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Pathophysiology of diabetes mellitus type 2: beyond the duo "insulin resistance-secretion deficit"

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Abstract

T2DM involves at least two primary pathogenic mechanisms: (a) a progressive decline in pancreatic islet cell function resulting in reduced insulin secretion and (b) peripheral insulin resistance resulting in a decrease in the metabolic responses to insulin. This dynamic interaction between insulin secretion and insulin resistance is essential to the maintenance of normal glucose tolerance (NGT). The transition from the normal control of glucose metabolism to type 2 diabetes mellitus occurs through the intermediate states of altered metabolism that worsen over time. The first state of the disease is known as prediabetes, and consists of a set of metabolic disorder characterized by a great hyperglycemia, enough to increase of retinopathies, nephropathies and neuropathies incidence.

If we advance in the T2DM temporal sequence we found a remarkable change in the pancreatic cells population that form the Langerhans islets, mainly caused by amylin fibers accumulation over these cells from polypeptide hormone called amyloid polypeptide or IAPP. The IAPP hypersecretion and amylin fibers deposition attached to the endoplasmic reticulum stress caused by excessive workload due to biosynthesis overproduction of insulin and IAPP result in β-cell apoptosis. In addition to these alterations, we must also consider the changes observed in incretins profiles like GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide 1) directly related to glucose homeostasis maintenance. Risk factors that predispose to a healthy individual to develop T2DM are several, but the most important is the obesity. The body mass index (BMI) has been used in numerous epidemiological studies as a powerful indicator of T2DM risk. Lipotoxicity caused by circulating free fatty acids increased, changes in lipoprotein profiles, body fat distribution and glucotoxicity caused by cells over-stimulation are other risk factors to consider in T2DM developing.

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Key words: *Diabetes. Insulin resistance. Glucose.*

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FISIOPATOLOGÍA DE LA DIABETES MELLITUS TIPO 2: MÁS ALLÁ DEL DÚO "RESISTENCIA INSULINA - DÉFICIT DE SECRECIÓN"

Resumen

El desarrollo de la DMT2 está provocado principalmente por dos mecanismos patogénicos: (a) un progresivo deterioro de la función de las células de los islotes pancreáticos que provoca una disminución de la síntesis de insulina y (b) una resistencia de los tejidos periféricos a la insulina que da como resultado un descenso de la respuesta metabólica a la insulina. Esta interacción entre la secreción y resistencia a la insulina es esencial para el mantenimiento de una tolerancia normal de la glucosa. El desarrollo de la diabetes mellitus tipo 2 puede describirse como una serie de alteraciones celulares y metabólicas que afectan y deterioran la homeostasis de la glucosa. La transición desde el control normal del metabolismo de la glucosa a la diabetes mellitus tipo 2 se produce a través de estados intermedios alterados de dicho metabolismo que empeoran con el tiempo. El primer estado de la enfermedad se conoce como prediabetes, y consiste en un conjunto de desordenes metabólicos caracterizados por una gran hiperglucemia, suficiente para incrementar la incidencia de retinopatías, nefropatías y neuropatías.

Cuando avanzamos en la secuencia temporal de la DMT2 encontramos una notable alteración en la población de células del páncreas que componen los islotes de Langerhans, provocada principalmente por la acumulación sobre estas células de fibras de amilina procedentes de la hormona polipeptídica llamada polipéptido amiloide de los islotes o IAPP. Esta hipersecreción de IAPP y deposición de fibras de amilina junto al estrés del retículo endoplásmico provocado por el exceso de carga de trabajo debido a la sobreproducción en la biosíntesis de insulina e IAPP dan como resultado la apoptosis de las células β. A todas estas alteraciones debemos sumar las observadas en los perfiles de incretinas como GIP (glucose-dependent insulinotropic polypeptide) y GLP-1 (glucagon-like peptide 1) relacionados directamente con el mantenimiento de la homeostasis de la glucosa. Los factores de riesgo que predisponen a una persona sana a desarrollar la DMT2 son varios, pero sobresale por encima de todos la obesidad. El índice de masa corporal (IMC) ha sido utilizado en numerosos estudios epidemiológicos como un potente indicador del riesgo de padecer DMT2. La lipotoxicidad causada por el aumento de ácidos grasos libres circulantes, el cambio en los perfiles de las lipoproteínas, la distribución de la grasa corporal y la glucotoxicidad provocada por la sobre-estimulación de las células son otros de los factores de riesgo a tener en cuenta en el desarrollo de la DMT2.

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Palabras clave: *Diabetes. Resistencia a la insulina. Glucosa.*

Background

Type 2 Diabetes mellitus (T2DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia, which results from resistance to insulin actions on peripheral tissues as well as inadequate secretion of insulin[1] and an impaired suppression of glucagon secretion in response to ingested glucose. Thus, T2DM involves at least two primary pathogenic mechanisms: (a) a progressive decline in pancreatic islet cell function resulting in reduced insulin secretion and inadequate suppression of glucagon secretion[3,4] and (b) peripheral insulin resistance resulting in a decrease in the metabolic responses to insulin.[1] It is widely recognized that both insulin secretion and insulin resistance are important elements in the pathogenesis of type 2 diabetes. Subjects with insulin resistance require more insulin to promote glucose uptake by peripheral tissues, and genetically predisposed individuals may lack the necessary β-cell secretory capacity. The resulting insulin deficiency disrupts the regulation of glucose production in the liver and is a clue element in the pathogenesis of glucose intolerance.[5] In populations with a high prevalence of T2DM (eg. obese individuals), insulin resistance is well established long before the development of any impairment in glucose homeostasis, particularly in subjects with abdominal or ectopic (liver, muscle) fat accumulation. However, as long as the beta cell is able to secrete sufficient amounts of insulin to offset the severity of insulin resistance, glucose tolerance remains normal. This dynamic interaction between insulin secretion and insulin resistance is essential to the maintenance of normal glucose tolerance (NGT) and interruption of this crosstalk between the beta cell and peripheral tissues results in the progressive deterioration of glucose homeostasis.

The pathogenic mechanisms in T2DM involve not only insulin, but also glucagon, and it is the interplay between these two processes the key component in the understanding of the pathophysiology of T2DM. The prevalence of T2DM, its specific complications and the presence of other diseases that often accompany T2DM make this disease one of today's main social and public health problems.

Development of T2DM

Our knowledge about the time sequence, in which all cellular and metabolic alterations are developed during different disease stages are still insufficient. Which are the cellular and metabolic events chain and what are the main risk factors that cause the transition from a normal glucose homeostasis to DMT2 are questions to be answered in the near future.

Following glucose ingestion, the balance between endogenous glucose production and tissue glucose uptake is disrupted. The increase in plasma glucose concentration stimulates insulin release from the pancreatic beta cells, and the resultant hyperinsulinemia and hyperglycemia serves to stimulate glucose uptake by splanchnic (liver and gut) and peripheral (primarily muscle) tissues and to suppress endogenous glucose production by the liver.[6,7] Hyperglycemia, in the absence of hyperinsulinemia, exerts its own independent effect on muscle glucose uptake and suppress endogenous glucose production in a dose dependent fashion. The majority (~80-85%) of glucose that is taken up by peripheral tissues, in an insulin dependent manner, is disposed of in muscle, with only a small amount (~4-5%) being metabolized by adipocytes. Another 10% is disposed of by splanchnic tissues through non insulin dependent mechanisms. Although fat tissue is responsible for only a small amount of total body glucose disposal, it plays a very important role in the maintenance of total body glucose homeostasis. Insulin is a potent inhibitor of lipolysis and even small increments in the plasma insulin concentration exert a potent antilipolytic effect, leading to a marked reduction in adipose tissue release of fatty acids and subsequently a decrease in plasma free fatty acids (FFA) level. The decline in plasma FFA concentration facilitates an increased glucose uptake in muscle and contributes to the inhibition of hepatic glucose production. Thus, changes in the plasma FFA concentration in response to increased plasma levels of insulin and glucose play an important role in the maintenance of normal glucose homeostasis.[12-15] Glucagon also plays a central role in the regulation of glucose homeostasis.[9,16]

During the post-absorptive state (10-12 hours fasting overnight), hepatic glucose output depends on a delicate equilibrium between basal glucagon secretion (stimulatory effect), and basal insulin secretion (inhibitory effect). Approximately 75% of the total effect depends on the stimulatory action of glucagon.[96]

Normal glucose homeostasis

The metabolic response to ingested carbohydrate is markedly different in individuals with normal glucose tolerance compared to those with T2DM. Individuals with normal glucose metabolism have a typical insulin, glucose, and glucagon profile in plasma in response to the ingestion of a carbohydrate meal.

In the post-absorptive state, the majority of glucose that is removed from the body occurs in insulin-independent tissues. Approximately 50% of all glucose utilization occurs in the brain, another 25% of glucose uptake occurs in the splanchnic area (liver plus gastrointestinal tissues) and the remaining 25% uptake of glucose in the post-absorptive state takes place in insulin-dependent tissues, primarily muscle. Basal glucose utilization averages ~2.0 mg/kg.min and is precisely matched by the rate of endogenous glucose production. Approximately 85% of endogenous glucose production is derived from the liver, and the remaining amount is produced by the

kidney. Approximately half of basal hepatic glucose production is derived from glycogenolysis and half from glyconeogenesis.[6-11]

Prediabetes

Diabetes mellitus is defined as a cluster of metabolic disorders, characterized by hyperglycemia high enough to significantly increase the incidence of a specific an unique type of microangiopathy (retinopathy, nephropathy and neuropathy).

Prediabetes is a condition in which blood glucose levels are higher than normal, but not high enough for a diagnosis of diabetes. Prediabetes, also known as Dysglycemia, usually have no symptoms. People may have this condition for several years without noticing anything. Prediabetes can be separated into two different conditions: impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), depending on the type of test and timing (fasting *vs* postprandial) used for diagnosis.

IFG and IGT represent intermediate states of abnormal glucose regulation that exist between normal glucose homeostasis and diabetes. IFG is now defined by an elevated fasting plasma glucose (FPG) concentration (≥ 100 and < 126 mg/dl).[92] IGT is defined by an elevated 2-h plasma glucose concentration (≥ 140 and < 200 mg/dl) after a 75-g glucose load on the oral glucose tolerance test (OGTT) in the presence of an FPG concentration < 126 mg/dl.[92]

The pathophysiology of IFG seems to include the following key defects: reduced hepatic insulin sensitivity, stationary beta cell dysfunction and/or chronic low beta cell mass, altered GLP-1 secretion and inappropriately elevated glucagon secretion.[93] Conversely, the prediabetic state of isolated IGT (IGT without IFG) is mainly characterized by reduced peripheral (muscle) insulin sensitivity, near-normal hepatic insulin sensitivity and a reduced second phase insulin secretion. Individuals developing combined IFG/IGT exhibit severe defects in both peripheral and hepatic insulin sensitivity, as well as a progressive loss of beta cell function.[93] In conclusion, the transition from the prediabetic states to overt type 2 diabetes is characterized by a non-reversible vicious cycle that includes severe deleterious effects on glucose metabolism.

Type 2 Diabetes and obesity

Obesity is a complex disorder, where genetic predisposition interacts with environmental exposures to produce a heterogeneous phenotype.[17] Today, we know that some of these obesity phenotypes are associated with a high risk of developing T2DM.[18] There is also strong evidence that, for a given adiposity, there is a large heterogeneity in the metabolic risk mainly linked to the location of excessive adipose tissue. Visceral adipose tissue accumulation is an important predictive factor of lipid, glucose or atherogenic disturbances, while location of adipose tissue in the lower part of the body is not associated with increased metabolic alterations.

BMI *vs* DMT2 risk

Many epidemiologic studies have shown that body mass index (BMI) is a powerful predictor of type 2

Table I
Pathophysiology of the prediabetic states

Pathophysiology	*i-IFG*	*i-IGT*	*IFG/IGT*
Muscle			
Insulin sensitivity	Unaltered	Reduced	Reduced
Liver			
Insulin sensitivity	Reduced	Unaltered	Reduced
Hepatic glucose production	Elevated	Unaltered	Elevated
Pancreas			
First-pashe insulin response	Reduced	Reduced or unaltered	Reduced
Disposition index	Reduced	Reduced	Reduced
Glucagon secretion	Elevated	Elevated	Elevated
Gut			
GLP-1 secretion	Reduced or elevated	Reduced or elevated	¿?
GIP secretion	Unaltered	Reduced or elevated	¿?
Adipose tissue			
Insulin sensitivity	Reduced	Reduced	¿?
NEFA release	Unaltered	Elevated	¿?
Adipocytokine release	¿?	¿?	¿?
Brain	¿?	¿?	¿?
Kidney	¿?	¿?	¿?

diabetes.[19,20] For example, Field et al.[21] reported that both men and women with a BMI of 35.0 were 20 times more likely to develop diabetes than were their same-sex peers with a BMI between 18.5 and 24.9. In another investigation from the Nurses' Health Study, overweight and obesity was the single most important predictor of type 2 diabetes in 30-55-y-old women.[22]

Furthermore, this general obesity measure has consistently been associated with adverse health outcomes, but certain sub-phenotypes of obesity have been recognized that appear to deviate from the apparent dose-response relationship between BMI and its consequences. Ruderman and others[23,24] identified metabolically obese normal-weight (MONW) individuals who, despite having a normal-weight BMI, demonstrate metabolic disturbances typical of obese individuals. These disturbances include insulin resistance (IR) and increased levels of central adiposity, low levels of high density lipoprotein-cholesterol (HDL-C) and elevated levels of triglycerides, dysglycemia and hypertension. This clustering of risk factors has been called the metabolic syndrome (MetS).[25] Others have described metabolically healthy obese (MHO) individuals, who, despite having BMI exceeding 30 kg/m^2, are relatively insulin sensitive and lack most of the metabolic abnormalities typical of obese individuals.[26,27] MONW and MHO individuals are interesting because these phenotypes separate obesity from its usual metabolic consequences, offering insight into risks associated with risk factor clustering or IR that are largely independent of overall obesity (MONW) or risks associated with obesity that are largely independent of adiposity's intermediate metabolic abnormalities (MHO). Characteristics of BMI-metabolic risk sub-phenotypes have been described in selected study samples, but their prevalence in a community-based sample is not well established.

Fat distribution *vs* T2DM risk

It has been theorized that the reduced normal inhibitory action of insulin ("insulin resitance") on Hormone Sensitive Lipase (HSL) in adipocytes, accelerates lipolysis and raises the levels of FFAs, which worsen both peripheral and hepatic insulin resistance.[28] However, despite the strong association, visceral fat does not seem to have a direct role in the development of peripheral insulin resistance. On the other hand, visceral fat is an important source of inflammatory cytokines such as TNF-alpha, TGF-beta, and IL6 that. can directly affect insulin-mediated glucose uptake.[29] Visceral adipocytes are more sensitive than subcutaneous adipocytes to the catecholamines (mainly epinephrine), ACTH and glucagon lipolytic effects and less sensitive to the insulin antilipolytic and fatty acid re-esterification effect,[29] a phenomenon which could further enhance free fatty acids efflux (FFA) in those who are predisposed to store fat in the visceral area. Furthermore, the venous effluent of visceral fat depots leads directly into the portal vein, resulting in greater FFA flux to the liver in viscerally obese individuals than in those with predominantly subcutaneous obesity. Although visceral fat depots have been estimated to represent only approximately 20% of total body fat mass in men and 6% in women,[31,32] approximately 80% of hepatic blood supply is derived from the portal vein.[33] This not only promotes hepatic fat accumulation but can also cause hepatic insulin resistance.[34] While there is a consensus that visceral fat has a strong association with cardiovascular risk factors, particularly dyslipidemia, hypertension and hyperinsulinemia,[35] this relationship has been challenged by Abate et al.[36] and Goodpaster et al.[37] These researchers found that abdominal subcutaneous fat, as determined by magnetic resonance imaging and computed tomography, was at least as strong a correlate of insulin sensitivity (evaluated by the euglycemic clamp) as visceral fat and retained independent significance after adjusting for visceral fat.[37]

Cellular and metabolic disorders

Insulin resistance requires increased insulin output both in the basal state and in response to stimulation, to maintain normal glucose tolerance, whereas improvements in insulin sensitivity place the β-cell in the position of having to reduce insulin release to avoid hypoglycemia. These changes in insulin sensitivity that require adjustment of insulin output can occur quite rapidly or over longer periods of time.[44,45] The mechanisms responsible for these changes clearly vary and involve changes in both β-cell function and β-cell mass, although in most instances it appears that functional changes predominate (at least in the short term). In addition to functional adaptation to such rapid changes in insulin sensitivity, the β-cell must also alter its activity when this critical modulator changes for more prolonged periods. Under such conditions one envisages both -cell secretory function and β-cell mass playing complementary roles.

Islets of Langerhans Dysfunction

The most notable alteration that occurs in the islets of Langerhans in type 2 diabetes is the amyloid deposition derived from the polypeptide hormone islet amyloid polypeptide (IAPP, "amylin"). In 1986 it was understood that it is a polymerization product of a novel β-cell regulatory product.[46,47] It has been argued that the amyloid may not be of importance since there is no strict correlation between the degree of islet amyloid infiltration and the disease. However, it is hardly discussable that the amyloid is important in subjects where islets have been destroyed by

pronounced islet amyloid deposits. Even when there is less islet amyloid the deposits are widely spread, and -cells show ultrastructural signs of cell membrane destruction.[48,49] It is suggested that type 2 diabetes is heterogeneous and that in some individuals aggregation of IAPP into amyloid fibrils could determine a progressive loss of β-cells.

Loss of mass and β-cell function

As in DMT1, prospective studies of DMT2 indicate a progressive decline in -cell function preceding relatively abrupt diabetes onset.[50,51] However there is no means to establish to what extent, if at all, this decline in β-cell function is due to impaired β-cell mass or simply due to declining function. Autopsy studies of patients with T2DM have revealed a β-cell mass of ~0-65% compared to body mass index matched non-diabetic patients controls.[52] There is also increased β-cell apoptosis compared to controls,[53] implying that the loss of β-cell mass is likely progressive unless there is concurrently increased β-cell formation. In a study in which pancreatic tissue from patients with type 2 diabetes mellitus and control subjects was obtained from 124 autopsies, the rate of β-cell replication and neogenesis was similar (indeed, very low) in all cases, with no difference between diabetic and control groups. However, the frequency of β-cell apoptosis was increased 10-fold in the lean and 3-fold in the obese cases of type 2 diabetes (64, 65). So that, the real determinant of lower β-cell mass in T2DM is an increased rate of apoptosis.

Several studies have linked type 2 diabetes with a variety of proapoptotic mechanisms,[60] including glucose-induced synthesis of IL-1,[61,62] endoplasmic reticulum (ER) stress,[63] mitochondrial overload and pro-islet amyloid polypeptide secretion.[66] Given the wide range of β-cell mass in nondiabetic humans, the possibility exists that vulnerability to T2DM is based in part upon the β-cell mass accomplished as an adult. In the face of insulin resistance, those individuals with the lowest β-cell mass would have the highest requirement per β-cell for pro-insulin and pro-islet amyloid polypeptide synthesis and processing.

– *Disposition index:* Current evidence points to β-cell dysfunction as the first demonstrable defect with limited capacity to compensate for the presence of insulin resistance. However, the modulating effect of insulin sensitivity on β-cell function has to be considered for the assessment of insulin release in individuals at risk of developing DM2. The nature of this relationship is such that insulin sensitivity and β-cell function are inversely and proportionally related, whereby the product of these two parameters is constant, being referred to as the disposition index,[54] and in turn can be interpreted as a measure of the ability of the β-cell to compensate for insulin resistance. Mathematically, this relationship is described by the hyperbolic relationship between the acute insulin response (AIR) and the metabolic action of insulin to stimulate glucose disposal (M) and is referred to as glucose homeostasis, with glucose concentration assumed to remain constant along the hyperbola.

Loss of α-cell function

Despite the importance of the α-cell and glucagon secretion in the regulation of glycaemia and nutrient homeostasis, little is known about the physiology of these cells compared with the overwhelming information about β-cells. Several factors may explain this lack of information regarding glucagon secretion. First, the scarcity of this cell population in islets of animal models such as mice and rats along with several technical limitations of conventional methods for evaluation of α-cell function has made it more difficult to study α-cell s than beta-cells.[55] Second, the lack of functional identification patterns has also been an important limitation in α-cell research. Abnormal α-cell function is an important determinant of the magnitude of hyperglycemia found in diabetes.

The evidence for this can be summarized as follows: Fasting hyperglycemia and insulin requirements are lower in pancreatectomized patients lacking glucagon.[56] Moreover, in such individuals[56] and in insulin-dependent diabetics whose glucagon secretion is suppressed with somatostatin,[57] hyperglycemia following acute withdrawal of insulin is markedly diminished. The failure to suppress glucagon secretion appropriately after meal ingestion increases postprandial hyperglycemia in people with impaired glucose tolerance and diabetes. Nevertheless, the above studies suggest association, and investigations using selective glucagon secretion or receptor antagonists would help to fully evaluate contribution of glucagon dysfunction in the pathogenesis of diabetes.[58]

Lipotoxicity

Diabetes is associated with dyslipidemia and characterized by an increase in circulating free fatty acids (FFAs) and changes in lipoprotein profile. In healthy humans, besides the insulin resistance and hyperinsulinemia induced by an acute elevation of FFAs, there is also an increase in glucose-stimulated insulin secretion after prolonged "low grade" FFA infusion (48 and 96 h)[37,38] but not in nondiabetic individuals genetically predisposed to developing DM2.[38] In healthy control subjects, the FFA-induced insulin resistance was compensated by the enhanced insulin secretion, whereas persistently elevated FFAs may contribute to progressive β-cell failure (β-cell lipotoxicity) in individuals genetically predisposed to DMT2 and also has been implicated as an acquired cause of impaired β-cell

function, as individuals progress from IGT to overt type 2 diabetes mellitus. Within the beta cell, long-chain fatty acids are converted to their fatty acyl-CoA derivatives, which lead to increased formation of phosphatidic acid and diacylglycerol. These lipid intermediates activate specific protein kinase C isoforms, which enhances the exocytosis of insulin. Long-chain fatty acyl-CoA also stimulate exocytosis, cause closure of the K+-ATPase channel, stimulate Ca2+-ATPase and increase intracellular calcium, thus augmenting insulin secretion. In contrast to these acute effects, chronic beta cell exposure to elevated fatty acyl-CoA inhibits insulin secretion through operation or activation of the Randle cycle. Increased fatty acyl-CoA levels within the beta cells also stimulate ceramide synthesis, which augments inducible nitric-oxide synthase. The resultant increase in nitric oxide increases the expression of inflammatory cytokines, including interleukin-1 and tumor necrosis factor alfa, which impair β-cell function and promote beta cell apoptosis.

Glucotoxicity

Unger and colleagues first introduced the concepts of glucotoxicity.[59] In their initial glucose toxicity paper, they put forward the concept that continuous overstimulation of the β-cell by glucose could eventually lead to depletion of insulin stores, worsening of hyperglycemia, and finally deterioration of β-cell function. The main action of the glucotoxicity on the pathophysiology of T2DM is the formation of reactive oxygen species (ROS) through its relationship with oxidative stress that affects the beta cells. Reports that β-cells have very low levels of antioxidant enzymes compared with other tissues suggest that the β-cell is particularly vulnerable for oxidative stress.[67]

Once glucose enters cells, it is primarily and progressively metabolized to glyceraldehyde-3-phosphate, 1:3 bis-P-glycerate, glyceraldehyde-3-phosphate, and pyruvate. Pyruvate then enters the tricarboxylic acid cycle to undergo oxidative phosphorylation, during which formation of ATP and ROS occurs. However, when excess glucose is available to the cell, alternative pathways exist through which excess glucose can be shunted and ROS can be formed from glucose.[66]

Alterations in incretins profiles

To date, only glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide 1 (GLP-1) fulfill the definition of an incretin hormone in humans. Furthermore, studies have shown that these two peptides potentiate glucose-stimulated insulin secretion in an additive manner, likely contribute equally to the incretin effect and together can fully account for the majority of the incretin effect in man. The actions of both are receptor-mediated. Incretins bind to specific heterotrimeric membrane receptors in beta cells, resulting in activation of adenyl cyclase and increased cellular cAMP levels, enhancing in this way the release of insulin. The profiles of these two incretins are altered in patients with T2DM.[68] While GIP concentration is normal or modestly increased in patients with T2DM[84] the insulinotropic actions of GIP are significantly diminished.[85] Thus, patients with T2DM have an impaired responsiveness to GIP with a possible link to GIP-receptor downregulation or desensitization. In contrast to GIP, the secretion of GLP-1 has been shown to be deficient in patients with T2DM.[85]

– *GLP1: Secretion, metabolism and influence in T2DM:* Glucagon-like peptide 1 (GLP-1) is an intestinal hormone that exerts profound effects in the regulation of glycemia, stimulating glucose dependent insulin secretion, proinsulin gene expression, and -cell proliferative and anti-apoptotic pathways, as well as inhibiting glucagon release, gastric emptying, and food intake.[69] Although the proglucagon gene is expressed in enteroendocrine L-cells and pancreatic β-cells,[70] GLP-1 is synthesized by post-translational processing of proglucagon only in the intestine. The L-cells are predominantly located in the ileum and colon, although have also been localized in the stomach and proximal gut[98] and have been identified as open-type epithelial cells that are in direct contact with nutrients in the intestinal lumen.[71] Furthermore, L-cells are located in close proximity to both neurons and the microvasculature of the intestine,[72,73] which allows the L-cell to be affected by both neural and hormonal signals. Bioactive GLP-1 exists in two equipotent forms, GLP-$1^{7\text{-}36\ NH2}$ and GLP-$1^{7\text{-}37}$, in the circulation, of which the first one is predominant.[74] Secreted GLP-1 is rapidly degraded by the ubiquitous enzyme dipeptidyl peptidase IV (DPP-IV),[75] resulting in an extremely short half-life for GLP-1 of ~2 min.[74] Nutrient ingestion is the primary physiological stimulus to the L-cell and results in a biphasic pattern of GLP-1 secretion. An initial rapid rise in circulating GLP-1 levels occurs 15-30 min after a meal, followed by a second minor peak at 90-120 min.[76] Glucose and fat have been found to be potent stimulators of GLP-1 secretion when ingested,[77] but also after direct administration into the intestinal lumen[75,78] or into perfused ileal segments (79). Unlike glucose and fat, protein does not appear to stimulate proglucagon-derived peptide secretion from L-cells,[77] although protein hydrolysates have been found to stimulate GLP-1 release in a perfused rat ileum model and in inmortalized human L-cells.[79,80] Several studies suggest that impairments at the level of the L cell may account, at least in part, for the reduced GLP-1 secretion that is observed in patients with type 2 diabetes,[81,82] as well as in obesity.[83] This common view that GLP-1 secretion in T2DM patients is deficient and that this applies to a lesser degree in individuals with impaired

glucose tolerance has been recently review by Nauck et al.[98] This review summarises the literature on the topic, including a meta-analysis of published studies on GLP-1 secretion in individuals with and without diabetes after oral glucose and mixed meals and the findings does not support the contention of a generalized defect in nutrient-related GLP-1 secretory responses in type 2 diabetes patients, which has been the rationale for replacing endogenous incretins with GLP-1 receptor agonists or re-normalising active GLP-1 concentrations with dipeptidyl peptidase-4 inhibitors.[98]

– *GIP: Secretion, metabolism and influence in T2DM:* GIP is a single 42 amino acid peptide derived from the processing of a 153 amino acid precursor, whose 10 Kb spanning gene is located on chromosome 17 in humans. Is secreted in a single bioactive form by K cells and released from the proximal small intestine (duodenum and jejunum), in response to the oral ingestion of carbohydrates and lipids. GIP receptors are expressed in the pancreatic islets, gut, adipose tissue, heart, pituitary, adrenal cortex and in several regions of the brain.[88] As GLP-1, GIP is rapidly degraded by the enzyme DPP-IV, that cleaves the biologically active forms at the position 2 alanine (N-terminal), resulting in inactive or weak antagonist peptide fragments. When incretins are administered intravenously in normal subjects and in diabetic patients, the plasma half-life (t1/2) of exogenous GIP is about 5-7 minutes.[86,87,97]

These findings suggest that the majority of GIP and GLP-1 released in the portal circulation is inactivated by DPP-4 before entry into the systemic circulation. In addition to cell-surface membrane-bound form, DPP-4 also exists as a soluble protein in the circulation. Thus, a minor amount of secreted incretins reach the pancreatic β-cells. The effects of GIP are mediated after binding to specific plasma membrane receptors. They belong to the 7 trans-membrane-domain receptor family coupled to G proteins. Binding of GIP to their respective receptor causes the activation of adenyl cyclase via G protein, and leads to an increase of intracellular cyclic AMP levels. Subsequent activation of protein kinase-A results in a cascade of intracellular events, such as increased concentrations of cytosolic Ca2+ and, in the case of pancreatic β-cells, enhanced exocytose of insulincontaining granules. Other signalling pathways may also be activated such as MAP kinase, phospho-inositol-phosphate PIP3, and protein kinase B (PKB) pathways.[88] Results of studies in humans as well as studies in mice lacking both the GIP and the GLP-1 receptors showed an additive effect on insulin secretion.[89] There is experimental evidence indicating that GIP regulates fat metabolism in adipocytes, including enhanced insulinstimulated incorporation of fatty acids into triglycerides, stimulation of lipoprotein lipase activity, stimulation of fatty acids synthesis.[90] In addition GIP has been shown to promote β-cell proliferation and cell survival in islet cell line studies.[91]

Summary

The pathophysiology of T2DM is multi-faceted and includes deficient insulin secretion from pancreatic islet cells, insulin resistance in peripheral tissues, and inadequate suppression of glucagon production. These processes result in inadequate uptake, storage, and disposal of ingested glucose accompanied by elevated hepatic glucose production and hyperglycemia. As now believed, insulin resistance is very much part of the natural history of Type 2 diabetes and may be present many years before the clinical diagnosis. Loss of -cell mass in the pancreatic islets can progress to a clinically significant degree even in patients with IGT, such that at the time of diagnosis of DMT2, a significant number of cells may already be lost. The glucose sensitivity of the beta cell is also progressively deteriorated. Thus, early in the development of T2DM, fasting glucose concentrations are often within normal ranges while postprandial hyperglycemia is already present.

Obesity and type 2 diabetes mellitus are linked in several ways. Obesity is implicated in the pathological process culminating in the development of type 2 diabetes[94,95] through the promotion of both insulin resistance and secretion deficit. Fat distribution, in particular visceral fat, with an excess FFA release secondary to lack of inhibition of lipolysis by insulin (insulin resistance at the visceral adipocytes) may aggravate the state through an overstimulation of ectopic fat accumulation in skeletal muscles and liver, which deteriorates insulin sensitivity in these tissues. Moreover, ectopic FFA accumulation in the pancreas, mediated by their fatty acyl-CoA derivatives, can also deteriorate insulin secretion.

The incretin hormones include glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP), both of which may also promote proliferation/neogenesis of beta cells and prevent their decay (apoptosis). Both hormones contribute to insulin secretion from the beginning of a meal and their effects are progressively amplified as plasma glucose concentrations rise. The current interest in the incretin hormones is due to the fact that the incretin effect might be reduced in patients with T2DM, even though this concept has been challenged recently. In addition, there is hyperglucagonaemia, which is not suppressible by glucose and stimulates basal glucose output from the liver. In such patients, the secretion of GIP is near normal, but its effect on insulin secretion, particularly the late phase, is severely impaired. They potentiate glucose-induced insulin secretion and may be responsible for up to 70% of postprandial insulin secretion.

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