Islet amyloid polypeptide (IAPP) or amylin, a recently discovered minor secretory peptide of the β-cell related to calcitonin gene-related peptide (CGRP), is a constituent of amyloid deposits in the islets of many non-insulin-dependent (type II) diabetic individuals and some elderly nondonabetic subjects. IAPP is synthesized as a small precursor at a level of ~1% that of insulin and is processed, amidated, stored in β-granules, and released along with insulin and C-peptide. Analysis of its gene (located on chromosome 12) supports an evolutionary relationship to calcitonin and CGRP, peptides with which it shares some biological actions. Like CGRP, IAPP antagonizes the action of insulin mainly at the level of muscle glycogen synthesis, but the levels required for this effect seem to be considerably higher than reported circulating levels. No evidence for overproduction of IAPP in diabetic subjects has been found thus far, but much more work is necessary to define its normal secretory rates and clearance. Other proposed actions of IAPP include serum calcium-lowering effects and smooth muscle relaxation; the latter effect might promote the uptake of insulin into the circulation within the islets. Deposition of amyloid is species selective due to structural differences within the central part of the molecule and may be initiated intracellularly in type II diabetes by several mechanisms. No differences in the structure of IAPP or its precursor have been found in individuals with maturity-onset diabetes of the young or type II diabetes. The evidence available at this time does not support the view that IAPP plays a significant role in the insulin resistance of type II diabetes or that deposition of amyloid is a primary event in its pathogenesis. However, further studies of the expression and roles of IAPP may provide new insights into islet molecular biology and physiology. 


Although it is usually assumed that the pancreatic β-cell releases only a single hormonal product into the blood—insulin and its related precursor forms—studies over the past decade have revealed that β-cells also secrete smaller amounts of several other peptides and proteins. By far the most intriguing of these is the recently discovered 37-amino acid neuropeptidetlike molecule islet amyloid polypeptide (IAPP) or amylin. This peptide is a major component of the amyloid deposits that occur in the islets of elderly diabetic individuals (i.e., those with non-insulin-dependent [type II] diabetes mellitus), in many benign insulinomas of the pancreas, and in the normal pancreases of the aged (1,2). The presence of amyloid-like material in specimens of human pancreas was first noted in 1901 by the pathologist Opie (3), but it was not until 1986 that its constituents were solubilized. When analyzed, this material turned out to consist mainly of the single peptide IAPP (Fig. 1). Determination of its amino acid sequence quite unexpectedly revealed that IAPP is similar in structure to a 37-amino acid neuroendocrine peptide, calcitonin gene-related peptide (CGRP) (1,2). CGRP is a second product of one of the calcitonin genes and is generated through alternative splicing of the calcitonin I gene in neural tissues (4).

HUMAN IAPP PRECURSOR AND ITS GENE

Analyses of cDNAs encoding IAPP precursors from humans and other mammals have shown these to be relatively small proteins of ~90 amino acids (5–7). The structure of the rather typical IAPP precursor is shown in Fig. 1. The presence of a glycine residue just after the COOH-terminal tyrosine of the IAPP sequence followed by the basic dipeptide cleavage signal indicates that IAPP is carboxyamidated, as are CGRP and many other neuropeptide peptides. Analysis of the human IAPP gene has shown this to be a single-copy gene with an intron-exon pattern similar to the CGRP genes (8).
This gene is located on the short arm of chromosome 12 (8,9), whereas the CGRP genes are located on the homologous chromosome 11. These relationships are consistent with the notion that IAPP, CGRP, and calcitonin all arose from the same ancestral gene.

**SPECIES VARIATIONS IN IAPP STRUCTURE**

It has been known for many years that amyloid deposition occurs in the islets of diabetic animals only in certain species, among them several primates, cats, raccoons, and the degu (Octodon degus), a New World rodent related to the guinea pig (1,7,10). The partial amino acid sequence of cat IAPP revealed several interesting differences in the central portion of the IAPP molecule (11). Glenner et al. (11) have shown that this region within IAPP (residues 20–29; Fig. 1) has a high probability of forming insoluble β-sheet structures. Synthetic peptides spanning this region form fibrils spontaneously in solution, as does intact IAPP in some species (11–13).

We have used the powerful technique of polymerase chain reaction to determine the structures of IAPP precursors from numerous mammals, including the macaque, rat, mouse, cat, dog, guinea pig, hamster, and degu (Fig. 2). Interestingly, in all these species, the central region of IAPP shows the greatest interspecies variations. Westermark et al. (12), Betsholtz et al. (13), and Jordan et al. (14) have concluded that residues 25 and 26 are the most important determinants of amyloid deposition. Replacement of residue 25 with proline seems to be especially critical for preventing deposition of amyloid in all the rodents except the degu (14); the central region in degu IAPP differs only by a single substitution from that of the guinea pig (15), one of the species that lacks amyloid deposits. However, Hellman et al. (16) have recently found that degu amyloid consists of insulin rather than IAPP, and the significance of this observation will be discussed below.

The cDNA sequences have also demonstrated that IAPP is highly conserved, consistent with its probable role as a hormone (7). Proregions 1 and 2 of the precursor are much more variable, reminiscent of the proinsulin C-peptide, and thus probably have no biological activity (Fig. 1). Comparison of the sequences of IAPP and CGRP reveals canonical similarities and differences between these peptides that suggest they may bind to structurally related but not identical receptors (10).

**BIOSYNTHESIS AND LEVELS OF IAPP IN ISLETS**

Studies with antibodies specific for IAPP have demonstrated that it is present in normal islets in significant amounts, as judged by immunocytochemical staining (17), and it has been localized by electron microscopy to the secretory granules of the β-cells (18,19). Very low levels of IAPP mRNA have been detected in the stomach and other regions of the gastrointestinal tract, in the lung, and also in the dorsal root ganglia of the spinal cord (20). The significance of the extraislet expression of IAPP is unknown. Recent biosynthetic studies in our laboratory indicate that prepro-IAPP is handled very similarly to preproinsulin (S.N., D.F.S., unpublished observations). In normal rat islets, pro-IAPP is efficiently processed into the mature amidated IAPP, stored, and subsequently cosecreted with insulin. We have not observed any significant nongranule secretion of either pro-IAPP or IAPP except in insulinoma lines, such as the mouse βTC3 line, which usually exhibit more prominent constitutive or unregulated hormone secretion.

One rather surprising result has been the finding that IAPP is a very small fraction of the level of insulin in the β-cell. Leffert et al. (6) reported that the content of IAPP mRNA in isolated rat islets is ~10% that of insulin mRNA. However, high-performance liquid chromatography analysis of freshly isolated rat islets in our laboratory showed that IAPP amounted to only ~1–2% of the level of insulin on a molar basis (9). Other studies with islets or whole-pancreas extracts also indicate that IAPP-related peptides amount to only ~1% of the level of insulin (i.e., ~0.1–0.2 nmol IAPP/g; 21–23). Biosynthetic labeling experiments confirm that IAPP synthesis in rat islets occurs at a rate that is ~100-fold lower than that of insulin and suggest that IAPP mRNA is less efficiently translated than insulin mRNA (S.N., D.F.S., unpublished observations). Obviously, a higher synthetic rate would be expected to lead to a higher level of stored IAPP than has actually been observed unless it is selectively degraded before secretion. Numerous studies in animals and humans have shown that IAPP secretion is stimulated by glucose and usually amounts to 2–5% of the amount of insulin released (23–27). However, in the basal state, IAPP secretion is very low (1.8±1 ng/mg wet wt) compared to that of insulin (17.8±1.5 ng/mg wet wt; unpublished observations). A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.

**FIG. 1.** A: structure of human islet amyloid polypeptide (IAPP). Extended region (residues 20–29) is believed to nucleate β-sheet structures in forming amyloid fibrils (11). B: structure of IAPP precursor. G, glycine; K, lysine; R, arginine.

**FIG. 2.** Comparison of known islet amyloid polypeptide amino acid sequences. Note that differences are more frequent in central amyloidogenic portion of molecule and may partially explain species differences in amyloid occurrence (see text). Sources of sequences: human (1,2,5); rat (6,7); cat (7,13); mouse, guinea pig (7); degu (14); hamster (54); dog and monkey (15; S.O., M.N., G.L.B., D.F.S., unpublished observations). A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.
amounts to only ~30% of the total immunoreactive material
due to the presence of smaller circulating fractions (24).
Basal values for IAPP in humans are typically reported to be
1.5–2.5 pM rising to 7–10 pM after glucose ingestion. Higher
levels are found in obesity (27), but no study shows any
increase in IAPP levels in individuals with type II diabetes
relative to suitable controls (25,26). As expected, IAPP levels
are markedly reduced in individuals with insulin-dependent
diabetes receiving insulin (26).

BIOLGICAL ACTIONS OF IAPP
Great controversy surrounds the possible biological actions
of IAPP in modifying the secretion or responses to insulin in
the organism. Synthetic rat IAPP-amide inhibits insulin se-
cretion from rat islets of Langerhans, but the doses required
for this effect (10^{-5} M) are extremely high (28). At lower doses
(10^{-2}–10^{-9} M), no significant effects of IAPP (amidated or
nonamidated) on either insulin secretion or biosynthesis in
isolated rat islets have been seen. On the other hand, Leigh-
ton and Focht (29) and Cooper et al. (30) have shown that
10 nM IAPP significantly inhibits glycogen synthesis in mus-
cle exposed to the peptide in vitro, an effect it shares with
CGRP. Moreover, euglycemic glucose-clamp experiments with
dogs (31) and rats (32) have demonstrated that IAPP-amide
inhibits insulin-stimulated glycosal disposal over short influ-
sion periods. Again, similar effects were noted with CGRP
(32). In these experiments, the rates of IAPP infusion were
3- to 6-fold (31) or 385-fold (32) higher on a molar basis than
the rates of insulin infusion. Such high ratios of secretion of
IAPP relative to insulin cannot conceivably occur under nor-
mal physiological conditions in vivo, where IAPP is, at most,
10% of the level of insulin. Binding of IAPP to liver mem-
branes has been reported (33), but no effects on insulin sensi-
tivity were found in perfused liver by Roden et al. (34).
Thus, the observed induction of an insulin-resistant state in
vivo must be viewed as a pharmacological rather than phys-
iological effect.

A more plausible possibility might be that IAPP plays a
local role in the islets, although it does not appear to affect
the secretion of insulin (28) or the other islet hormones (35).
However, it may affect the surrounding acinar tissue or alter
the rate of blood flow through the islets when insulin release
is stimulated. The potent vasodilating effects of CGRP are
shared by IAPP (36), lending credence to the latter possi-
bility. An additional interesting action of IAPP is its serum
calcium-lowering effects in animals in vivo and cell-culture
systems (37). A direct effect on uptake of calcium by bone
tissue has been demonstrated, but it is not clear whether
this effect is mediated via calcitonin or IAPP receptors.
MacIntyre (37) proposed that IAPP may be secreted along
with insulin to promote the utilization of ingested calcium;
however, the physiological relevance of such an action re-
 mains to be demonstrated.

Because IAPP seems to share some actions of CGRP, a
family of neuropeptides that are expressed in the nervous
system and at nerve endings in many organs throughout the
body (4 10,38,39), it is plausible that they both act through
similar receptors. The main function of CGRP in peripheral
tissues appears to be mediated via cAMP and involves
smooth muscle relaxation leading to bronchial dilation, low-
ering of blood pressure, and decreases in intestinal motility
(39). CGRP may also play a role in regulating growth hor-
mone secretion (40) or as a growth factor, regulating the
development of certain neurons during embryogenesis (41).
Although CGRP binding sites have been identified in some
structures, the nature of its receptor has not been well char-
acterized. In view of its modulating effects on adenylate cy-
clase, it is conceivable that the CGRP (and IAPP) receptors
are members of the G-protein–coupled receptor family (42).

MECHANISM OF AMYLOID DEPOSITION
IN DIABETIC ISLETS
Amyloid fibrils occur in various disease syndromes, but all
of them are characterized by the deposition of β-pleated
sheets arranged in insoluble fibrillar arrays, often caused by
mutations or cleavages in proteins that render them sus-
cetable to fibril formation (43). The presence of IAPP in islet
amyloid has been demonstrated by both light and electron
microscopic immunocytochemistry (17,18). Although, in nor-
mal β-cells, IAPP is found only within the insulin secretory
granules (19,20), in some patients with type II diabetes, fi-
brillar immunoreactive amyloid deposits have also been
found within the cytoplasm of β-cells (17). High concentra-
tions of IAPP immunoreactivity have been noted in lysosomes
and lipofuscin bodies within the β-cells of the islets of both
nondiabetic and diabetic individuals (44,45). These findings
suggest that, in some individuals, amyloid forms during the
intracellular degradation of secretory granules, as occurs in
the normal turnover of unused secretory stores, a process
known as cribophagy. It is possible that, during cribophagy,
acidic conditions within the lysosomes may bring about the
precipitation of protease-resistant aggregates of IAPP. This
material may then remain behind, along with other unde-
gradable by-products, e.g., lipofuscin, and be extruded from
the β-cell. Alternatively, it may be retained, possibly
leading to altered cell function, degeneration, and necrosis
(10,44,45).

What is it about the diabetic state that leads to amyloid
deposition? One possibility, often discussed, is that insulin
is overproduced in type II diabetes due to acquired or in-
herent resistance to its action (46). This may also result in
increased secretion of IAPP (46–48). On the other hand,
there is also a large body of evidence that glucose respon-
siveness is impaired in the islets of individuals with type II
diabetes (49). This could result in the intracellular accu-
mulation of increased numbers of secretory granules, formed
in response to hyperglycemia but not released normally.
These granules will eventually age and then undergo cri-
rophagy, as discussed above, generating fibrillar material
in the lysosomes and multisvesicular bodies that later will be
extruded from the cells. Both of the foregoing hypotheses
envision overproduction of IAPP (and insulin) as a primary
factor, but the latter theory posits an associated block in
granule release, resulting in increased intracellular turnover
of both IAPP and insulin in type II diabetes. Selective over-
expression of IAPP (relative to insulin) occurs in some islet
cell tumors and could account for the selective deposition of
amyloid in insulinomas in the dog (50; S.N., D.F.S., un-
published observations). The dog is curious, because al-
though its IAPP has essentially the same amyloidogenic se-
quence as the cat (Fig. 2), islet amyloid deposition is never
seen (14). Dexamethasone administration and streptozocin-
induced diabetes have both been reported to lead to the relative enhancement of IAPP gene expression in rats (51). Although the latter finding seems paradoxical in view of the loss of β-cells, this kind of mechanism could conceivably play a role in the increased deposition of amyloid in some diabetic individuals and not others.

Antisera against the NH₂-terminal propeptide of the IAPP precursor have demonstrated immunoreactivity in amyloid deposits (Fig. 1), suggesting a possible role for altered processing of IAPP in the generation of the deposits (52). This immunoreactivity could either represent intact pro-IAPP or its NH₂-terminal prosegment (proregion 1), which, after proteolytic cleavage, would probably be cosecreted with IAPP. However, note that pro-IAPP-related peptide sequences have not been described as components of solubilized amyloid. We recently sequenced the IAPP genes of 25 selected individuals with type II diabetes without finding any abnormalities in the structure of either IAPP or its precursor (53). The fact that amyloid indistinguishable from that occurring in diabetic individuals is formed to a lesser extent in normal islets during aging argues strongly that amyloid deposition is simply a secondary manifestation of disordered islet function. The fact that islet amyloid consists of insulin in the diabetic dog (16) also greatly strengthens the conclusion that IAPP is not per se a diabetogenic molecule but rather is deposited as a result of disordered β-cell function associated with diabetes and aging. Whether the amyloid deposits intensify islet dysfunction in type II diabetes remains an unresolved issue.

Much remains to be learned about the intracellular processing and secretion of IAPP and the genetic mechanisms that may modulate its expression as well as its receptors and mechanism of action. Its role in the normal physiology of the islets of Langerhans represents a challenging and unresolved issue and, in the final analysis, may prove to be more illuminating than its proposed role in the causation of type II diabetes.

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REFERENCES

Islet amyloid polypeptide (IAPP) or amylin is a newly identified 37-amino acid COOH-terminal–amidated polypeptide that is the major protein constituent of amyloid deposits in insulinomas and amyloid deposits in pancreatic islets of non-insulin-dependent (type II) diabetic humans and adult diabetic cats. IAPP is stored with insulin in β-cell secretory vesicles and is cosecreted with insulin in response to glucose and several secretagogues. IAPP has been demonstrated in normal pancreatic islets of many species, but IAPP-derived amyloid develops commonly in the islets of only a few species (e.g., humans and cats), especially in association with age-related diabetes. IAPP from the human and cat inherently contains a short amyloidogenic sequence that is not present in species that do not form islet amyloid. Studies in animals indicate that an aberration in the synthesis or processing of IAPP, leading to a local increase in concentration of IAPP in the islet, is also required to facilitate the conversion of IAPP to amyloid. The formation of islet amyloid may contribute to the development of type II diabetes by causing disruption of islet cells and by replacement of islets. It has also been proposed that an abnormality of IAPP homeostasis underlies the pathogenesis of type II diabetes. A significant causal relationship between IAPP and type II diabetes is based on reports that IAPP inhibits glucose-stimulated insulin release by β-cells and that IAPP inhibits insulin-stimulated rates of glycogen synthesis and glucose uptake by skeletal muscle cells. These findings clearly have potentially great relevance to type II diabetes in that impaired insulin secretion and peripheral resistance to insulin are the clinical hallmarks of this form of diabetes. However, studies generally have not supported a role for IAPP as a physiologically relevant modulator of insulin secretion, and it is yet to be demonstrated whether IAPP in physiological concentrations can induce the peripheral insulin resistance that is characteristic of type II diabetes. The potential role of this newly identified pancreatic polypeptide in the genesis of type II diabetes thus needs further investigation and confirmation in model systems utilizing physiological concentrations of IAPP. The significance of the strikingly greater responsiveness of IAPP secretion relative to insulin in severely hyperglycemic states also is not clear. However, this observation may provide an important clue to the normal function of IAPP and points to an important area of future exploration. Diabetes 40:310–14, 1991

The recent discovery of a previously unknown pancreatic islet protein, known as islet amyloid polypeptide (IAPP) or amylin, has provided a new focus of interest and investigation in the field of diabetes. These investigations have led to the consideration of IAPP as a significant pathogenetic factor in the development of non-insulin-dependent (type II) diabetes mellitus, a condition in which IAPP is known to aggregate and form islet amyloid deposits in the vast majority of cases. A considerable amount of information has been obtained about IAPP since the identification of its partial sequence in 1986, but significant aspects of the relationship between IAPP and diabetes are yet to be clearly elucidated. The implications of these various findings with respect to the development of type II diabetes are discussed here.

Is IAPP a New Islet Hormone?
"Hyalinosis" of the pancreatic islets (1), now known to represent localized amyloid deposits, was detected as a common morphological feature of type II diabetic humans as early as 1900. These islet amyloid deposits, also known to occur in diabetic nonhuman primates (2) and adult diabetic cats (3,4), are composed of characteristic 8- to 10-nm pro-
tein fibrils that bind Congo red dye and subsequently elicit green birefringence when viewed with polarized light (5).

The significance of islet amyloid and its role in the pathogenesis of type II diabetes have always been a matter of controversy. Its potential significance was especially obscured (and often dismissed) as a simple consequence of aging due to its occasional presence in the pancreatic islets of apparently nondiabetic adults (5–8). Also, its significance was questioned because it is not a feature of insulin-dependent (type I) diabetes and does not occur in commonly studied animal models of diabetes.

Our early investigations clearly showed that islet amyloid in humans and cats was histochemically and physicochemically distinct from the so-called primary or secondary (i.e., reactive) systemic forms of amyloid that commonly affect the liver, kidneys, and spleen (9–11). These observations led us to postulate that islet amyloid was derived from a local secretory product and that determination of the chemical nature of this amyloid protein might provide important new clues or insight into the pathogenesis of type II diabetes. This rationale was significantly linked to the knowledge that islet amyloid deposits are present in the islets of >90% of type II diabetic humans (12) and ~60% of adult diabetic cats (13), which is a much greater incidence than in non-diabetic age-matched control subjects.

Delineation of the chemical nature of the islet amyloid protein was a significant challenge because of the extreme insolubility and low concentration of islet amyloid in the pancreas. Using amyloid-containing human insulinoma (14) and pancreases from type II diabetic humans and aged diabetic cats (15,16), we purified the major protein component of islet-derived amyloid and showed that it was composed of a previously unknown 37–amino acid polypeptide. This newly identified protein, which we named IAPP, has substantial NH2- and COOH-terminal homology to the 37–amino acid neuropeptides identified as calcitonin gene–related peptides (CGRP) 1 and 2 (17,18), CGRP 1 and 2 are widely distributed in the nervous system and have been reported to have several biological effects, including vasodilation, inhibition of gastric acid secretion, and inhibition of insulin secretion. A group of investigators at Oxford University subsequently isolated IAPP from pancreases of patients with type II diabetes (19) and later called the polypeptide amylin (20).

Several reviews of IAPP have already been published (21–23); refer to these for more complete details of studies related to this putative hormone. Briefly, investigations have shown that IAPP is normally stored with insulin in β-cell secretory vesicles (24–26) and is cosecreted with insulin in response to glucose and several secretagogues (27–33). Studies employing in situ hybridization with cDNA probes for IAPP have also shown that the β-cells are the predominant site for IAPP expression (34). These findings explain why islet amyloidosis is not known to occur in type I diabetes, in which β-cells have been selectively destroyed. Genomic and cDNA studies indicate that human and rat IAPP are derived from 89– and 93–amino acid prepro-IAPP molecules, respectively, and that IAPP is normally carboxamidated (22,34–36). The NH2- and COOH-terminal regions are highly conserved between species (and also with CGRP), whereas considerable heterogeneity is present between species within the 20–29 region. Therefore, the NH2- and COOH-terminal regions are probably important for the biological activity of IAPP. Biological activity of IAPP also appears to be importantly linked to amidation of tyrosine at position 37 and the presence of an intramolecular disulfide bond between cysteine residues at positions 2 and 7 (37). The gene coding IAPP in humans is located on the short arm of chromosome 12, which may be an evolutionary homologue of chromosome 11, where the CGRP genes are located (38,39).

It is interesting that IAPP, which is cosecreted with insulin by islet β-cells, was not discovered until nearly 65 yr after the discovery of insulin by Banting, Best, and colleagues. It is also ironic that the islet amyloid deposits, which were observed for >85 yr but considered by many to be relatively insignificant bystanders in the development of type II diabetes, provided the abnormally high concentration of hormone that importantly facilitated the discovery of IAPP.

AMYLOIDGENICITY OF IAPP

Only certain species (e.g., humans, nonhuman primates, and cats) develop islet amyloid, usually in conjunction with diabetic syndromes that are associated with aging (21). Several avenues of in vitro and in vivo investigations have provided important clues to factors contributing to the polymerization of IAPP to form islet amyloid in these species. It is not likely that an abnormal form of IAPP is involved in the formation of islet amyloid, because the structure of IAPP derived from islet amyloid is identical to the sequence predicted via cDNA. However, the normal inherent differences in the primary structure within the 20–29 region of IAPP between different species appear to be importantly linked to the ability of IAPP to aggregate and form amyloid fibrils. For example, synthetic IAPP peptides corresponding to the human (36,40) and cat (41) sequence in this region aggregate to form Congoophilic amyloidlike fibrils in vitro, whereas synthetic IAPP 20–29 of the hamster, rat, and mouse (which do not develop islet amyloid in vivo) lacks the ability to form fibrils (42,43). The 25–28 region of human and cat IAPP is identical in structure (i.e., Ala-Ile-Leu-Ser [AILS]) and appears to be the most important amyloidogenic sequence common to human and cat IAPP. Single–amino acid substitutions in the 25–28 region of synthetic human IAPP 20–29 significantly reduce or eliminate the amyloidogenicity of the peptides in vitro (43). Also, IAPPs from species that do not form islet amyloid in vivo diverge significantly from the human and cat in the 25–28 region.

We have recently shown that dog IAPP, like human and cat IAPP, incorporates the putative amyloidogenic AILS sequence at positions 25–28 (44). However, dogs do not develop IAPP-derived islet amyloid but do form IAPP-derived amyloid deposits in insulinomas (45). The studies in dogs show that a species-specific IAPP structural motif alone is clearly not adequate for the conversion of IAPP to amyloid fibrils in vivo. It appears likely that aberrations in β-cell synthesis (or processing) of IAPP, leading to increased concentration of IAPP in the local milieu, provides a second prerequisite for the conversion of IAPP to amyloid. We have also demonstrated increased IAPP immunoreactivity in β-cells of normoglycemic cats with impaired glucose tolerance (13). These cats have an increased incidence of IAPP-derived islet amyloid, which provides additional evidence for
an aberration in IAPP production and/or processing that facilitates amyloidogenesis. However, we do not know whether the increased IAPP immunoreactivity in the β-cells of cats reflects a primary or secondary β-cell alteration.

**BILOGICAL FUNCTION OF IAPP AND ITS RELATIONSHIP TO DIABETES**

The biological functions and roles of IAPP are yet to be clearly elucidated. However, IAPP is a highly conserved β-cell hormone that has been shown by numerous investigations in humans, animals, and in vitro systems to be cosecreted in a biphasic pattern (in parallel with insulin) in response to glucose administration (27–33). Interestingly, IAPP output in hyperglycemic states (or supraphysiological ranges of glucose) far exceeds that of insulin output, i.e., the effects of glucose on IAPP and insulin release are strikingly dissociated when high glucose levels are achieved. It has been shown in perfused rat pancreases, for example, that although glucose or arginine stimulated the secretion of insulin and IAPP in a parallel fashion and in similar relative potencies, the amount of IAPP relative to insulin increased with the more potent combined glucose-arginine stimulus (28). Utilizing perfused pancreases from rats made severely hyperglycemic, we also observed extremely high IAPP secretion with high IAPP-to-insulin ratios (unpublished observations). Similarly, in adult rats injected with 12 daily injections of dexamethasone, a 16-fold elevation in pancreatic IAPP mRNA was observed in contrast to only a 4-fold increase in insulin mRNA levels (46). The relatively greater responsiveness of IAPP secretion relative to insulin in hyperglycemic states appears paradoxical if it is presumed that the physiological role of IAPP is to oppose insulin release or activity, i.e., the demands of glucose homeostasis would seem to require suppression of IAPP synthesis in this situation (46). The explanation for this apparent paradox is not clear on the basis of our knowledge of IAPP.

A significant pathogenetic relationship between IAPP and type II diabetes has been considered probable on the basis of both early and recent observations. This hormone, which is cosecreted with insulin by islet β-cells in response to hyperglycemia, is known to be conserved and expressed in humans and many animal species. Islet amyloid, which is the most consistent and conspicuous morphological feature of type II diabetes, is a polymerized product of IAPP known to occur in the islets of only a relatively few species (e.g., humans, cats, nonhuman primates) that also develop age-related diabetes. Also, IAPP is structurally similar to CGRP, and CGRP has earlier been shown to inhibit insulin secretion in several animal species (47).

The potential roles of IAPP in the pathogenesis of type II diabetes may be classified into at least three general categories: 1) formation of islet amyloid with resultant damage to and replacement of β-cells, 2) local (or paracrine) effects on the secretion of insulin or other islet hormones, and 3) hormonal effects on peripheral tissues. It is possible that more than one of these mechanisms or other as yet undefined roles may be operative.

Potentially significant causal relationships between IAPP and type II diabetes have recently been proposed by reports indicating that IAPP can inhibit glucose-stimulated insulin release by β-cells and that IAPP is a potent inhibitor of insulin-stimulated rates of glycogen synthesis and glucose uptake by skeletal muscle cells. These observations clearly have potentially great relevance to type II diabetes in that impaired insulin secretion and peripheral resistance to insulin are the clinical hallmarks of this form of diabetes.

The relationship of IAPP to insulin secretion has been evaluated in several laboratories. An initial in vitro study indicated that insulin secretion by rat pancreatic islets was significantly inhibited by synthetic IAPP but only at the very high dose of 10⁻⁵ M (48). Subsequent in vitro and in vivo studies clearly have not supported a role for IAPP as a physiologically relevant modulator of insulin secretion (49–53). The finding that IAPP does not inhibit insulin secretion at dose levels used in previous CGRP-induced insulin suppression models (53) is especially interesting and somewhat surprising in that there is a high degree of NH₂- and COOH-terminal homology between IAPP and CGRP. The recent studies by Nagamatsu et al. (54), showing no effect of 10⁻⁶ M IAPP on insulin mRNA levels or of 10⁻⁴–10⁻⁶ M IAPP on proinsulin biosynthesis by isolated rat islets, are also consistent with the likelihood that IAPP is not a physiologically relevant modulator of insulin secretion.

Cooper et al. (22) proposed that IAPP is a glucoregulatory hormone that can contribute to the pathogenesis of type II diabetes when it is overproduced by islet β-cells. They proposed that IAPP is normally a glucoregulator that can act in concert with insulin as a signal to switch the site of carbohydrate disposal from glycogen in skeletal muscle to longer-term stores of triglyceride in adipose tissue. It was suggested that this could be achieved by making skeletal muscle relatively insulin resistant while leaving rates of insulin-stimulated carbohydrate metabolism in adipose tissue unaltered (22). These investigators thus proposed a specific role for IAPP in the development of peripheral insulin resistance in type II diabetes based on the premise that increased secretion of this polypeptide can downregulate insulin-stimulated rates of glycogen synthesis and glucose disposal in skeletal muscle cells (20,55–57). The postulation that IAPP is responsible for the insulin resistance observed in type II diabetes is based on in vitro and in vivo studies utilizing 10⁻⁴ M concentrations of IAPP and CGRP (20,55–57). Therefore, although the rates of insulin-stimulated glycogen synthesis and glucose disposal were inhibited by >50% with both CGRP and IAPP, the concentrations used to produce these effects were ~1000-fold greater than the circulating levels (i.e., 2–20 pM) of IAPP that have been documented in nondiabetic humans. Therefore, it is questionable whether IAPP in physiological concentrations can be responsible for the insulin resistance observed in type II diabetes.

Hothersall et al. (58) recently reported that CGRP and IAPP at 1-µM concentrations inhibited insulin-stimulated 2-deoxy-([³H])glucose transport in isolated rat diaphragm by 30 and 60%, respectively. Their study thus implicated decreased glucose transport rather than reduced glycogen synthesis (as reported by Leighton and Cooper [55] and Leighton and Fool [57]) as the specific mechanism for insulin antagonism by IAPP. The significance of this study, implying a potential role for IAPP in causing increased peripheral insulin resistance by impairment of insulin-stimulated glucose transport,
is obviously also questionable on the basis of the extremely high concentrations of IAPP and CGRP used in the study.

Although impaired glucose tolerance and decreased glucose clearance have been reported in cats (59) and dogs (60), other in vivo efforts to modify glucose tolerance with IAPP have provided negative results. Bretheron-Watt et al. (49) were unable to demonstrate any effect of IAPP-amide on glucose clearance in seven nondiabetic humans that were infused to circulating IAPP plasma levels >1 nM. Likewise, Ghatei et al. (51), after administration of a single intravenous bolus of IAPP-amide (500 pmol) to rats or a continuous infusion of IAPP-amide in rabbits, failed to demonstrate either suppressed plasma insulin levels or elevated blood glucose levels.

In summary, the role of IAPP in the pathogenesis of type II diabetes has not as yet been clearly established. In particular, studies have not supported a role for IAPP as a physiologically relevant modulator of insulin secretion. However, based on evidence that an increased local concentration of IAPP is a necessary factor for amyloidogenesis within the islet, a possible paracrine effect of IAPP that is in fact associated with unusually high hormone levels within the islets cannot be ruled out. The implicated role for IAPP in the induction of the peripheral resistance in type II diabetes is of substantial potential significance, but confirmation for such a role is needed in model systems utilizing physiological concentrations of IAPP.

SUMMARY AND FUTURE DIRECTIONS
Evidence most clearly indicates that IAPP is cosecreted with insulin by islet β-cells in response to hyperglycemic states. A relatively greater responsiveness of IAPP secretion relative to insulin secretion is observed in marked hyperglycemia. The significance of this profound responsiveness to marked hyperglycemia is not clear at this time. We have considered a possible role for IAPP in the prevention of glucose-induced modifications of structural proteins, which are known to occur in prolonged hyperglycemic states. This appears to be an important area of future exploration in that evidence for such a role for IAPP would obviously have important ramifications in the treatment of diabetes.

Prolonged hyperglycemia may provide the essential stimulus for increased production of IAPP leading to a concentration in the local milieu that promotes the aggregation of IAPP to form islet amyloid deposits. However, aggregation of IAPP to form amyloid occurs only in those few species (e.g., humans and cats) where IAPP inherently contains the short amyloidogenic sequence (i.e., AILS) at positions 25–28. Therefore, islet amyloid is not a morphological marker for chronic hyperglycemia (i.e., diabetes) in other species. Islet amyloid deposition in humans, cats, and monkeys may contribute to the further development of the diabetic condition through its progressive deposition and local disruption of islet morphology and function. Islet amyloid is not a feature of the prolonged hyperglycemic condition induced in type I diabetes because of the selective destruction and subsequent absence of islet β-cells. A primary defect in the synthesis of IAPP by β-cells, resulting from genetically determined aberrations in expression of the IAPP gene, cannot be excluded on the basis of available information.

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