prédisposés à un diabète de type 2, l'incapacité de la cellule β à répondre à l'augmentation des besoins conduit à une élévation progressive de la glycémie puis à un diabète franc. Une fois l'hyperglycémie installée, l'insulinosécrétion décline avec le temps du fait de la glucotoxicité et de la lipotoxicité, et de l'agression radicalaire. Une réduction importante de la masse β-cellulaire a été mise en évidence par des études autopsiques du pancréas de patients atteints de diabète de type 2, avec une augmentation du taux d'apoptose des cellules β, non compensée par une augmentation de la néogenèse.

Keywords: Type 2 diabetes mellitus; Pathogenesis; Genetics; Insulin secretion; Pulsatility; Insulin deficiency; First phase insulin secretion; Environmental factors; Reduction in b-cell mass; Apoptosis; Free radicals; Review.

Mots clés : Diabète de type 2 ; Physiopathologie ; Génétique ; Environnement ; Insulinosécrétion ; Pulsatilité ; Phase précoce d'insulinosécrétion après glucose ; Insulinopénie ; Pro-insuline ; Réduction de la masse β–cellulaire ; Apoptose ; Radicaux libres ; Revue générale.

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1. Introduction

According to the World Health Organization (WHO), and to the American Diabetes Association, type 2 diabetes is defined as resulting from defects both in insulin secretion and in insulin sensitivity. Since the discovery of plasma insulin radioimmunoassay by Salomon Berson and Rosalyn Yalow [1], evidence was obtained that insulin secretion is severely impaired in type 2 diabetes. Numerous functional defects, known as β-cell dysfunction, and pathological abnormalities have been described in type 2 diabetic patients. Functional alterations, or β-cell dysfunction, include abnormalities in kinetics of insulin secretion, quantitative and qualitative abnormalities of insulin secretion, and progression of the defects with time. Pathological abnormalities include β-cell loss and its progression, and reduced β-cell mass.

2. Functional defects: β-cell dysfunction

2.1. Alterations in insulin secretion kinetics

2.1.1. Alterations in pulsatile insulin release

Insulin, like many hormones, displays rapid variations in plasma concentrations, with secretory peaks every 5-10 minutes, and larger oscillations every 60-120 minutes [2]. In non-diabetic subjects, when endogenous insulin secretion is experimentally abolished by somatostatin infusion, pulsatile insulin administration is more effective in controlling glycaemia than continuous administration [3]. Moreover, in type 1 diabetic patients, pulsatile insulin administration is associated with a 40% reduction in insulin doses for maintaining normal glycaemic control [4]. The lowest efficacy of continuous administration regimen is related to the down-regulation of insulin membrane receptors. Pulsatile insulin release is related to oscillations in Ca^{++} intracytosolic concentrations, which regulate exocytosis of insulin granules [2]. Lack of oscillatory secretory may alter islets pattern [5], through excess in calcium intracytosolic concentrations. Prolonged exposition of islets to high calcium intracytosolic concentrations has been shown to be associated with apoptosis signals in the β-cell [2]. β-cell « *pace-maker* » is severely altered in type 2 diabetes. In type 2 diabetic patients, a reduction or an absence of rapid secretory peaks is observed, these abnormalities being present in the early phases of the disease [6-8].

2.1.2. First-phase insulin secretion

In normoglycaemic subjects, insulin secretion stimulated by intravenous glucose infusion is characterized by a biphasic pattern, with an early peak rising abruptly 3-5 min after the beginning of the test, and lasting for 10 min, then followed by a slower and more progressive increase in insulin levels. This second or late insulin secretion phase lasts as long as the glucose infusion. At the time of the diagnosis of type 2 diabetes, first-phase insulin secretion is abolished [9-12], and late phase is reduced and delayed. Early phase of insulin secretion is pivotal in the transition from fasting state to fed state, with different functions: to suppress hepatic glucose production [13, 14], to suppress lipolysis [14], and to cross endothelial barrier for preparing target cells to the action of insulin [15]. Reduction of first-phase insulin secretion takes place early in the course of the disease, as it has been reported in subjects with impaired glucose tolerance [16], as well as normoglycaemic first-degree relatives of patients with type 2 diabetes. [17].

The abolition of first-phase insulin secretion has been found not only in patients with overt type 2 diabetes mellitus, but also at the initial stage of the disease, i.e. impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). It predicts in such patients further conversion to overt diabetes. Reduction of first-phase insulin secretion has also been demonstrated in normoglycaemic first-degree relatives of type 2 diabetic patients. Therefore, use of first-phase insulin secretion as a marker of type 2 diabetes mellitus has been proposed by some authors.

2.1.3. First-phase insulin secretion and initial stages of type 2 diabetes

The decrease in first-phase insulin secretion after intravenous glucose in patients with mild abnormalities of glucose tolerance has been reported well before impaired glucose tolerance (IGT) received its definition by WHO [18]. Long-term follow-up studies of patients with IGT have demonstrated conversion from IGT to type 2 diabetes in more than 50% of the cases. Thus, IGT should be considered as an « at high risk » state for further development of type 2 diabetes. Most of the studies performed in patients with IGT disclosed the abolition or decrease in first-phase insulin secretion [17-20]. Conflicting results have been also published. Discrepancies seem mostly related to an insufficient account for degree of associated insulin resistance, while metabolic heterogeneity of the population of patients with IGT cannot be ruled out. However, most of available data indicate that IGT shares the same pattern of alterations in insulin secretion than type 2 diabetes .The same holds true for impaired fasting glucose, as reported a long time ago by Brunzell *et al* [21] in a study of patients with different plasma glucose levels. First-phase insulin secretion was abolished as soon as fasting plasma glucose levels were in excess of 1.15 g/l (6.4 mmol/l).

2.1.4. First-phase insulin secretion in relatives of patients with type 2 diabetes

Another high-risk state for type 2 diabetes is a history of type 2 diabetes in a first-degree relative. A risk about 30% has been calculated in families of European origin, and similar, or even higher rates, have reported in other populations. In subject's first-degree relatives of patients with type 2 diabetes, impairment of first-phase insulin secretion has been reported by different studies [22,23].