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The International Journal of Biochemistry & Cell Biology 38 (2006) 726–736
IJBCB
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Review

Role of islet amyloid in type 2 diabetes mellitus

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Available online 17 January 2006

Abstract

Diabetes mellitus is one of the most common metabolic diseases worldwide and its prevalence is rapidly increasing. Due to its chronic nature (diabetes mellitus can be treated but as yet not cured) and its serious complications, it is one of the most expensive diseases with regard to total health care costs per patient. The elevated blood glucose levels in diabetes mellitus are caused by a defect in production and/or secretion of the polypeptide hormone insulin, which normally promotes glucose-uptake in cells. Insulin is produced by the pancreatic 'β-cells' in the 'islets of Langerhans', which lie distributed within the exocrine pancreatic tissue. In type 2 diabetes mellitus, the initial defect in the pathogenesis of the disease in most of the patients is believed to be 'insulin resistance'. Hyperglycemia (clinically overt diabetes mellitus) will not develop as long as the body is able to produce enough insulin to compensate for the reduced insulin action. When this compensation fails ('β-cell failure') blood glucose levels will become too high.

In this review, we discuss one of the mechanisms that have been implicated in the development of β-cell failure, i.e. amyloid formation in the pancreatic islets. This islet amyloid is a characteristic histopathological feature of type 2 diabetes mellitus and both in vitro and in vivo studies have revealed that its formation causes death of islet β-cells. Being a common pathogenic factor in an otherwise heterogeneous disease, islet amyloidosis is an attractive novel target for therapeutic intervention in type 2 diabetes mellitus.

Keywords: Type 2 diabetes mellitus; Insulin deficiency; β-Cell failure; Islet amyloid; Islet amyloid polypeptide

Contents

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doi:10.1016/j.biocel.2005.12.009

1. Introduction

Diabetes mellitus (DM) is characterized by inappropriately elevated glucose levels in the blood (hyperglycemia). It is one of the most common metabolic diseases worldwide, with an estimated 170 million patients in the year 2000, and its prevalence is rapidly increasing (Wild, Roglic, Green, Sicree, & King, 2004). It is a heterogeneous disease, both with respect to etiology, clinical presentation and therapeutic strategies. DM has many serious complications, including blindness, kidney failure and cardiovascular disease. In combination with its high and rapidly increasing prevalence, and its clinical complexity, the chronic nature of DM poses the society with a huge medical and socioeconomic problem (Pardes et al., 1999; Zimmet, 2003). In general two main types of DM are distinguished: In type 1 (DM1), previously also referred to as 'insulin-dependent DM' or IDDM, the insulin producing and secreting β-cells in the pancreatic islets of Langerhans (Fig. 1A) are destroyed by an auto-immune reaction of the body, leading to an insulin deficiency often already at a young age (Cnop et al., 2005). In type 2 (DM2), previously also referred to as 'non-insulin-dependent DM' or NIDDM, the initial defect in the pathogenesis of the disease in most of these patients is believed to be 'insulin resistance' (Stumvoll, Goldstein, & Van Haeften, 2005). This means that the target cells of insulin, notably muscle and liver, do not respond properly to the insulin, which initially is available even at elevated concentrations (to compensate for its reduced activity), hence the former name NIDDM. Thus, in early stages of DM2 development, basal blood glucose levels can still be normal due to an elevated insulin production and secretion (hyperinsulinemia). Apart from this elevated production of insulin, a defect in insulin action at this stage can become apparent by a 'glucose tolerance test' or GTT (Sorkin, Muller, Fleg, & Andres, 2005). If blood glucose levels at 2 h after a 75 g glucose administration are still above the basal level, this is referred to as 'impaired glucose tolerance' (IGT) or 'glucose intolerance' (Costa, Conget, & Gomis, 2002). At later stages of the disease, the compensatory increase in insulin production apparently cannot keep up with the increased insulin demand. This leads to a relative, rather than absolute, insulin shortage and a rise in basal blood glucose levels, i.e. hyperglycemia or 'overt DM'. The transition from IGT to overt DM2, as a consequence of relative insulin deficiency (in the context of insulin resistance) is referred to as 'β-cell decompensation' or 'β-cell failure' (Kahn, 1998; Larsson & Ahrén, 1996). Recent data indicate that during development of DM2, increased β-cell apoptosis is the main mechanism responsible for β-cell failure and the onset of hyperglycemia (Rhodes, 2005).

Contrary to DM1, DM2 clearly is an age-related disease, with the prevalence in the population increasing with age (Wild et al., 2004). The crucial role of insulin shortage in both DM1 (absolute insulin deficiency) and DM2 (relative insulin deficiency) is evident from the fact that both types of DM can be treated with administration of exogenous insulin. Therefore it is appropriate that the name DM2 should be preferred instead of NIDDM when referring to this type of the disease.

2. Pathogenic factors for DM2: insulin resistance

DM2 is a heterogeneous disease, involving both genetic and environmental factors. Probably there is not one major DM2 gene which is responsible for this disease in the majority of the patients. An exception is MODY (Maturity Onset Diabetes of the Young), for which several predisposing genes have been identified in affected families (Barroso, 2005; Tsakiris & Ioannou, 2004). Within these families, the mutated MODY gene appears to be the prime determinant for disease development by impairing insulin production.

In the vast majority of 'common' DM2 patients, the disease seems to be the result of a combination of several, different genetic determinants (that may affect insulin production and/or insulin sensitivity) and environmental factors, notably excess food intake and a sedentary lifestyle (lack of physical exercise), which promote development of insulin resistance (Stumvoll et al., 2005).

Apart from man, DM2 is also known in mammals such as monkey (Wagner et al., 2001) and cat (O'Brien, 2002). Also in the most common laboratory mammals, mouse and rat, DM2 can occur, although specifically in specific strains of these species, carrying a genetic defect (Kim, Nishina, & Naggert, 1998). In all of these five species of mammals, DM2 is associated with obesity. This may not sound surprising considering the well-known association between obesity and insulin resistance (Roth, Qiang, Marban, Redelt, & Lowell, 2004). Approximately one-third of obese people develop DM2 and on the other hand the majority of DM2 patients are obese. However, the molecular mechanisms underlying the association between obesity and DM2 turned out to be more complex than initially thought. The main mediators of obesity-related insulin resistance, notably in skeletal muscle and liver, were thought to be high concentrations of free fatty acids. However, in the past few years it has become evident that adipocytes are also endocrine cells, secreting a number of hormones which can influence insulin sensitivity, such as resistin (Wolf,

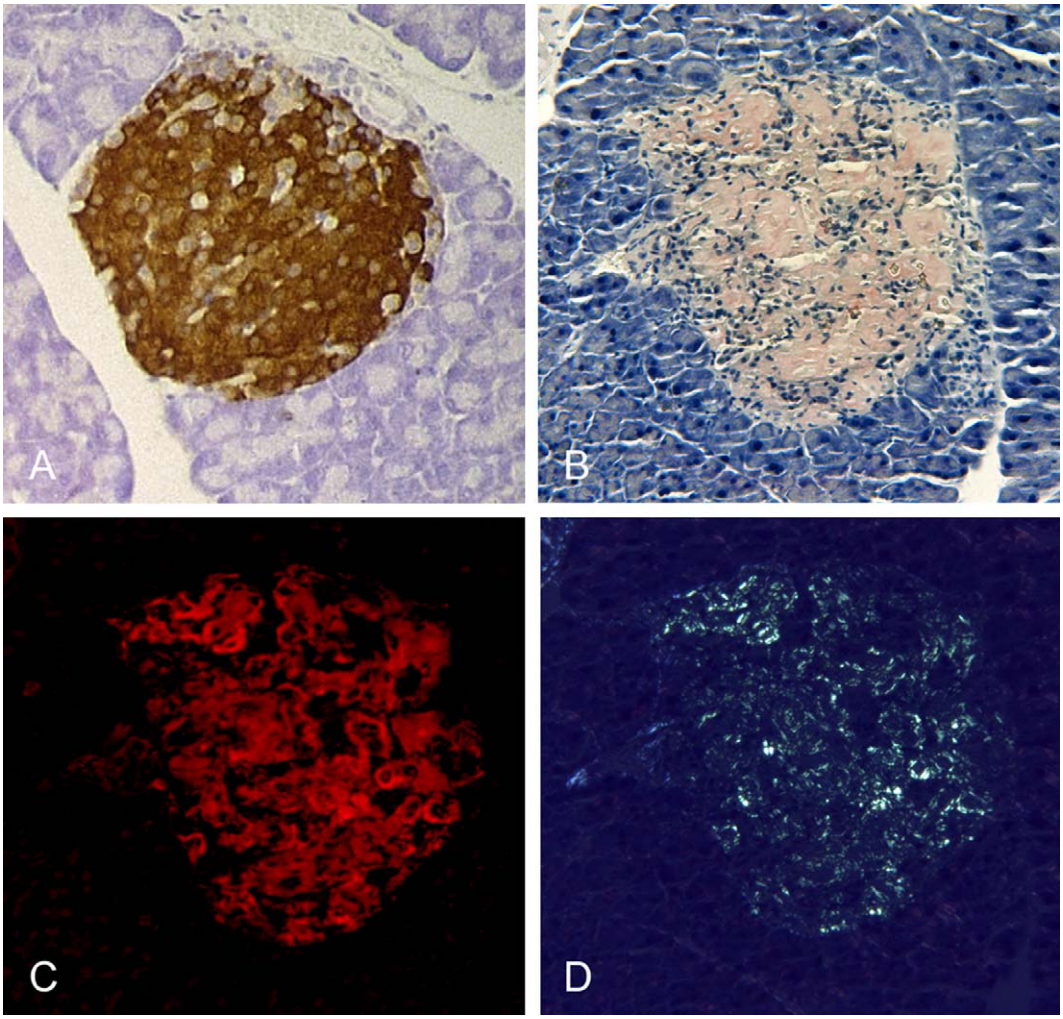

Fig. 1. Microscopic sections of mouse pancreatic tissue, including an islet of Langerhans. (A) Using an immunohistochemical staining with an antiserum raised against insulin, the insulin-producing β-cells in this healthy islet of a non-transgenic mouse are clearly visible (brown staining) amongst the exocrine tissue (purple counterstaining). (B) Using the amyloid-specific dye Congo red, the presence of amyloid can easily be detected in this islet of a hIAPP transgenic mouse. Using brightfield light microscopy, the Congo red stained amyloid is visible as pink deposits. In this severely affected islet, the β-cell mass is largely reduced. (C) Due to autofluorescence of amyloid-bound Congo red, the amyloid can be visualized even better with fluorescence microscopy (bright red colour). (D) Using polarized light microscopy, the amyloid is identified by birefringence of the Congo red stained material (greenish colour). B–D represent images obtained from the same pancreatic islet section.

2004) and adiponectin (Weyer et al., 2001). In the ob/ob mouse strain, it is the genetically determined absence of leptin (another adipocyte-derived hormone which acts as a satiety factor in the brian) which causes hyperphagia, obesity, insulin resistance and DM2 (Murphy et al., 1997). In humans however, a causative role of leptin in common DM2 development is less evident.

3. Pathogenic factors for DM2: β-cell failure

The ob/ob mice beautifully demonstrate that even in the presence of severe insulin resistance, hyperglycemia can be reverted to normoglycemia by (strongly) elevated insulin production (Höppener et al., 1999), in accordance with the previously mentioned notion that hyperglycemia does not develop until insulin production fails to compensate for insulin resistance.

The molecular mechanism(s) of this β-cell failure are not yet firmly established. Total β-cell mass is the resultant of individual β-cell size, proliferation of existing β-cells, neogenesis of new β-cells from pancreatic ductal precursor cells and β-cell apoptosis. Obviously the first three processes can cause an increase in β-cell mass, whereas apoptosis leads to loss of β-cells. By now

there are several indications that β-cell failure in DM2 development is mainly caused by an increased apoptosis, rather than a decreased proliferation or decreased neogenesis of β-cells (Rhodes, 2005).

In general, aberrant adipose tissue functioning is considered a link between obesity and DM2 by promoting the development of lipotoxicity, i.e. cell damage as a consequence of elevated intracellular lipid concentrations, in peripheral tissues (Lelliott & Vidal-Puig, 2004), However, approximately 20% of human patients with DM2 is lean, making lipotoxicity less likely to be the primary cause of β-cell failure, at least in such patients. In addition, hyperglycemia and thus β-cell failure are reverted in older ob/ob mice, despite the sustained presence of obesity (Höppener et al., 1999). Also, not all obese and insulin resistant people develop DM2. Although these findings may argue against lipotoxicity as a general, primary factor causing β-cell failure, lipotoxicity may well be involved in progression of β-cell failure (Schaffer, 2003).

Glucose-toxicity, i.e. β-cell damage as a consequence of elevated glucose concentrations, is another candidate for causing β-cell failure (Kaiser, Leibowitz, & Nesher, 2003). This effect may be mediated by, e.g. increased glycosylation of substances (so-called 'advanced glycosylation endproducts', or AGEs) and oxidative stress causing cell damage and ultimately cell death (Robertson, 2004). In patients with overt DM, hyperglycemia is likely to contribute to impaired β-cell function. In particular the combination of both high glucose and high fatty acid levels seems to cause β-cell abnormalities, and this is referred to as gluco-lipotoxicity (Buteau et al., 2004; Prentki, Joly, El-Assaad, & Roduit, 2002). However, increased β-cell death by apoptosis was recently shown to be present already in individuals with IGT, apart from those with DM2 (Butler et al., 2003a). Thus it seems unlikely that glucose-toxicity is the primary trigger of β-cell failure, initiating the transition from IGT to hyperglycemia during the development of DM2.

What else could there be? We believe that an important clue was provided by a pathologist from Johns Hopkins Medical Institutions in Baltimore, who described hyaline degeneration in the pancreatic islets of Langerhans of patients with diabetes (Opie, 1901).

4. Islet amyloid

Already in 1901, Eugene Opie suspected a relation between this phenomenon of islet hyalinisation and diabetes, not yet knowing that the pancreatic islets are the source of insulin, which was not discovered until 1922

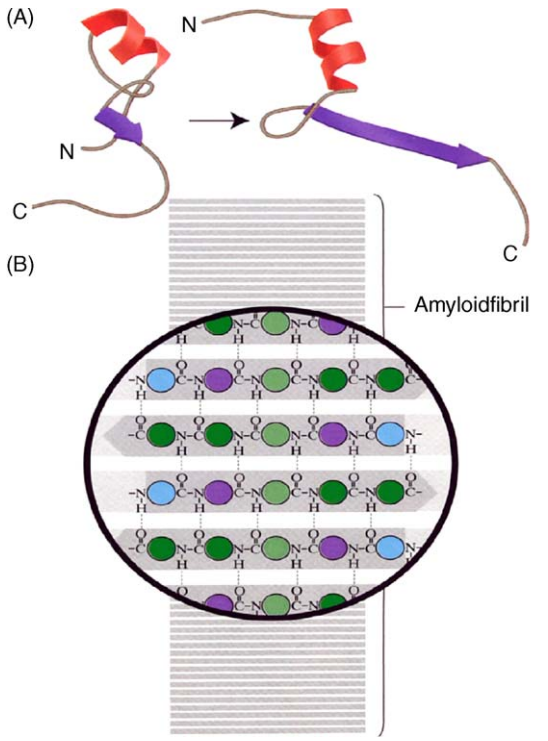

Fig. 2. Schematic illustration of fibril formation from an amyloidogenic protein molecule. (A) The constituent molecule of an amyloid fibril undergoes a conformational change, enabling it to participate in fibrillogenesis: in 'amyloidogenic circumstances' there is an increase in β-pleated sheet structure (blue, red is α-helix). (B) Intermolecular aggregation occurs through stacking of the molecules via H-bridges between the amino acids (coloured circles) in the β-pleated sheet. In this process, the constituent molecules may be oriented in an anti-parallel fashion, as indicated here (reprinted from Höppener, Nieuwenhuis, Vroom, & Lips, 2000b, with kind permission of the publisher), or in a parallel fashion, possibly depending on the amphiphilicity of the constituent molecules (Gordon, Balbach, Tycko, & Meredith, 2004; Jayasinghe & Langen, 2004).

(Rosenfeld, 2002). Initially this extracellular, hyaline material (Fig. 1B) was thought to be composed of carbohydrates, because it could be stained histochemically with dyes which stain starch. Hence the name 'amyloid', meaning 'starch-like', which was given to this material at that time (Virchow, 1854). However, later on it became apparent that this amyloid mainly involves proteinaceous deposits, which also contain heparan sulfate proteoglycans (Ancsin, 2003). In addition it was shown that amyloid has a characteristic ultrastructure: it is composed of fibrils in which the constituent protein molecules are stacked onto one another due to hydrogen bonds between regions of the molecules which have adopted a 'β-pleated sheet' structure (Booth et al., 1997; Glenner, 1980) (Fig. 2).

Amyloidosis occurs in several diseases and is associated with malfunction of the organ in which it takes place (Gillmore, Hawkins, & Pepys, 1997). Localized amyloid formation, i.e. amyloidosis in one particular organ, is associated with aging and age-related diseases. The two best-known and most prevalent of these are DM2 and Alzheimer's disease. In autopsy studies, amyloid in the pancreatic islets ('islet amyloid') has been detected in 50–90% of patients with DM2 (the actual percentage also depending on the ethnic groups investigated) and at (much) lower frequencies in non-diabetic age-matched controls (Westermark, 1994; Zhao et al., 2003). Also in monkeys (O'Brien et al., 1996) and cats (Rand, 1999) with DM2, islet amyloid has been described, but not in mice or rats.

5. Islet amyloid polypeptide

In 1986, Per Westermark, again a pathologist, published part of the amino acid sequence of the major constituent protein purified from islet amyloid deposits of the cat (Westermark, Wernstedt, Wilander, & Sletten, 1986). In 1987 he published the complete amino acid sequence of the corresponding human peptide and named it "islet amyloid polypeptide" or IAPP (Westermark et al., 1987). Independently, Cooper et al. purified and identified a similar peptide which they published in 1987 and which they named "Amylin" (Cooper et al., 1987). Both names are still used in the scientific literature, but it is evident that they refer to one and the same peptide of 37 amino acids, encoded by a single-copy gene localized on human chromosome 12 (Mosselman et al., 1988). For the remainder of this paper we will use the name IAPP, because it was introduced by the investigators who first identified this peptide.

It turned out that the amino acid sequence of IAPP in a particular animal species is an important, though not sufficient, requirement for islet amyloidosis (Westermark, Engström, Johnson, Westermark, & Betsholtz, 1990) (Fig. 3). Additional factors, e.g. overproduction, apparently are involved. Mouse and rat IAPP cannot form a 'β-pleated sheet' structure and amyloid fibrils, whereas human, monkey, feline and canine IAPP can do both. In the dog, IAPP amyloid has been described in insulinomas (islet β-cell tumours) (Jordan et al., 1990; O'Brien, Westermark, & Johnson, 1990), but not (yet) in diabetic animals. However, unlike the situation in cats, DM in dogs is mostly DM1 and this type of diabetes mellitus is not associated with islet amyloid formation.

Expression of the IAPP gene occurs almost exclusively in the pancreatic islet β-cells (Leffert, Newgard, Okamoto, Milburn, & Luskey, 1989; Rotondo et al., 2003). Thus, the same cells which produce insulin also produce the building block of islet amyloid fibrils. In fact, IAPP and insulin are co-secreted from the same β-cell granules and the production of these two β-cell specific hormones is co-regulated due to common, β-cell specific regulatory elements in the promotor regions of the encoding genes (Cluck, Chan, & Adrian, 2005; German, Moss, Wang, & Rutter, 1992).

	1	20	29	37
Man	KCNTATCATQRLANFLVHS	***SNNFGAILSS***	TNVGSNTY	
Monkey	----------R-----T----	-----	----D--	
Cat	----------IR---L-----	P	--------	
Dog	----------RT---L-----	P	--------	
Mouse	----------R---L-PV-PP		--------	
Rat	----------R---L-PV-PP		--------	

Fig. 3. Amino acid sequence (in single-letter code) of IAPP in several mammals. In particular the region of amino acids 20–29 (italic/bold) is important for the ability of the peptide to form amyloid fibrils via β-pleated sheet mediated hydrogen bonds. Dashes indicate amino acid residues which are identical to the corresponding human residue at that position. Differences with the human sequence are indicated. The amino acid sequences of IAPP from the different species were identified by Westermark et al. (1987) (human), O'Brien et al. (1996) (monkey), Nishi, Chan, Nagamatsu, Bell, and Steiner (1989) (cat), Jordan et al. (1990) (dog), and Betsholtz et al. (1989) (mouse and rat).

6. IAPP, islet amyloid and DM2

As a consequence of their co-regulation, increased insulin requirement as in states of insulin resistance, will lead to increased production of both insulin and IAPP (Gulli, Rossetti, & DeFronzo, 1997; Ludvik, Kautzky Willer, Prager, Thomaseth, & Pacini, 1997). High concentrations of amyloidogenic proteins promote their aggregation and fibril formation and thus insulin resistance is prone to promote islet amyloidosis from IAPP. Many in vitro studies have shown that IAPP fibril formation can cause death of β-cells by inducing apoptosis (e.g. Zhang, Liu, Dragunow, & Cooper, 2003). Already in 1994 it was shown that amyloidogenic human IAPP (hIAPP) is cytotoxic when added to islet cells in vitro (Lorenzo, Razzabon, Weir, & Yankner, 1994), indicating that amyloid formation may directly kill cells. However, more recent studies have provided strong support for the notion that it is the process of amyloid fibril formation, rather than the mature amyloid fibril itself, which is the most cytotoxic (e.g. Butler, Janson, Soeller, & Butler, 2003b). In particular, it are the prefibrillar aggregates (soluble oligomers) of amyloidogenic peptides which are considered most detrimental to cell viability (Kayed et al., 2003). The mechanism of hIAPP cytotoxicity may involve membrane destabi-

lization (Janson, Ashley, Harrison, McIntyre, & Butler, 1999; Kayed et al., 2004), formation of aspecific ion channels or 'amyloid pores' (Caughey & Lansbury, 2003; Mirzabekov, Lin, & Kagan, 1996) and/or oxidative stress (Janciauskiene & Ahrén, 2000). Similar results have been obtained for other amyloidogenic peptides, such as the Alzheimer's Aβ peptide (Selkoe, 2000) and the prion protein involved in Creutzfeldt Jakob disease and in its bovine equivalent 'mad cow disease' (BSE: bovine spongiform encephalopathy) (Liberski, Sikorska, Bratosiewicz-Wasik, Gajdusek, & Brown, 2004) indicating that there may be (a) common mechanism(s) for amyloid associated cell death (Bucciantini et al., 2002).

A β-cell damaging effect of IAPP fibril formation in vivo would certainly support a pathogenic role of islet amyloidosis in development of β-cell failure in DM2.

7. Islet amyloid and DM2: cause or consequence?

The role of islet amyloid formation in the pathogenesis of DM2 has been an issue of discussion among diabetologists for a long time. In particular the question has been: "Is islet amyloidosis a cause of DM2 (i.e. a pathogenic factor by itself) or rather a consequence of this disease (i.e. an epiphenomenon)". The finding that islet amyloid can be detected in those species which 'spontaneously' develop DM2, i.e. man, monkey and cat, but not in species which do not, may indicate a role of these deposits in development of the disease. In addition, longitudinal studies in monkeys have shown that during development of DM2, the degree of islet amyloidosis strongly correlated with reduced β-cell mass (De Koning, Bodkin, Hansen, & Clark, 1993) (Fig. 4). However, such descriptive studies can merely assess an association between two factors. To prove an actual causal relation, experimental studies were required. A major breakthrough which has enabled the design of such experiments, providing an answer to the "cause or consequence" question, has been the identification of IAPP as the building block of islet amyloid.

In order to investigate the role of hIAPP and islet amyloidosis in the pathogenesis of DM2 in vivo, we and others have generated transgenic mice that have incorporated the hIAPP gene in their chromosomal DNA and thus can transmit it to their offspring. Due to the presence of an insulin promoter in front of the hIAPP gene, the transgene is expressed in the islet β-cells of these mice and thus these cells endogenously produce and secrete hIAPP (Höppener et al., 1993). Subsequently, several groups have demonstrated that hIAPP transgenic mice can develop islet amyloid and hyperglycemia (Janson et al., 1996; Verchere et al., 1996). Using our hIAPP transgenic mouse model, cross-bred with the ob/ob mouse, we demonstrated in vivo that insulin resistance induces hIAPP overproduction and promotes islet amyloidosis (Höppener et al., 1999) (Fig. 5). Similar results were independently obtained with another hIAPP transgenic mouse model, cross-bred with another insulin resistant mouse strain, the Agouti^{vy} mouse (Soeller et al., 1998). In addition we have shown that the degree of islet amyloidosis was related to reduced insulin production and worsening of the diabetes (expressed as ratio of plasma glucose:insulin) (Höppener et al., 1999). Since presence and expression of the hIAPP gene was the only difference between the hIAPP mice and their non-transgenic littermates, these in vivo experiments have unequivocally proven that, at least in these mice, hIAPP-related islet amyloidosis is a pathogenic factor and not merely an epiphenomenon during the development of DM2. In addition, these experiments have shown that islet amyloidosis is first consequence (of insulin resistance) and later on cause (of relative insulin deficiency) of

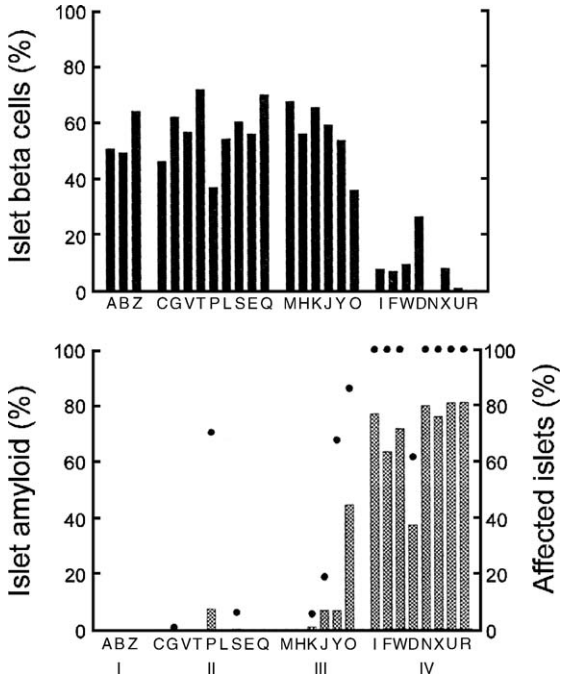

Fig. 4. Reduced islet β-cell mass associated with islet amyloid in type 2 diabetic monkeys (*Macaca mulatta*). Top panel, average islet content occupied by β-cells; bottom panel, average islet content occupied by amyloid (bars) as well as percentage of amyloid-containing islets (dots), in each of the 26 animals investigated. Group I: normoglycemic, normoinsulinemic, younger than 10 years. Group II: normoglycemic, normoinsulinemic, older than 10 years. Group III: normoglycemic, hyperinsulinemic. Group IV: diabetic (reprinted from De Koning et al., 1993, with kind permission of Springer Science and Business Media).

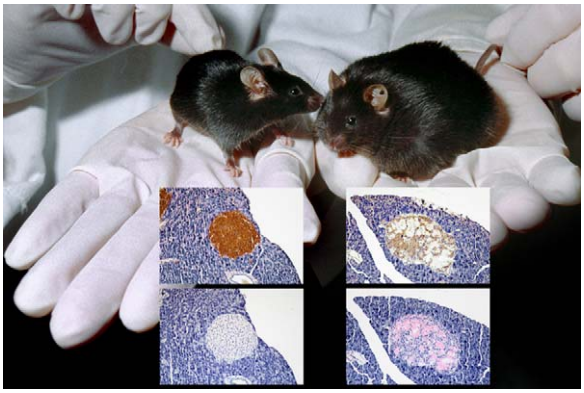

Fig. 5. Human IAPP ob/ob mouse as an in vivo model for islet amyloidosis. When hIAPP-producing transgenic mice are cross-bred to leptin-deficient ob/ob mice, obesity develops (left, hIAPP transgenic mouse; right, hIAPP transgenic ob/ob mouse). This is associated with insulin resistance, IAPP overproduction and pancreatic islet amyloidosis. The degree of amyloid formation correlated with reduced insulin production and severity of the diabetes. Upper panels, brown staining is insulin immunoreactivity; lower panels, pink staining is Congo red positive amyloid (reprinted with kind permission from Scan 3/00, 2-monthly publication from the University Medical Center Utrecht, Utrecht, The Netherlands).

DM2 (Höppener, Nieuwenhuis, Vroom, Ahrén, & Lips, 2002).

8. Mechanisms involved in islet amyloid formation

The notion that islet amyloidosis is not a direct consequence of hyperglycemia per se, but rather of IAPP overproduction, as indicated by transgenic mouse studies, is also supported by recent findings in a rat model transgenic for human IAPP. Also in these animals, as in hIAPP transgenic mice, islet amyloid is present already at a young age, when blood glucose levels are still normal (Butler et al., 2004). In addition, hIAPP-derived amyloid is present in approximately 50% of insulinomas (insulin-overproducing islet β-cell tumours which often also overproduce IAPP), thus in patients who are hypoglycemic rather than hyperglycemic (Van Hulst et al., 1999).

Most obese, insulin resistant people do not develop DM2, despite elevated insulin and IAPP levels (Enoki et al., 1992; Gulli et al., 1997). This indicates that although IAPP overproduction is an important factor in islet amyloidosis, other factors are likely to be involved as well. There are several indications, both from immunohistochemical studies (Westermark, Steiner, Gebre-Medhin, Engstrom, & Westermark, 2000) and from experimental studies (Paulsson & Westermark, 2005) that (impaired) proteolytic processing of the hIAPP precursor (pre-proIAPP) may be involved. In addition, the N-terminal region of proIAPP has been shown to contain a binding site for proamyloidogenic heparin sulfate, which is lost during normal processing of proIAPP to generate the mature 37 amino acids peptide (Park & Verchere, 2001). Both proIAPP and proinsulin are cleaved by the same proteolytic enzymes (Higham et al., 2000; Marzban et al., 2004; Wang et al., 2001) and proinsulin:insulin ratios are increased in diabetes (Ahrén, 2005). This indicates that a more general, diabetes-related β-cell defect in protein folding, processing and/or intracellular trafficking (Marzban, Trigo-Gonzalez, & Verchere, 2005) may be involved in islet amyloid formation.

9. Anti-amyloid therapy

As described above, studies in both hIAPP transgenic mice (Butler et al., 2003b; Höppener et al., 1999; Soeller et al., 1998), hIAPP transgenic rats (Butler et al., 2004) and with human autopsy material (Butler et al., 2003a) have directly shown that islet amyloidosis is associated with increased β-cell apoptosis and reduced β-cell mass. These findings support an important role of islet amyloid formation in development of β-cell failure and ultimately hyperglycemia in DM2. Being a common pathogenic factor in an otherwise heterogeneous disease, islet amyloid is an attractive target for development of novel therapeutic strategies for DM2, as discussed previously (Höppener, Ahrén, & Lips, 2000a). Until such therapy is available to directly prevent or neutralize islet amyloid fibril formation, beneficial effects are likely to be obtained by reducing the production of its building block, IAPP. This notion is supported by experiments with cats, which showed that the degree of islet amyloidosis could be reduced by exogenous insulin administration, thus reducing the degree of endogenous insulin and IAPP production (Hoenig et al., 2000). Similar effects are likely to be obtained by dietary influences on insulin requirement. Indeed, it has been shown in hIAPP transgenic mice that a high fat diet promotes islet amyloidosis and worsens glucose homeostasis (Hull et al., 2003; Verchere et al., 1996; Höppener et al., unpublished results). Consequently, a diet which reduces insulin requirement, and thus also IAPP production, would be expected to have beneficial effects with respect to islet amyloidosis, β-cell failure and development of DM2. In accordance with this notion, it was recently shown that long-term treatment of hIAPP transgenic mice with the thiazolidinedione rosiglitazone and metformin (both drugs improve insulin sensitivity and thereby reduce β-cell secretory demand), reduced islet amyloid formation (Hull et al., 2005). Also other experimental and clinical studies indi-

cate that thiazolidinediones can prevent or delay β-cell failure in DM2 (Walter & Lubben, 2005). If reduction of hIAPP production is not feasible, harmful effects on islet β-cells and insulin-producing capacity might be prevented by preventing aggregation and fibril formation from this amyloidogenic protein, e.g. by the use of β-sheet blockers (Rijkers, Höppener, Posthuma, Lips, & Liskamp, 2002), heparin sulfate proteoglycan derivatives (Kisilevsky et al., 2003), serum amyloid P (SAP) inhibitors (Pepys et al., 2002) or vaccination strategies (Janus et al., 2000; Morgan et al., 2000).

Acknowledgements

The work described in this paper was supported in part by the Dutch Organization for Scientific Research (NWO), the Dutch Diabetes Research Fund (DFN), the Royal Dutch Academy of Sciences (KNAW) and University Medical Center Utrecht, The Netherlands.

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