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Mini-Review

Islet amyloid polypeptide and type 2 diabetes

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Abstract

Type 2 diabetes is associated with progressive β-cell failure manifest as a decline in insulin secretion and increasing hyperglycemia. A growing body of evidence suggests that β-cell failure in type 2 diabetes correlates with the formation of pancreatic islet amyloid deposits, indicating that islet amyloid may have an important role in β-cell loss in this disease. Islet amyloid polypeptide (IAPP; amylin), the major component of islet amyloid, is co-secreted with insulin from β-cells. In type 2 diabetes, this peptide aggregates to form amyloid fibrils that are toxic to β-cells. The mechanism(s) responsible for islet amyloid formation in type 2 diabetes is still unclear but it appears that an increase in the secretion of IAPP, per se, is not sufficient. Other factors, such as impairment in the processing of proIAPP, the IAPP precursor, have been proposed to contribute to the development of islet amyloid deposits. Inhibitors of islet amyloid fibril formation might prevent the progression to β-cell failure in type 2 diabetes and should therefore be considered as a therapeutic approach to treat this disease.
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1. Islet amyloid

Islet amyloid deposits are a characteristic pathologic feature of the pancreas in type 2 diabetes (Kahn et al., 1999). Although islet amyloid was first described as a hyaline substance in diabetic pancreas by Eugene Opie a century ago, its potential importance in type 2 diabetes has gained attention only recently. In 1987, Westermark and Cooper led separate groups that identified the major component of islet amyloid as a 37 amino acid peptide and named it islet amyloid polypeptide (IAPP) (Westermark et al., 1987) or amylin (Cooper et al., 1987), two terms that are used interchangeably today. IAPP is a neuroendocrine peptide hormone that is produced and co-secreted along with insulin from the pancreatic β-cells (Kahn et al., 1990). This peptide belongs to a family of structurally related peptides that includes calcitonin, calcitonin gene-related peptide and adrenomedullin. In type 2 diabetes, IAPP aggregates to form fibrils that are thought to be toxic to β-cells. IAPP-containing amyloid deposits are also found in insulinomas (Westermark et al., 1987) and form rapidly in cultured (de Koning et al., 1994) and transplanted islets (Westermark et al., 1995). Other pathologic conditions associated with localized amyloid formation include Alzheimer's disease and medullary thyroid carcinoma (Kahn et al., 1999).

2. Biological role of IAPP

IAPP is co-localized with insulin in the islet β-cells and is co-secreted with insulin in response to β-cell stimulation by both glucose and non-glucose secretagogues (Kahn et al., 1990). In healthy people, plasma IAPP concentrations generally range between 4 pmol/l (fasting) and 25 pmol/l (postprandial) (Young, 1997). The physiological function(s) of IAPP is still not completely understood but proposed biological actions of IAPP include suppression of food intake, gastric emptying, and arginine-stimulated glucagon secretion from pancreatic α-cells. Supraphysiological concentrations of IAPP have been shown to have inhibitory effects on both insulin secretion and action but the physiological relevance of those findings has been questioned (Gebre-Medhin et al., 2000). Recently, it was

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shown that mice lacking IAPP do not have a remarkable phenotype, although they have modestly enhanced glucose-induced insulin secretion and glucose clearance compared to wild-type mice (Gebre-Medhin et al., 1998), suggesting that IAPP may have a role in carbohydrate metabolism.

High affinity IAPP binding sites have been identified in different regions of the brain, including the *area postrema*, *nucleus accumbens* and *dorsal raphe* (Sexton et al., 1994). Although an IAPP receptor has not been unequivocally identified, IAPP is thought to act via either the calcitonin receptor-like receptor or the calcitonin receptor, two members of the G-protein-coupled receptor family whose ligand affinity is determined by co-expression of receptor activity modifying proteins (RAMPs) (Zumpe et al., 2000).

3. Islet amyloid and type 2 diabetes

Type 2 (non-insulin dependent) diabetes mellitus is a chronic metabolic disease, which occurs with increasing frequency in aged individuals and is characterized by fasting hyperglycemia that worsens as the disease progresses. Type 2 diabetes is thought to arise from genetic and/or acquired defects in both insulin action at insulin sensitive tissues and insulin secretion from islet β-cells. Data from the UK Prospective Diabetes Study (UKPDS) have shown that an almost inevitable progressive β-cell failure occurs despite the use of various therapies aimed at ameliorating hyperglycemia (Turner et al., 1996). Because of the loss of β-cell function, a significant proportion of patients with type 2 diabetes eventually require insulin therapy. Several mechanisms may contribute to the progressive β-cell failure in type 2 diabetes including loss of β-cell mass, β-cell exhaustion and the cytotoxic effects of elevated glucose and lipid levels. A growing body of evidence suggests that islet amyloid deposits may play an important role in the loss of β-cells and the progressive decline in insulin secretion characteristic of type 2 diabetes. First, islet amyloid is found in up to 90% of patients with type 2 diabetes at autopsy (Kahn et al., 1999) and the degree of amyloid deposition correlates with severity of the disease in humans (Westermark, 1994). Second, islet amyloid formation is associated with reduced β-cell mass in both diabetic human (Clark et al., 1988) and non-human primates (de Koning et al., 1993). Third, it has been shown that the lesion precedes the onset of hyperglycemia in monkeys (de Koning et al., 1993). Taken together, these findings suggest a close relationship between islet amyloid deposition and the development and progression of type 2 diabetes.

4. Islet amyloid and β-cell toxicity

Several in vitro studies have demonstrated that both intracellular and extracellular accumulation of human IAPP is associated with β-cell death, although the mechanisms are likely different. Overexpression of amyloidogenic human (but not non-amyloidogenic rat) IAPP has been shown to induce apoptosis in COS-1 cells (Hiddinga and Eberhardt, 1999). Furthermore, exposure to human IAPP fibrils induces death of both human and rat islet β-cells in vitro (Lorenzo et al., 1994). Moreover, synthetic human IAPP that spontaneously aggregates into fibrils in vitro is toxic to β-cells, whereas synthetic rodent IAPP that does not form fibrils is not toxic to β-cells (Lorenzo et al., 1994; Hiddinga and Eberhardt, 1999). Thus, only the aggregated (fibrillar) form of IAPP kills β-cells, whereas the soluble form of the peptide is not toxic. The same appears to be true of the β-amyloid protein, the major constituent of amyloid plaques found in Alzheimer's disease: only the fibrillar form of the peptide is toxic and is capable of killing neurons (Lorenzo et al., 1994). The mechanisms by which IAPP fibrils induce β-cell apoptosis are still not well understood but the finding that islet amyloid fibrils lie in close proximity to the external cell surface of β-cells in vivo (Verchere et al., 1996) and that extracellular accumulation of this peptide is associated with β-cell death, support the idea that islet amyloid might induce β-cell apoptosis via interaction of amyloid fibrils (or protofibrils) with the β-cell membrane and subsequent activation of specific intracellular caspases, the primary intracellular mediators of apoptosis (Xu J., Kennedy M., Verchere C.B., unpublished data). It has been shown that cytotoxic human (but not non-cytotoxic rat) IAPP fibrils cause formation of ion-permeable pores in lipid bilayer membranes, which could disrupt ionic homeostasis across the cell membrane and potentially induce apoptotic cell death (Mirzabekov et al., 1996; Anguiano et al., 2002).

5. Processing and secretion of proIAPP

IAPP is synthesized primarily by β-cells as a 67-amino acid precursor, proIAPP, that is processed to IAPP within β-cell secretory granules (Kahn et al., 1999) by the action of prohormone convertase enzymes PC2 and PC3 (also known as PC1) (Wang et al., 2001). As with proinsulin, normal processing of proIAPP depends on the cleavage at two well-conserved dibasic sites: $Lys^{10}–Arg^{11}$ at the (amino) NH_2-terminus and $Lys^{50}–Arg^{51}$ at the (carboxy) COOH-terminus (in humans). Based on studies in mice lacking PC2, we have proposed that cleavage of proIAPP at its NH_2- and COOH-terminal cleavage sites is mediated by PC2 and PC3, respectively (Wang et al., 2001). Mature IAPP is secreted from β-cells along with insulin, in a molar ratio (IAPP: insulin) of approximately 1:100 (Kahn et al., 1990). Insulin and IAPP secretion tend to change in parallel. Following a glucose challenge, plasma IAPP levels rise along with those of insulin (Kahn et al., 1998). In obese persons, both IAPP and insulin secretion are increased, while in type 2 diabetes and normal aging both tend to decline (Kahn et al., 1998, 1999). Prolonged exposure to high glucose concentrations

has been shown to increase the cellular content of IAPP precursors in human and rat β-cells (Hou et al., 1999).

6. Possible mechanisms for islet amyloid formation

IAPP is the major, but not the sole, component of islet amyloid and these localized deposits contain a variety of other products including serum amyloid P component (SAP), apolipoprotein (apo) E, and the heparan sulfate proteoglycan perlecan (Kahn et al., 1999). Although the role of these components in islet amyloid formation is not completely understood, the finding that these molecules are also present in other types of amyloid deposits (e.g. senile plaques in Alzheimer's disease) suggests that similar mechanisms might underlie amyloid formation in different pathologic states. While the forms of IAPP found in humans and non-human primates are inherently amyloidogenic, rodent IAPP does not appear to be capable of forming amyloid in vitro (Westermark et al., 1990; Kahn et al., 1999). Accordingly, islet amyloid is not found in diabetic rodents. The presence of an amyloidogenic region in the mid-portion of the human IAPP (amino acid positions (24–28) (GAILS) has been shown to be necessary for fibril formation (Westermark et al., 1990; Kahn et al., 1999), whereas three proline substitutions in the mid-portion of rodent IAPP makes this molecule soluble (Jaikaran et al., 2001). Recent findings suggest that the NH_2- and COOH-terminal regions of IAPP, which are well conserved among mammals including rodents, may also contain fibrillogenic regions, specifically amino acids 8–20 (Jaikaran et al., 2001) and amino acids 30–37 (Nilsson and Raleigh, 1999).

Several mechanisms have been proposed for islet amyloid fibril formation in type 2 diabetes. One widely accepted mechanism is that in type 2 diabetes, increased production and secretion of IAPP associated with increased demand for insulin might result in accumulation and aggregation of IAPP. The finding that non-diabetic obese and/or insulin resistant subjects with elevated IAPP production rarely develop islet amyloid (Kahn et al., 1999) speaks against the idea that a simple increase in the level of IAPP secretion is sufficient for amyloid formation in type 2 diabetes. Moreover, several groups have reported that transgenic mice with β-cell overexpression of human IAPP (hIAPP) develop islet amyloid deposits which are associated with β-cell death and development of hyperglycemia (Verchere et al., 1996; Hoppener et al., 1999). However, in each of these strains islet amyloid only develops if a predisposing genetic or environmental factor such as administration of glucocorticoid, high fat diet, or genetic obesity and hyperlipidemia (ob/ob) is also present in addition to human IAPP overexpression (Verchere et al., 1996; Soeller et al., 1998; Hoppener et al., 1999). Each of these factors is known to impact β-cell function. Taken together, these findings suggest that overexpression of IAPP is important but not sufficient for amyloid formation in type 2 diabetes.

A second possible mechanism of islet amyloid formation is that mutations in the proIAPP gene might facilitate the aggregation process by undesired alterations in the structure of IAPP. This hypothesis is supported by the finding that a serine → glycine substitution at position 20 (S20G) in the IAPP molecule in a subpopulation of Japanese people with type 2 diabetes (frequency 4.1%) is associated with an earlier onset and more severe form of disease (Sakagashira et al., 1996). However, other studies have failed to demonstrate any linkage between abnormality of the IAPP gene and type 2 diabetes (Nishi et al., 1990). Therefore, it appears that mutations in the IAPP gene cannot explain amyloid formation in most type 2 diabetic patients, but it may be a contributor in some patients.

A third potential mechanism underlying islet amyloid formation in type 2 diabetes is that impaired processing of the IAPP precursor molecule, proIAPP, by islet β-cells may lead to hypersecretion of unprocessed or partially processed forms of proIAPP that may have a higher tendency for aggregation compared to mature IAPP (Porte and Kahn, 1989). Although it is unknown whether proIAPP processing is impaired in type 2 diabetes, it seems likely in light of the fact that proinsulin processing is impaired in this disease, and proIAPP is processed in parallel with proinsulin, by the same β-cell prohormone convertase enzymes (PC2 and PC3). Moreover, immunoreactivity for the NH_2-terminal flanking region of proIAPP has been found in islet amyloid deposits in pancreas from type 2 diabetic patients (Westermark et al., 1989), suggesting that NH_2-terminally extended proIAPP may be an important molecule in islet amyloid formation. Recently, we showed that NH_2-terminally extended human proIAPP contains a heparin binding domain, which is lost during the normal processing of proIAPP to IAPP (Park and Verchere, 2001). Heparan sulfate proteoglycans are an important component of basement membranes and are produced by many tissues including β-cells and endothelial cells, adjacent to which amyloid tends to accumulate (Verchere et al., 1996). The heparan sulfate proteoglycan perlecan is also a component of islet amyloid. We have proposed that defective processing of proIAPP may result in increased secretion of an unprocessed form(s) of proIAPP which then binds to heparan sulfate proteoglycans, forming a nidus for amyloid formation (Fig. 1). Interestingly, recent studies have demonstrated that prolonged exposure of human β-cells to high glucose concentrations (20 mM) increases the relative proportions of proIAPP and its partially processed NH_2-terminally extended form (Hou et al., 1999). Furthermore, in vitro studies have shown that prolonged exposure of β-cells to free fatty acids results in impaired processing of proinsulin due to decreased activation of PC2 and PC3 (Furukawa et al., 1999). It is therefore plausible that hyperglycemia and/or hyperlipidemia associated with type 2 diabetes may contribute to islet amyloid formation

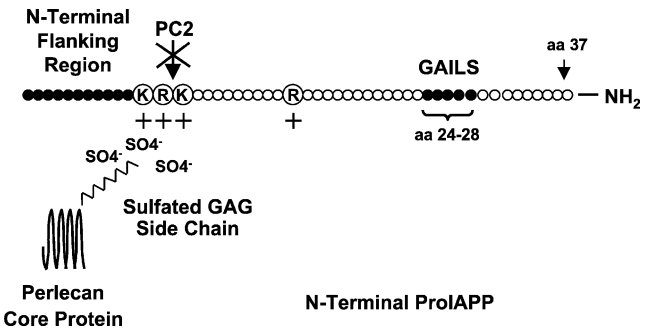

Fig. 1. Proposed pathway for islet amyloid formation in type 2 diabetes. Impaired processing of proIAPP in type 2 diabetes may result in an increase in the secretion of NH_2-terminally unprocessed proIAPP which has affinity for the glycosaminoglycan (GAG) side chains of the heparan sulfate proteoglycan perlecan. Binding of proIAPP to perlecan in the basement membrane of islet β-cells may create a nidus for amyloid formation.

indirectly by impairing proIAPP processing, possibly via alterations in the activity of PC2 and PC3 and increased secretion of NH_2-terminally extended proIAPP. Disproportionate secretion of incompletely processed (pro)IAPP and subsequent binding to basement membrane heparan sulfate proteoglycans may induce conformational changes in proIAPP that favor β-sheet formation and initiate islet amyloid deposition (Park and Verchere, 2001). Targeting the interaction between proIAPP and proteoglycans may therefore have therapeutic value.

7. Conclusions

A growing body of evidence from both human and transgenic mouse studies suggests that islet amyloid has an important role in progressive loss of β-cell mass and development of hyperglycemia in type 2 diabetes. Whether these pathologic lesions are indeed a major contributor to β-cell failure needs further investigation. The mechanism underlying islet amyloid formation in vivo is still not well understood but it appears that although an increase in the production of IAPP may be an important contributor, it is likely that an additional β-cell defect must also be present such as altered processing of the IAPP precursor, proIAPP. Inhibitors of islet amyloid fibril formation that act by targeting IAPP production, aggregation or processing might prevent progression to β-cell failure and therefore, are potential therapeutic agents for type 2 diabetes.

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