FEBS Letters xxx (2013) xxx–xxx

FEBS Letters

journal homepage: www.FEBSLetters.org

Review

Islet amyloid: From fundamental biophysics to mechanisms of cytotoxicity

Ping Cao [a], Peter Marek [a], Harris Noor [a], Vadim Patsalo [b], Ling-Hsien Tu [a], Hui Wang [a], Andisheh Abedini [c], Daniel P. Raleigh [a,*]

[a] Department of Chemistry, Stony Brook University, Stony Brook, NY 11794-3400, United States
[b] Department of Applied Mathematics, Stony Brook University, Stony Brook, NY 11794-3600, United States
[c] Diabetes Research Program, NYU School of Medicine, 522 First Avenue, New York, NY 10016, United States

ARTICLE INFO

Article history:
Received 5 December 2012
Revised 22 January 2013
Accepted 23 January 2013
Available online xxxx

Edited by Wilhelm Just

Keywords:
Islet amyloid polypeptide
Amylin
Amyloid
Type 2 diabetes
IAPP

ABSTRACT

Pancreatic islet amyloid is a characteristic feature of type 2 diabetes. The major protein component of islet amyloid is the polypeptide hormone known as islet amyloid polypeptide (IAPP, or amylin). IAPP is stored with insulin in the β-cell secretory granules and is released in response to the stimuli that lead to insulin secretion. IAPP is normally soluble and is natively unfolded in its monomeric state, but forms islet amyloid in type 2 diabetes. Islet amyloid is not the cause of type 2 diabetes, but it leads to β-cell dysfunction and cell death, and contributes to the failure of islet cell transplantation. The mechanism of IAPP amyloid formation is not understood and the mechanisms of cytotoxicity are not fully defined.

1. Introduction

The deposition of amyloid in the islets of Langerhans in the pancreas is a characteristic pathological feature of type 2 diabetes (T2D). Hyaline lesions in the pancreas were first described more than 110 years ago [1], and were later identified as amyloid. The deposits were initially assumed to be composed of insulin or pro-insulin or fragments of insulin, but in 1987 two groups independently showed that the major protein component of islet amyloid is a 37 residue polypeptide pancreatic hormone denoted as islet amyloid polypeptide (IAPP) or amylin [2,3]. IAPP has been found in all mammals studied to date. The molecule is stored together with insulin in the β-cell secretory granules and is released in response to the stimuli that lead to insulin secretion [4–6]. IAPP is normally soluble and is natively unfolded in its monomeric state, but forms islet amyloid in T2D [2,3,7]. IAPP can be readily induced to form amyloid in vitro and is one of the most amyloidogenic naturally occurring sequences known. Islet amyloid is not the cause of T2D, but it does lead to β-cell dysfunction and cell death, and contributes to loss of islet β-cell mass [8–10]. Rapid amyloid formation likely contributes to the failure of islet cell transplantation and prevention of amyloid formation can prolong graft survival [7,11,12].

In this review we briefly discuss the processing and normal function of IAPP, and then focus on amyloid formation by IAPP. There are a number of critical outstanding issues in the field. The mechanisms of IAPP amyloid formation in vivo and in vitro are still not understood, particularly in vivo. The site of initiation of amyloid formation in vivo is controversial. The nature of the toxic species generated during IAPP amyloid formation are not well defined, nor are the mechanisms of cell death completely understood. The mechanisms of clearance of IAPP amyloid in vivo and the role this may play in islet amyloid formation and cytotoxicity are not fully elucidated. Inhibitors of IAPP toxicity are less well developed than for other amyloidogenic proteins and most studies have made use of in vitro assays of toxicity.

2. The physiological role of IAPP

2.1. IAPP is synthesized as a pre-pro hormone

IAPP is synthesized as a 89 residue pre-pro form [13]. The 22 amino acid signal peptide is cleaved to give the 67 amino acid pro-form (proIAPP). ProIAPP is processed in the Golgi and in the insulin secretory granule [14]. The short C- and N-terminal flanking

* Corresponding author. Fax: +1 631 632 7960.
E-mail address: daniel.raleigh@stonybrook.edu (D.P. Raleigh).

0014-5793/$36.00 © 2013 Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies.
http://dx.doi.org/10.1016/j.febslet.2013.01.046

peptides of proIAPP are cleaved by the pro hormone convertases PC2 and PC1/3 [13]. The C-terminal cleavage leaves a Gly-Lys-Arg tri-peptide sequence at the C-terminus. The dibasic residues at the C-terminus are removed by carboxypeptidase E and the Gly serves as the nitrogen donor for amidation of the C-terminus by the peptidyl amidating mono-oxygenase complex (PAM). Amidation and disulfide bond formation lead to mature IAPP (Fig. 1). Incorrect processing of proIAPP has been proposed to play a role in islet amyloid formation in vivo (see below).

IAPP is stored in the insulin secretory granule where it is localized in the halo region while insulin is found in the dense core of the granule. The concentration of IAPP in the granule is about 1–2% that of insulin, and this is much higher than the level required to promote rapid amyloid formation in vitro [15,16]. Thus, there must be factors which inhibit the premature, irreversible aggregation of IAPP in the granule. The low pH environment of the granule likely contributes since the rate of IAPP amyloid formation is strongly pH dependent and is slower at intragranule pH [17–19]. Soluble insulin is an inhibitor of IAPP aggregation and this may play a role in controlling intragranule aggregation, however insulin is found in a partially crystalline state in the granule [20–24].

2.2. IAPP receptors

IAPP binds the calcitonin (CT) receptor with low affinity, but the affinity is significantly enhanced when the CT receptor forms a complex with receptor activity-modifying proteins (RAMPs). IAPP receptors are generated from co-expression of the CT receptor with one of three RAMPs [25]. Interaction with RAMPs changes the specificity of the CT receptor towards IAPP [26,27]. The CT receptor has two splice variants, so there could be six different subtypes of IAPP receptors. Despite the physiological importance of IAPP and its potential clinical relevance, it is not known whether different receptors are active in the peripheral tissue and CNS. It is also not known which receptor subtype(s) binds the FDA approved analog of IAPP, pramlintide. Thus, a more detailed understanding of IAPP receptors is needed [28]. There are currently no approved small molecule agonists of IAPP receptors.

2.3. IAPP has multiple physiological roles

IAPP is co-secreted with insulin from the β-cells following nutrient influx. The circulating concentration of IAPP is 3–5 picomolar in rats, rising to 15–20 picomolar upon elevation of blood glucose [29]. The local concentration after release from the granule will be much higher and is the more relevant number for amyloid formation. The physiological roles of soluble IAPP are not completely understood, but IAPP is believed to play a role in controlling gastric emptying, in maintaining glucose homeostasis, in the suppression of glucagon release and in controlling satiety [7,30,31]. IAPP has been proposed to play a role in regulating blood glucose levels by inhibiting insulin secretion from the pancreas [32,33], but the main sites of action appear to be in the CNS [34,35]. IAPP has also been proposed to act as an adiposity signal [36]. The polypeptide has been reported to inhibit insulin-stimulated glucose uptake and the synthesis of glycogen in isolated rat skeletal muscle [37]. However, these effects were studied at concentrations of the polypeptide that are higher than physiological levels, thus the details of IAPP's role are still not completely clear. Several recent reviews of the function of IAPP have recently appeared and provide a more in depth discussion [7,29,31].

3. Residue specific effects on amyloid formation

3.1. Differences in the primary sequence of IAPP correlate with amyloid formation in vitro and in vivo

IAPP is a member of the calcitonin related peptide family which consists of calcitonin α- and β-calcitonin gene-related peptide (CGRP), adrenomedullin and intermedin. The peptides share limited amino acid sequence identity, but have several important structural features in common (Fig. 2). They all have an intramolecular disulfide bridge near the N-terminus and an amidated C-terminus.

IAPP is most similar to CGRP. Both are 37 residues in length, have a conversed disulfide bond between residues two and seven, contain an amidated aromatic residue at the C-terminus, and have a tendency to form low levels of transient helical structure over part of the sequence in their monomeric states [38–40]. Early studies showed that human IAPP (hIAPP) readily forms amyloid in vitro, but that CGRP does not. The two peptides have reasonable sequence similarity, with the greatest homology at the N- and C-terminal regions, but differ most between residues 20 and 29 [41]. These observations led to the hypothesis that the sequence within the 20–29 region determines the ability of IAPP to form amyloid. Only humans, non-human primates, and cats form islet

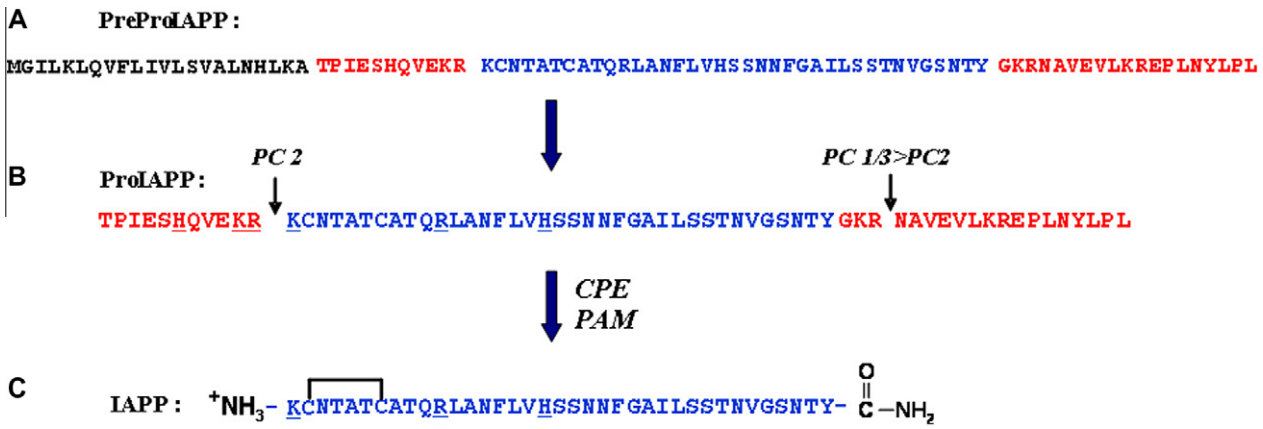

Fig. 1. Processing of human PreProIAPP to form mature IAPP. (A) The primary sequence of human PreProIAPP, the peptide length is 89 residues. The 22 residue signal sequence is shown in black, the N- and C-terminal proIAPP flanking regions are shown in red, and the mature sequence in blue. (B) The primary sequence of the 67-residue human proIAPP. ProIAPP is cleaved by the prohormone convertases PC(1/3) and PC2 at the two dibasic sites, indicated by the arrows. Additional processing by CPE/PAM leads to an amidated C-terminus of IAPP. (C) The sequence of the mature 37-residue human IAPP. The biologically active peptide has an amidated C-terminus and a disulfide bridge between Cys-2 and Cys-7.

Please cite this article in press as: Cao, P., et al. Islet amyloid: From fundamental biophysics to mechanisms of cytotoxicity. FEBS Lett. (2013), http://dx.doi.org/10.1016/j.febslet.2013.01.046