Functional pancreatic beta-cell mass: Involvement in type 2 diabetes and therapeutic intervention

M. Karaca a,*, C. Magnan a, C. Kargar b

a CNRS, université Paris-Diderot, 4, rue Marie-Andrée-Lagroua, 75205 Paris cedex 13, France
b Institut de recherches Servier, Suresnes, France

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Abstract

In the adult, the pancreatic β-cell mass adapts insulin secretion to meet long-term changes in insulin demand and, in particular, in the presence of insulin resistance that is either physiological, such as pregnancy, or pathophysiological, such as obesity. The failure of β cells to compensate for insulin resistance is a major component of impaired glucose homeostasis and overt diabetes. This defect is clearly the consequence of a decline of insulin response to glucose due to functional β-cell deficiency. It is also the consequence of an inability of the endocrine pancreas to adapt the β-cell mass to insulin demand (pancreas plasticity), which eventually leads to a decrease in functional β-cell mass. This idea has resulted in considerable attention being paid to the development of new therapeutic strategies aiming to preserve and/or regenerate functional β-cell mass.

The latter is governed by a constant balance between β-cell growth (replication from pre-existing β cells and neogenesis from precursor cells) and β-cell death (mainly apoptosis). Disruption of this balance may lead to rapid and marked changes in β-cell mass. Glucagon-like peptide-1 (GLP-1), an incretin, enhances β-cell survival (by activating β-cell proliferation and differentiation, and inhibiting β-cell apoptosis), thus contributing to the long-term regulation of insulin secretion by maintaining a functional β-cell mass. The development of drugs regulating this parameter will be the major challenge of the next few years in the management of type 2 diabetes.

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Keywords: Endocrine pancreas plasticity; Functional β-cell mass; Adaptation; Insulin resistance; Incretins; Review

Résumé

Masse fonctionnelle des cellules β : implication dans le diabète de type 2 et intervention thérapeutique.

Chez l’adulte, la masse des cellules β varie pour une adaptation à long terme de la sécrétion d’insuline, en particulier dans des situations d’insulinorésistance physiologique telle que la gestation ou physiopathologique telle que l’obésité. L’incapacité de la cellule β à compenser pour l’insulinorésistance est la composante majeure de la perturbation de l’homéostasie glucidique et de l’installation du diabète. Ce défaut est la conséquence, d’une part, du déficit fonctionnel au niveau de la cellule β individuelle et, d’autre part, d’une inhabilité du pancréas endocrine à adapter la masse des cellules β à la demande insulinique (plasticité du pancréas) conduisant à une perte du nombre de cellules β fonctionnelles. Ce concept a pris une importance considérable dans l’optique du développement de nouvelles stratégies thérapeutiques visant à préserver et/ou à régénérer la masse fonctionnelle de cellules β. Cette dernière est déterminée par un équilibre dynamique entre croissance (par prolifération/néogenèse) et mort (essentiellement par apoptose) des cellules β. Une rupture de cet équilibre peut conduire à des changements rapides et marqués de la masse des cellules β. Le glucagon like peptide-1 (GLP-1), une incrétine, favorise la survie des cellules β (en activant la prolifération et la différenciation et en inhibant l’apoptose), et contribue ainsi à la régulation à long terme de la sécrétion d’insuline et au maintien d’une masse β fonctionnelle. Le développement de nouveaux médicaments visant à réguler ce paramètre est un des enjeux majeurs des années à venir dans le domaine du diabète de type 2.

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Mots clés : Plasticité du pancréas endocrine ; Masse de cellules β fonctionnelle ; Adaptation ; Insulinorésistance ; Incretines ; Revue générale

1. Introduction

The failure of pancreatic β-cell function to compensate for insulin resistance is a major component of impaired glucose
homeostasis and overt diabetes. This defect is clearly the consequence of a decline of insulin response to glucose due to functional β-cell deficiency. However, mounting evidence now supports the idea that it is also the consequence of an inability of the endocrine pancreas to adapt the β-cell mass to insulin demand (pancreas plasticity), thereby eventually leading to a decrease in functional β-cell mass.

Thus, over the past few years, this concept has been the focus of considerable attention as regards diabetes aetiology, and especially in terms of the development of new therapeutic strategies aiming to preserve and/or to regenerate the functional pancreatic β-cell mass.

2. Endocrine pancreas plasticity

2.1. Experimental data

Endocrine pancreas plasticity may be defined as the ability of the organ to adapt the β-cell mass to variations in insulin demand, to ensure optimal control of glucose homeostasis (Fig. 1). This property is essential and can be considered to be the long-term regulation of insulin secretion. It is well illustrated in physiological and physiopathological conditions such as pregnancy and obesity, respectively [1,2].

In mammals, including humans, pregnancy results in profound changes in maternal metabolism and insulin secretion to allow an optimal nutrient supply to the fetus. Dynamic changes in the β-cell mass and insulin secretion have been studied in detail in rodents. During the last third of pregnancy, there is marked insulinresistance accompanied by a dramatic increase in the insulin response to glucose and an almost doubling of the β-cell mass (Fig. 1B). After parturition, rat β-cell mass and insulin secretion decrease progressively to reach normal values at around 10 days postpartum [3,4]. Failure to compensate for the increased demand during pregnancy is thought to lead to gestational diabetes. With an incidence of 3–5%, this represents one of the main health concerns of pregnancy. Although gestational diabetes disappears after delivery, mothers remain at risk of developing type 2 diabetes later in life.

Although obesity is associated with insulinresistance, most obese individuals remain normoglycaemic because of compensatory hyperinsulinaemia (Fig. 1B) [5]. This has been attributed to β-cell hyperplasia and increased insulin secretion. Indeed, β-cell overactivity has been shown to be the consequence of an increased low-Km glucose metabolism of islets that increases sensitivity of β cells to glucose [6]. In contrast, a defect in pancreas plasticity may contribute to the progressive failure of the insulin response to glucose and explain, in part, the development of diabetes in some obese subjects (Fig. 1C). Several animal models accurately illustrate the phenomena of β-cell plasticity, characterized by an increase in both β-cell mass and β-cell function and, in contrast, the lack of β-cell compensation in the face of increased insulin demand.

We have previously shown that a prolonged (48-hour) glucose infusion in normal rats led to a twofold increase in β-cell mass as a result of both hypertrophy and hyperplasia [7]. This β-cell mass enlargement correlated with a marked increase in islet responsiveness to glucose both in vivo and in vitro [7]. Such β-cell compensation is also well illustrated by Zucker fatty (ZF) rats, which possess a leptin-receptor defect that results in obesity and insulinresistance [8]. However, these animals remain normoglycaemic via compensatory hyperinsulinaemia. Adaptation to insulinresistance occurs via a fourfold increase in the β-cell mass [9] together with enhanced insulin secretion [10,11], thereby allowing the maintenance of glucose homeostasis.

Successive inbreeding of the most glucose-intolerant ZF rats led to the development of the Zucker diabetic fatty (ZDF) rat colony [8]. The obese male ZDF (mZDF) rat is characterized by hyperinsulinaemia and hyperglycaemia from around 6–7 weeks of age. Glucose levels then increase over the next 3–4 weeks to reach around 500 mg/dL. At this time, insulin levels peak and then decrease over the next 4–6 weeks to a level of about 1 ng/mL. Insulin levels continue to drop to below this level over time. Complications of diabetes become evident as the animal ages [12,13]. In the prediabetic state, both mZDF and mZF rats are obese and insulinresistant. During the initiation of hyperglycaemia, mZDF rats display excess insulinresistance and insufficient β-cell mass adaptation [14]. Progressive reductions in β-cell mass and function are then seen after the development of overt hyperglycaemia.

Another relevant model is the gerbil Psammomys obesus (P. obesus), or sand rat, fed in captivity with a relatively high-energy (HE) diet instead of its usual low-calorie diet. These rodents, characterized by innate insulinresistance, quickly become obese and diabetic on switching from a low-energy diet to HE feeding [15,16]. The HE diabetogenic diet results in a marked increase in postprandial blood glucose levels, already apparent in 50% of these animals after 24 hour of HE feeding [17,18]. The initial hyperinsulinaemia that accompanies hyperglycaemia is associated with an 80–90% reduction in pancreatic insulin content before any change in β-cell mass is observed [18]. Deficiency of insulin release at this stage results from inappropriate coupling of insulin secretion and production rather than a decrease in β-cell mass [18]. A 50% reduction in β-cell mass was observed on days 2 and 5 of the HE diet [18]. However, by day 22, there was spontaneous recovery of β-cell mass back to its initial, prediabetic level, with no concomitant increase in either pancreatic islet content or improvement of glucose homeostasis [18]. In this model, a dramatic decrease in β-cell mass associated with hypoinsulinaemia was observed in the end stages of diabetes [18]. Thus, in P. obesus, there is a clear dissociation between the pancreatic insulin reserve and β-cell mass during most stages of diabetes.

A model similar to P. obesus in terms of an imbalance between β-cell mass and function is the 48-hour glucose-infused rat previously rendered mildly diabetic by a single injection of a low dose of streptozotocin (STZ). The STZ rats are characterized by:

- a slight basal hyperglycaemia and hypoinsulinaemia;
- a severe glucose intolerance;
- an impaired insulin secretion in response to glucose and a 65% reduction of β-cell mass [7].
After a 48-hour glucose infusion, the β-cell mass was completely restored, but this impressive recovery did not result in any clear improvement in β-cell function when investigated both in vivo and in vitro [7].

These observations suggest that the β-cells that reappear under conditions of HE nutrition in P. obesus and with glucose infusion for STZ rats do not achieve functional maturity. Taken altogether, these studies indicate that variations in functional β-cell mass determine the ability of the endocrine tissue to adapt to changes in insulin needs.

2.2. Clinical data

Although type 1 diabetes is clearly related to a reduction of β-cell mass, controversy persists over the relative contribution of a decrease in β-cell mass in type 2 diabetes [19,20]. Discrepancies are, in part, due to the lack of available data in humans, and the fact that pancreata are usually only available at autopsy and most likely represent only the end stages of type 2 diabetes disease. Furthermore, reliable clinical information for autopsy cases is often unavailable and, often, only small numbers of cases were studied, impeding an accurate analysis of cases according to their degree of obesity or duration of disease.

Nevertheless, recent studies have demonstrated that β-cell mass is decreased in type 2 diabetes [21–23]. In particular, a study of 124 human pancreata, from non-diabetic and diabetic patients matched for obesity, revealed that the relative β-cell volume—and, therefore, the presumptive β-cell mass—is decreased in both obese and lean humans with type 2 diabetes compared with their non-diabetic age- and weight-matched counterparts [20]. Interestingly, humans with impaired fasting glucose already have a decreased relative β-cell volume, suggesting that this is an early process that is probably a key factor in the development of type 2 diabetes [20]. However, it is important to remember that human studies are based on autopsy cases, which means that the measured β-cell mass is not the functional β-cell mass because of the lack of correlation with glycaemia, insulinaemia or β-cell function.

The development of tools to investigate the β-cell mass in situ in type 2 diabetics is a major issue for the coming years. In particular, the investigation of functional β-cell mass by non-invasive in vivo imaging could help to target treatments for subpopulations of diabetics with specific phenotypes, and for determining the evolution of the functional β-cell mass during the course of disease and in response to treatment.

3. Cellular mechanisms of β-cell mass regulation

The β-cell mass is governed by the maintenance of a constant balance between β-cell growth (replication from pre-existing β cells and neogenesis from precursor cells) and β-cell death (mainly apoptosis) (Fig. 2). Changes in individual cell size (hypertrophy or atrophy) also contribute to β-cell mass regulation [24,25]. Disruption of this balance can lead to rapid and marked changes in β-cell mass. The contribution made by each mechanism is variable, and depends on the stage of life, metabolic demands and animal species. Most of the data have emerged from studies of rodents, given the difficulty of obtaining pancreatic biopsies in humans.

Analysis of the regulatory parameters described above has shown that:

- there is growth of the β-cell mass throughout life;
- there is a continual cellular turnover governed by the renewal and loss of β cells [26].

A model of postnatal pancreatic β-cell growth in humans is now emerging from studies in both humans and rodents. Although some events at some stages are difficult to confirm in humans, it is thought to happen as follows. Cell differentiation gives rise to the initial β cells of an organism during early embryogenesis, and β-cell proliferation proceeds at a high rate during late embryogenesis [2], but begins to decline postnatally, while β-cell apoptosis occurs at very low rates [27]. There is a transient burst of β-cell replication just after birth, followed by a transitory rise in β-cell neogenesis [28]. In the later phase of this burst, there is a modest increase in apoptosis associated with substantial pancreatic remodelling [27].

Fig. 1. Endocrine pancreas plasticity: capacity to modulate functional β-cell mass to adapt insulin production to insulin demand. Under conditions of insulin resistance, there is an increase in functional β-cell mass. Defective plasticity leads to chronic hyperglycaemia.
The early burst in β-cell growth and minor apoptosis result in a marked increase in β-cell mass during the early years of life. Throughout childhood and adolescence, the rates of β-cell replication, neogenesis and apoptosis drop markedly. In adults, β-cell proliferation and apoptosis rates are very low so as to compensate for each other [28,29] and, as β-cell size stays relatively constant, an optimal β-cell mass can be maintained. It was suggested in mice that, postnatally, proliferation is the main process contributing to β-cell renewal rather than neogenesis [30]. During later adulthood, β-cell mass may decrease as apoptosis slightly outweighs β-cell growth [1].

Using genetically engineered mouse models with impaired postnatal β-cell proliferation, apoptosis and cell size, several molecular regulators have recently been implicated and identified in the postnatal β-cell mass, including: transcription factors such as Pdx1, Foxm1 and E2F; cell-cycle regulators such as cyclins and cyclin-dependent kinases; growth factors such as IGFs and cell-signalling proteins such as IRS and PKB/Akt; and many other factors thought to be involved in the regulation of β-cell growth [5].

In type 2 diabetic patients, both increased apoptosis and decreased proliferation may contribute to β-cell loss and a reduced β-cell mass (Fig. 2), although the precise mechanisms are yet to be fully elucidated. According to the glucolipotoxicity hypothesis, the deleterious effects of fatty acids (FA) on β cells (impairment of insulin secretion, impairment of insulin gene expression and induction of β-cell death) [31] may only occur in the presence of elevated glucose levels [32]. β Cells exposed to chronic hyperglycaemia generate excess levels of reactive oxygen species (ROS), leading to oxidative stress and β-cell dysfunction [33,34]. In the presence of excess glucose and FA levels, FA oxidation is inhibited and the esterification pathway activated, leading to cytosolic accumulation of lipid-derived signals such as ceramides and triglycerides, all of which are deleterious to β cells [35,36]. A variety of proapoptotic mechanisms, including endoplasmic reticulum (ER) stress, is also associated with the disease. In patients with type 2 diabetes, insulin resistance leads to prolonged stimulation of insulin biosynthesis. This means that such constant stimulation of the β cells may cause the physiological process—the biosynthesis of insulin—to change into a pathophysiological process: the demand exceeds...
the folding capacity of the ER and results in stress, caused by ER accumulation of misfolded or unfolded proteins, and leading finally to β-cell loss [37,38]. Under physiological conditions, ER stress can be elicited by the adaptive unfolded protein response (UPR) but, when ER stress is excessive or a defect is present in the UPR, the cells are unable to maintain ER homeostasis and undergo cell death. For these reasons, chronic ER stress in β cells can lead to β-cell dysfunction and death [37–39].

4. Incretins and β-cell mass

Glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the main incretins playing an insulinotropic role under physiological conditions. Besides its insulinotropic effect, GLP-1—through its Gs protein-coupled receptor—may also contribute to the regulation of β-cell mass. Indeed, the chronic effects of GLP-1 include enhanced β-cell survival, thus contributing to the long-term regulation of insulin secretion by maintaining a functional β-cell mass. Double incretin (GIP and GLP-1)-receptor knockout (DIRKO) mice, for example, have decreased islet numbers compared with their wild-type littermates [40]. Molecular mechanisms of the effects of GLP-1 on β-cell mass are still poorly understood. However, the data suggest the involvement of a protein kinase A (PKA)-dependent pathway. It has recently been shown that β-cell-specific G(s)-alpha subunit knockout (βGsKO) mice develop severe hyperglycaemia and glucose intolerance with severe hypoinsulinemia. In addition, βGsKO mice display a marked decrease in islet size and β-cell mass, due to reduced β-cell size and proliferation, and increased β-cell apoptosis [41]. The GLP-1 effect on β-cell survival has also been seen in in vitro studies. It has been demonstrated, for example, in human islets that GLP-1 exposure can prevent glucolipotoxicity [42]. In that study, the protective effect of GLP-1 was related to increased gene expression of antiapoptotic proteins (Bcl2, IAP-2). Moreover, involvement of both transcription factor NF-κB and protein kinase PKB–Akt was also observed [4].

Involvement of the PKA-dependent signalling pathway in response to GLP-1 is illustrated in Fig. 3. Briefly, in the absence of GLP-1, cAMP-response element-binding protein (CREB) is located within cytoplasm sequestered by transducer of regulated CREB activity-2 (TORC2) and 14-3-3 protein. Such interaction of TORC2–CREB–14-3-3 is only possible when TORC2 is phosphorylated by salt-inducible kinase-2 (SIK2). In the presence of GLP-1, production of cAMP leads to PKA activation. SIK2 is a PKA substrate, and its phosphorylation by PKA induces its inactivation (Fig. 3). Thus, in the presence of GLP-1, CREB is phosphorylated and activated by PKA, and TORC2 is released from 14-3-3 protein, allowing its interaction with phosphorylated CREB. The TORC2–CREB complex can then be translocated to the nucleus, where CREB interacts with cAMP response element (CRE) sequences, thus inducing transcription of the target genes involved in β-cell survival (Fig. 3). It must be pointed out that there is another, PKA-independent pathway involving cAMP-regulated guanine nucleotide exchange factor (cAMP-GEF), also called exchange protein activated by cAMP (EPAC). However, this pathway is implicated in exocytosis (especially its distal steps).

5. Development of incretin mimetic therapies

Only GLP-1, or its mimetics or enhancers, can be used for type 2 diabetic treatment because β cells are resistant to GIP action, partly due to the down regulation of its pancreatic receptors under diabetic conditions [43]. GLP-1 possesses properties that make it an ideal antidiabetic agent. In the pancreas, it stimulates glucose-dependent insulin secretion and inhibits glucagon secretion [44]. As described above, GLP-1 increases β-cell mass by activating β-cell proliferation and differentiation, and inhibiting β-cell apoptosis [45]. Furthermore, it has been shown that chronic exogenous administration of GLP-1 in humans promotes satiety and stimulates weight loss [46]. However, the use of the GLP-1 native peptide in clinical practice is hampered by its very short half-life (~1–2 minutes) in plasma due to its degradation by dipeptidyl peptidase-IV (DPP-IV). DPP-IV is a ubiquitously expressed serine protease that cleaves and inactivates polypeptides containing proline or alanine residues in their penultimate N-terminal position [47]. The enzyme is found in plasma, and on epithelial cells of the kidney, intestines, liver (bile duct) and pancreas, as well as on immune-cell leukocytes and capillary endothelial cells [48]. Two different strategies are cur-

![Fig. 3. Mechanisms of action of Glucagon-like peptide-1 (GLP-1) in the control of cell survival via the cAMP pathway. In the absence of cAMP, CREB interacts with TORC2 and 14-3-3 protein to form a complex with SIK2. In the presence of cAMP, PKA is activated, while SIK2 is phosphorylated and inactivated. TORC2 cannot be phosphorylated, and the complex formed with 14-3-3 is dissociated. CREB (phosphorylated by PKA) can be translocated to the nucleus where it plays a transcriptional role. PKA: protein kinase A; CREB: cAMP-response element-binding protein; TORC2: transducer of regulated CREB activity-2; SIK2: salt-inducible kinase-2.](image-url)
Table 1

<table>
<thead>
<tr>
<th>GLP-1 analogues</th>
<th>Trade name</th>
<th>Synonyms</th>
<th>Status</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Byetta®</td>
<td>AC-2993, Medisorb, Exendin-4, LY-2148568</td>
<td>Launched 2005</td>
<td>Amylin Pharmaceuticals</td>
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<td>Exenatide long-acting release, AC-2993 LAR</td>
<td>Phase III</td>
<td>Alkermes, Amylin Pharmaceuticals</td>
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<td>Liraglutide</td>
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<td>NN-2211, NNC-90-1170</td>
<td>Phase III</td>
<td>Novo Nordisk</td>
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<tr>
<td>DPP-IV inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sitagliptin phosphate</td>
<td>Januvia®</td>
<td>Gliclizide, MK-0431, MK-431, ONO-5435, Xelevia</td>
<td>Launched 2006</td>
<td>Merck &amp; Co</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Galvus®</td>
<td>LAF 237, LAF 237A, NVP</td>
<td>Launched 2007</td>
<td>Novartis</td>
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<tr>
<td>Sitagliptin + metformin</td>
<td>Janumet®</td>
<td>MK-0431 + metformin, MK-0431A, MK-431A</td>
<td>Launched 2007</td>
<td>Merck &amp; Co</td>
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<tr>
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<td>Eucreas®</td>
<td>SYR-322, Syrrx-1, SYR-110322, TAK-322</td>
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<tr>
<td>Saxagliptin + metformin</td>
<td></td>
<td></td>
<td>Phase III</td>
<td>Bristol-Myers Squibb</td>
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</tbody>
</table>

Currently used to improve the therapeutic efficacy of GLP-1 based therapies:

- the development of GLP-1 mimetics resistant to degradation by DPP-IV;
- the development of DPP-IV inhibitors.

Several GLP-1 analogues are undergoing human clinical trials or are already on the market (Table 1). Exenatide (Amylin Pharmaceuticals and Eli Lilly) was the first-in-class incretin mimetic to be approved by the US Food and Drug Administration (FDA) in April 2005 and by the European Medicines Evaluation Agency (EMEA) in November 2006. Exenatide is the synthetic peptide of exendin-4, a peptide isolated from the venom of the Gila Monster (*Heloderma suspectum*), which has a 53% sequence homology with human GLP-1. Amylin pharmaceuticals and Eli Lilly are also currently developing a long-lasting formulation of exenatide using Alkermes technology to encapsulate the peptide into polymer-based microspheres. When injected into the body, the microspheres degrade slowly to gradually release the drug at a controlled rate. This new formulation of exenatide, when administered subcutaneously once a week for 15 weeks to type 2 diabetes patients, induces a decrease of HbA1c (−1.4 ± 0.3% at the dose of 0.8 mg and −1.7 ± 0.3% at the dose of 2.0 mg), and of fasting and postprandial glycaemia [49]. Liraglutide (Novo Nordisk) is another promising GLP-1 analogue that is in the final stages of clinical development with a launch date in 2009. Liraglutide is a fatty acylated derivative of human GLP-1 that binds to serum albumin in a non-covalent manner, thus extending the half-life (to ~10–12 hour) of the molecule. Recently, liraglutide was shown to improve pancreatic β-cell function after 14 weeks of treatment in type 2 diabetic patients [50]. In particular, the first- and second-phases of insulin secretion were increased as well as arginine-stimulated insulin secretion during hyperglycaemia [50]. Adverse events related to GLP-1 analogues are generally associated with gastrointestinal side effects, including nausea and vomiting. However, a decrease in their frequency and severity is reported with continued therapy. More important, no cases of severe hypoglycaemia were observed with either exenatide or liraglutide [51].

DPP-IV inhibitors not only prolong and enhance the activity of endogenous GLP-1 but, as DPP-IV cleaves other substrates, they also have effects on, in particular, neuropeptides (PACAP, VIP, NPY, GHRP), intestinal peptides (GLP-2, PYY), and cytokines and chemokines [52]. These pleiotropic effects of the enzyme raise concerns especially in terms of the side effects that could emerge on inhibition of DPP-IV. However, in fact, DPP-IV inhibitors are well tolerated and appear to be safe. The few adverse events reported include an increased risk of infections (upper respiratory tract infections, sore throat) and headache [51]. DPP-IV inhibitors were proven to be efficacious in type 2 diabetic patients, in whom they act as postprandial stimulators of insulin secretion and regulators of blood glucose control. Several DPP-IV inhibitors are undergoing human clinical trials, and 2 are now on the market (Table 1). Sitagliptin (Merck & Co) was the first-in-class DPP-IV inhibitor approved by the FDA in
October 2006 and by the EMEA in January 2007. Vildagliptin (Novartis) was the second DPP-IV inhibitor to reach the market in 2007.

6. Conclusion

There is now a growing body of evidence that endocrine pancreatic plasticity is a key factor in regulating glucose homeostasis. Indeed, β-cell number needs to adapt to insulin demand—in particular, in the presence of insulinresistance that is either physiological, such as pregnancy, or pathophysiological, such as obesity. A decrease in functional β-cell mass may be the main event partly responsible for the chronic hyperglycaemia seen in diabetic patients. On the basis of both in vivo and in vitro data, it has been demonstrated that incretins are involved in the pancreatic β-cell mass by increasing cell survival. The development of drugs to regulate this parameter is the major research challenge of the coming years. It would also be of major interest to develop non-invasive imaging methods (such as PET, MRI) to study the longitudinal evolution of the β-cell mass in diabetic patients.

Conflict of interest

No conflict.

References


