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Aggregation of islet amyloid polypeptide: from physical chemistry to cell biology

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Amyloid formation in the pancreas by islet amyloid polypeptide (IAPP) leads to β-cell death and dysfunction, contributing to islet transplant failure and to type-2 diabetes. IAPP is stored in the β-cell insulin secretory granules and cosecreted with insulin in response to β-cell secretagogues. IAPP is believed to play a role in the control of food intake, in controlling gastric emptying and in glucose homeostasis. The polypeptide is natively unfolded in its monomeric state, but is one of the most amyloidogenic sequences known. The mechanisms of IAPP amyloid formation *in vivo* and *in vitro* are not understood; the mechanisms of IAPP induced cell death are unclear; and the nature of the toxic species is not completely defined. Recent work is shedding light on these important issues.

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Introduction

The presence of amyloid in the pancreatic islets of Langerhans is a pathophysiological feature of type-2 diabetes. Pancreatic islet amyloid deposits were first reported more than 110 years ago [1], but it was not until 1987 that a 37-residue polypeptide hormone, denoted as amylin or islet amyloid polypeptide (IAPP), was shown to be the protein component of islet amyloid [2,3]. IAPP is found in all mammals and is believed to play a role in controlling gastric emptying, glucose homeostasis and in the suppression of glucagon release [4]. IAPP is synthesized as a pre-proform [5], is processed in the Golgi and in the insulin secretory granule (Figure 1), and is released in response to stimuli which trigger insulin release. The concentration of IAPP in the granule is about 1–2% that of insulin. This is much higher than required to lead to rapid amyloid formation *in vitro*, so there must be mechanisms which inhibit irreversible aggregation in the granule [4].

The polypeptide is normally soluble and is natively unfolded in its monomeric state, but forms amyloid in type-2 diabetes (T2D) [2–4]. The process of islet amyloid formation leads to pancreatic β-cell dysfunction, cell death and the loss of islet β-cell mass [6–8]. Islet amyloid is not the cause of T2D; however it contributes to β-cell failure in T2D and the failure of islet cell transplantation [4,9,10•].

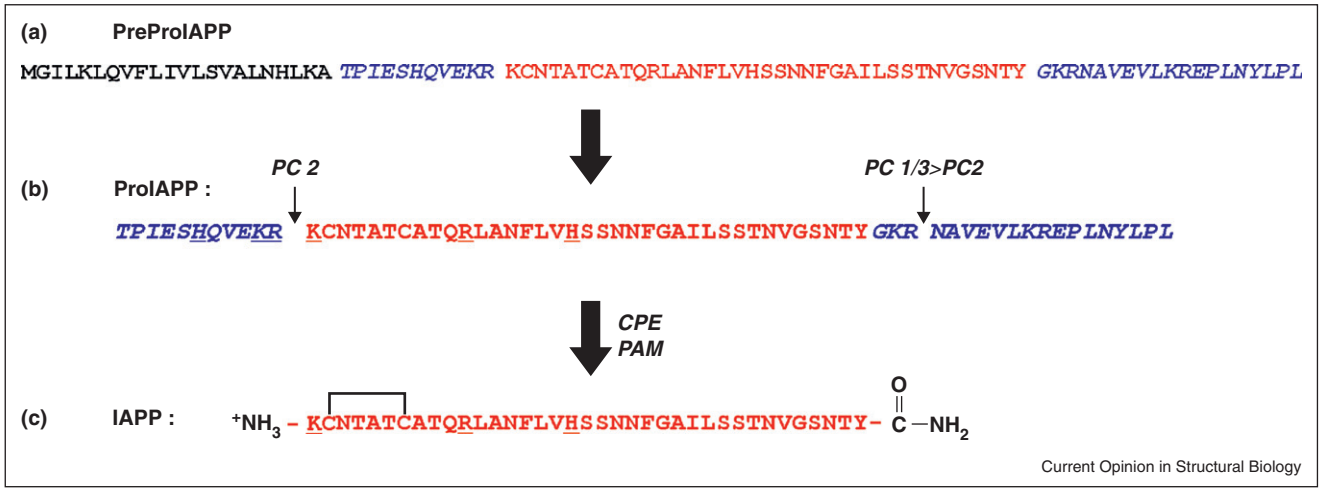
There is a large and growing body of work on the biophysics of IAPP amyloid formation and on the biological consequences of islet amyloid deposition. Unfortunately, space limitations prevent a detailed discussion of all aspects of the IAPP field and in this review we focus on the factors which control IAPP amyloid formation, on structural models of IAPP amyloid fibrils, on the nature of early intermediates, and on mechanisms of IAPP induced cytotoxicity. We provide citations to review articles which cover other topics.

Not all species form islet amyloid and its presence or absence correlates with differences in the primary sequence of IAPP

Mature IAPP is a 37 residue polypeptide that contains an intramolecular disulfide bridge between residues two and seven, and an amidated C-terminus (Figure 1). The only known polymorphism of mature human IAPP (hIAPP) that impacts amyloid formation *in vivo* is a Ser to Gly mutation at position 20, found at low levels in certain Asian populations [4]. This mutation accelerates amyloid formation *in vitro* [4,11]. Other factors leading to accelerated amyloid formation by hIAPP *in vitro* include spontaneous Asn deamidation. Asn deamidation can also lead to changes in the morphology of amyloid fibrils [12].

There is a correlation between the sequence of IAPP and its propensity to form amyloid (Figure 2) [13]. hIAPP, for example, forms amyloid readily while rat/mouse IAPP does not. The differences between the human and rat/mouse sequences occur at only six out of 37 positions, five of which are located between residues 20–29. Rat/mouse IAPP contains three Pro residues at positions 25, 28 and 29, while the human sequence does not contain any. The inability of rat/mouse IAPP to form amyloid is attributed to the Pro substitutions, consistent with the secondary structure disrupting effect of Pro. A non-aggregating

Figure 1

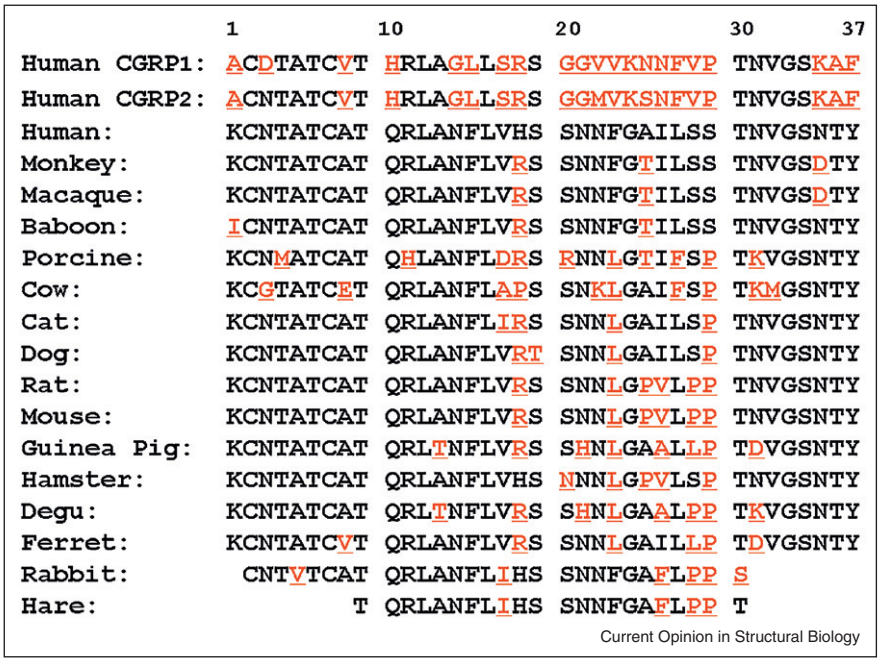


Post translational modification of human PreProIAPP to form the mature IAPP sequence: **(a)** The primary sequence of the 89-residue human PreProIAPP. The 22 residue signaling sequence is shown in black, the N-terminal and C-terminal proIAPP flanking regions are shown in blue, and the mature IAPP sequence is shown in red. **(b)** The primary sequence of the 67-residue human proIAPP. Before secretion, proIAPP is cleaved by the prohormone convertases PC2 and PC(1/3) at two dibasic sites, indicated by arrows. Further processing by the CPE/PAM complex results in an amidated Tyr at the C-terminus of mature IAPP. **(c)** The mature 37-residue human IAPP. The biologically active peptide has an intramolecular disulfide bridge between Cys-2 and Cys-7 and an amidated C-terminus. Positively charged residues are underlined in the ProIAPP and mature IAPP sequences.

variant of hIAPP, Pramlintide, which contains proline residues at the same positions as found in the rat/mouse sequence, has been approved by the FDA for treatment of diabetes [14].

Multiple Pro substitutions outside of the 20–29 region can abolish amyloid formation by hIAPP, as can replacement of Asn-14 or Asn-21 [15,16]. Conversely, replacement of residues Arg-18, Leu-23, and Val-26 in rat/mouse IAPP by

Figure 2



Primary sequences of IAPP from different species: residues that differ from the human sequence are underlined and highlighted in red. Only partial sequences are available for rabbit and hare. The biologically active mature sequence has a disulfide bridge between Cys-2 and Cys-7 and an amidated C-terminus. Primates and cats have been reported to form islet amyloid while dogs, rodents and cows do not. Porcine and ferret IAPP are significantly less amyloidogenic than human IAPP. The degue forms islet amyloid, but the deposits are derived from aggregation of insulin, not IAPP.