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.

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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, insulinopenie 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 insulinopenie et insulinosensibilité 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 radiculaire. 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 néogénèse.

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Mots clés : Diabète de type 2 ; Physiopathologie ; Génétique ; Environnement ; Insulinosécrétion ; Pulsalité ; Phase précoce d’insulinosécrétion après glucose ; Insulinopenie ; Pro-insuline ; Réduction de la masse β−cellulaire ; Apoptose ; Radicaux libres ; Revue générale.
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\(^{2+}\) 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 in 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].
2.2. Quantitative and qualitative alterations in insulin secretion

In type 2 diabetes, a marked decrease in basal and glucose-stimulated insulin plasma levels has been reported [24,25], whatever the body mass index, either normal or elevated [24]. Specific measurement of insulin and pro-hormones by immunoradiometric assay according to Hales et al [26] has revealed true insulin deficiency. This defect is masked in type 2 diabetes by excess in circulating insulin pro-peptides: proinsulin, split 32-33 proinsulin and 64-65 proinsulin. These peptides account for more than 40% of the circulating peptides compared to 5% in non-diabetic subjects [27]. Excess in proinsulin in type 2 diabetes is not a consequence of hyper stimulation of the β-cell, as it is absent of the states of secondary hyperinsulinism, such as obesity [28] and liver diseases [29]. It seems to indicate the status of disease of the β-cell rather than being a functional defect.

2.3. Progression of abnormalities of insulin secretion

2.3.1. Progression of abnormalities of insulin secretion when progressing to overt diabetes

Longitudinal studies, evaluating both early phase insulin secretion and insulin sensitivity, have shown that both defects can predict the development of overt diabetes [30,31]. Longitudinal studies have shown that the transition from normal glucose tolerance (NGT) to diabetes is associated with a progressive deterioration in early insulin secretion [31]. In Pima Indians, subjects progressing to IGT during a mean 5-year follow-up were compared to subjects who remained NGT. Progression to IGT was accompanied by a 27% reduction in acute insulin response (AIR), and by a further 51% reduction in AIR during progression from IGT to diabetes. Increase in body weight and a 31% decrease in insulin sensitivity were also observed in patients progressing to diabetes. By contrast, in patients who remained NGT, a similar decrease in insulin sensitivity was observed, but AIR increased by 30%. This compensatory effect of insulin resistance by the β-cells explains the absence of progression of these patients to diabetes. Similar conclusions can be drawn from a long-term (7-9 years) longitudinal study performed in normoglycaemic relatives of patients with type 2 diabetes [32]. β-cell function, evaluated by the disposition index (insulin sensitivity index x 1st phase insulin response to glucose stimulation) decreased by 38% in subjects who progressed from normal to impaired glucose tolerance, and by 20% only in subjects who remained normal glucose tolerant, i.e. a 50% difference.

2.3.2. Progression of abnormalities of insulin secretion in overt diabetes with time

Worsening of in insulin secretion deficiency with time is characteristic of overt type 2 diabetes too. This gradual reduction, while insulin sensitivity remained unchanged, has been evidenced by longitudinal studies of cohorts [33,34]. Studies in the control group of the UKPDS (United Kingdom Prospective Diabetes Study) indicated that residual insulin secretory capacity was decreased by 50% at the time of diagnosis of diabetes with a further decrease of 15% six years later (Fig. 1) [33]. This decrease was linear, at least during the 6-year follow-up. If one prolongs the line toward the left, i.e. toward the past, the actual beginning of the disease may have happen 10 years before. This extrapolation is consistent with the results drawn from the retinal status at diabetes diagnosis, according to Harris [35]. If one prolongs the line toward the right, i.e. toward the future, the line crosses the abscissa axis 10-12 years after the date of diagnosis of diabetes. Thus, these data suggest that natural history of the progressive death of the β-cell lasts 20 to 25 years.

Different explanations have been proposed to explain the progressive reduction in insulin secretion, including glucotoxicity [36] and lipotoxicity [37]. The role of advanced glycation of proteins (AGE), particularly of the insulin promoter gene, has been proposed [38,39], as well as the role of deposits in the islets of an amyloid substance, so-called amylin [40]. The more pertinent explanation is the toxic role of oxygen species, which are produced in excess in uncontrolled diabetes, and of the β-cell apoptosis [41,42]. In the β-cells, mitochondrial production of superoxydes ions induced by hyperglycaemia activates uncoupling protein 2 (UCP2), resulting in a decrease in ATP/ADP intracytosolic ratio, and of insulin secretion evoked by glucose [43]. Diabetic islets are characterized by reduction in glucose-evoked insulin secretion, decreased cytosolic ATP and ATP/ADP ratio, abnormal hyperpolarisation of the mitochondrial membrane, together with hyper expression of UCP2, of complexes I and V of the respiratory chain, and high levels of a marker of oxidative stress, nitro tyrosine [44].
2.4. Reduction in β-cell mass

Most of studies addressing the issue of the β-cell mass have concluded to a marked reduction in the number of the β-cells in post-mortem specimens of pancreas obtained at necropsy of patients with type 2 diabetes. Contrasting to the adaptive increase in β-cell mass observed in rodent models of obesity [45], and in obese subjects [46], a marked reduction in β-cell mass has been reported by numerous groups, in patients with type 2 diabetes. Recent data have provided new insights into islet pathology of type 2 diabetes mellitus, and into the mechanisms responsible for decreased β-cell mass [47]. Pancreatic tissue samples from 124 autopsies were included. Compared to control samples matched for weight, pancreas from overweight diabetic patients and from lean diabetic patients presented with a 63% and a 41% deficit in relative β-cell volume, respectively. A similar decrease (41%) was observed in samples from subjects with impaired glucose tolerance. No difference was seen according to previous treatment of the type 2 diabetic patients (diet, sulphonylureas or insulin). Relative β-cell volume was increased in overweight patients compared to lean ones, due to increased neogenesis. β-cell replication was found to be low in all groups. Neogenesis, while increased in overweight patients, was not different in overweight type 2 diabetic and in non-diabetic subjects, as well as in lean type 2 diabetic and in non-diabetic subjects.ym. The most marked abnormality observed in islet samples from diabetic patients was an increase in β-cell apoptosis. Frequency of β-cell apoptosis was increased 10-fold in samples from normal weight patients, and 3-fold in samples from overweight patients, compared to respective control groups. In this study, islet amyloid was present only in a minority of cases, around 10%, of patients with type 2 diabetes or impaired glucose tolerance. Two explanations may be raised: either small islet amyloid pancreatic peptide oligomers (non detectable by light microscopy) are present and responsible for β-cell loss, or islet amyloid is not crucial in pathogenesis of type 2 diabetes. The authors concluded that β-cell mass is decreased in type 2 diabetes mellitus, due to an increased β-cell apoptosis. A confirmation has been provided by recent in vitro data, indicating an increased rate of apoptosis in islets exposed to high glucose concentrations [48].

2.5. At the interface between insulin secretory and insulin sensitivity defects: the compensation of insulin resistance by the β-cell

In non-diabetic controls, β-cell adapts its secretion rate to the level required by insulin sensitivity, plasma glucose concentrations thus remaining normal. A hyperbolic relation has thus been observed between insulin secretion and sensitivity in non-diabetic subjects [31]. In uncomplicated obesity, insulin resistance is compensated by increased β-cell mass and insulin hyper secretion. [22,49,50]. If compensation is absent, or even incomplete, plasma glucose concentration rises gradually, defining in the incipient stages IFG or IGT, then overt diabetes. Inability of the β-cell to adjust its secretion rate to increased demand explains why glucose intolerance appears in the physiological setting of aging [51], and gestational diabetes.

2.6. Origin of β-cell dysfunction

As indicated supra, β-cell dysfunction is present at the early stages of the disease, i.e. IFG or IGT, and in normoglycaemic first-degree relatives of patients with type 2 diabetes [17,23,52]. These results rule out the hypothesis of a hyperinsulinism state preceding type 2 diabetes, which was evoked from results of studies performed using non-specific assay of insulin (over-estimating “true” insulin concentrations), or from pseudo-longitudinal studies describing the “Starling curve of the pancreas”. In fact, simultaneous plasma glucose levels, and insulin-sensitivity status were not taken in account in these studies. The phenomenon of compensation of insulin resistance by the β-cell has permitted to restore the correct sequence of events leading to the gradual decrease in insulin secretory capacities in type 2 diabetes [22].

2.6.1. Genetics and/or environment in the early life?

Genetic susceptibility for type 2 diabetes relies on results of family studies, disclosing high concordance for type 2 diabetes in monozygotic twins, contrasting with a lower one in heterozygotic ones (80-90% compared to 40-50%), high frequency of type 2 diabetes in subjects with family history of type 2 diabetes (50% if both parents affected, 25-30% if one only first degree relatives affected). Until now the search for the gene or genes responsible for type 2 diabetes mellitus has failed, except for uncommon monogenic and syndromic forms of diabetes (MODY, MIDD, neonatal diabetes). A weak association between type 2 diabetes and the calpain 10 gene had been demonstrated, and the rare known type 2 diabetes susceptibility variants (PPARG and E23K in KCNJ11) increased only slightly the risk, with odds ratios 1.2. Recently, a major type 2 diabetes susceptibility gene, accounting for 20% of cases, TCF7L2, has been identified by Grant et al in Icelanders [53]. Studies conducted in European Caucasian, Asian Indian and Afro-Caribbean populations of both sexes [54] have confirmed the ubiquitous distribution of the association. TCF7L2 is associated to
alterations in insulin secretion. Genotype-phenotype relationship studies disclosed severely impaired insulin secretion in carriers of type 2 diabetes susceptibility variants [55].

Non genetic factors, particularly insufficient supply of nutrients and amino-acids, during the foetal life and the first years of life, may also be involved in a defective development of the islets. This defect may result in a reduced β-cell mass, and/or a reduction in the ability to compensate when insulin resistance is present (pregnancy, excess weight or obesity, low physical exercise level, ageing). In this respect, Hales and Barker [56] have shown that subjects with birth weight in the lowest quintiles are more prone to IGT and type 2 diabetes in adulthood. Barker et al. proposed that type 2 diabetes associated with a low birth weight could be the consequence of impaired β-cell function. This would result from in utero under nutrition during a critical period of foetal life, and lead to abnormal development of the endocrine pancreas. This hypothesis has been supported by animal models studies [57]. In rodents involved to an overall reduction in maternal food intake (50% of the normal daily ration) during the last week of pregnancy and throughout the lactation, the offspring showed in utero growth restriction. They were born with a reduced β-cell mass proliferation rates. Moreover these alterations have consequences during adulthood: further inadequacies of the pancreas are generated in situations of increased insulin demand such as ageing or pregnancy, and are associated with deterioration in glucose tolerance, insulinopenia and β-cell mass reduction [58, 59].

In humans, one study published by Barker reported OGTT data showing that low birth weight was associated with defective insulin secretion in 21-year old adults [60]. However, the other groups do not confirm these data. An anatomo-pathological study has shown that small gestational age does not alter foetal pancreas development and morphology, in comparison to observed in foetal pancreas from foetuses with appropriate growth for gestational age [61]. In a case-control study comparing young adults born with small gestation age (SGA) or appropriate for gestational age, subjects born SGA did not demonstrate any evidence for an impairment in insulin secretion, either involving the first or the second phase [62]. Using another model, Flanagan et al. reached the same conclusion in another adult cohort [63]. In 8-year old Indian children, low birth weight is associated with insulin resistance without abnormality of insulin secretion [64].

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M. Virally has received fees for lectures and consultations from Novartis.


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