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Review

Mechanisms of islet amyloidosis toxicity in type 2 diabetes

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ABSTRACT

Amyloid formation by the neuropancreatic hormone, islet amyloid polypeptide (IAPP or amylin), one of the most amyloidogenic sequences known, leads to islet amyloidosis in type 2 diabetes and to islet transplant failure. Under normal conditions, IAPP plays a role in the maintenance of energy homeostasis by regulating several metabolic parameters, such as satiety, blood glucose levels, adiposity and body weight. The mechanisms of IAPP amyloid formation, the nature of IAPP toxic species and the cellular pathways that lead to pancreatic β-cell toxicity are not well characterized. Several mechanisms of toxicity, including receptor and non-receptor-mediated events, have been proposed. Analogs of IAPP have been approved for the treatment of diabetes and are under investigation for the treatment of obesity.

1. Introduction

Amyloids are partially ordered, fibrillar, protein aggregates that are rich in β-sheet structure. Amyloid formation has been implicated in more than 30 different human disorders including such debilitating diseases as Alzheimer's disease (AD), Parkinson's disease (PD) and type 2 diabetes (T2D) (Table 1). Amyloid formation is not restricted to in vivo pathological conditions; a large number of proteins that do not form amyloid in vivo can be induced to do so in vitro under non-physiological conditions [1–4]. Amyloid can, in some cases, be functional and beneficial [4]. In this review, we focus on amyloid formation by islet amyloid polypeptide (IAPP, amylin), a neuropancreatic hormone that forms pancreatic islet amyloid in T2D and contributes to β-cell dysfunction and death. We first outline the biosynthesis of IAPP and describe its normal physiological roles. We then discuss IAPP amyloid formation, with emphasis on potential mechanisms of toxicity, drawing analogy to proteins and physiological consequences documented in other amyloidosis diseases, which have not yet been characterized for islet amyloid. We conclude with a brief description of the clinical applications of IAPP analogs.

The kinetics of amyloid formation is complex and displays a sigmoidal profile with three observable phases. The initial steps of aggregation, which lead to formation of an active seed, occur in the lag phase and represent the rate limiting process. In this phase, monomers oligomerize and convert into species that nucleate an exponential fibril growth phase. Fibrils elongate by addition of peptide to their ends. Secondary nucleation that involves the catalyst of fibril formation from existing fibrils also occurs. This may involve breakage of existing fibrils to increase the concentration of free ends, or the templating of new fibrils on the surface of existing ones. Finally, a steady state is reached where soluble peptide is at equilibrium with amyloid fibrils. Off-pathway steps leading to amorphous aggregates also occur. Amyloid formation can be accelerated by the addition of small amounts of preformed fibrils in a process known as "seeding" (Fig. 1A).

Although there is no sequence homology or structural similarity between the proteins that form amyloid, all amyloid deposits share common characteristics. Amyloid fibrils are typically unbranched, 5–10 nm in width, variable in length, polymorphic, and form a cross β-sheet structure. This structure is defined by perpendicular orientation of the individual polypeptide chains to the long axis of the fibril; with the interchain hydrogen bonds aligned parallel to

Terms and definitions: Amyloid fibrils, protein aggregates having a cross-β structure and other characteristics, e.g., specific dye-binding; Amyloidosis, any pathological state associated with the formation of extracellular amyloid deposits; Functional amyloid, an amyloid structure found to have a beneficial function in living systems; Oligomers, clusters of small or large numbers of protein or peptide molecules without a fibrillar appearance; Protein deposition disease, any pathological state with the formation of intracellular or extracellular protein deposits; Protein misfolding, the conversion of a protein into a structure that differs from its native state

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Table 1
Common pathological amyloidoses and their major protein components.

Amyloidosis Disease	Amyloidogenic Protein	Deposition Type
Alzheimer's Disease; Inclusion-body myositis; Down's syndrome; Cerebral β-amyloid angiopathy	Amyloid-β peptides (1–40 and 1–42)	Neurodegenerative
Hereditary cerebral haemorrhage with amyloidosis	Mutants of Amyloid-β peptides	Neurodegenerative
Huntington's disease (HD)	Autosomal dominant mutation of human huntingtin leading to expanded polyglutamine inserts	Neurodegenerative
Parkinson's Disease and other synucleinopathies	α-Synuclein	Neurodegenerative
Familial amyotrophic lateral sclerosis (ALS); also known as motor neuron disease or Lou Gehrig's disease	Mutations in Superoxide dismutase (SOD1); TDP-43 and FUS/TLS	Neurodegenerative
Serpinopathies	Mutations in members of the serine protease inhibitor or serpin superfamily of proteins (Serpins)	Neurodegenerative or Local
Bovine spongiform encephalopathies (BSE or Mad Cow disease); Creutzfeldt-Jakob disease	Prions in the Scrapie form (Prp^{Sc})	Neurodegenerative
Intracytoplasmic neurofibrillary tangles; Tauopathies; Alzheimer's Disease	Tau protein	Neurodegenerative
Icelandic hereditary cerebral amyloid angiopathy (CAA); also known as hereditary cyctatin C amyloid angiopathy	Mutant of cystatin C	Neurodegenerative
Familial British dementia	ABri polypeptide (ABriPP)	Neurodegenerative
Familial Danish dementia	ADan polypeptide (ADanPP)	Neurodegenerative
Type 2 diabetes; pancreatic islet amyloidosis	Amylin, also known as Islet Amyloid Polypeptide (IAPP)	Local
Aortic medial amyloidosis	Medin (a fragment of lactadherin)	Local
Atrial amyloidosis	Atrial natriuretic factor	Local
Medullary carcinoma of the thyroid (MTC)	Pro-calcitonin	Local
Injection-localized amyloidosis	Insulin	Local
Critical illness myopathy (CIM)	Hyperproteolytic state of myosin ubiquitination	Local
Lichen amyloidosis	Keratins	Local
Restrictive amyloid heart; also known as cardiac amyloidosis, amyloid cardiomyophathy or ApoA-I amyloidosis	Apolipoprotein A-I (Apo-A1)	Local or Systemic
Cataract	Crystallin family of proteins	Local
Pituitary prolactinoma	Prolactin	Local
Pulmonary alveolar proteinosis (PAP)	Pulmonary surfactant protein C	Local
Familial amyloid polyneuropathy (FAP); Familial amyloid cardiopathy (FAC); Senile systemic amyloidosis (SAA)	Transthyretin (TTR)	Systemic
Familial amyloidosis of Finnish type (FAF)	Fragments of gelsolin mutants	Systemic
Amyloid light chain (AL) amyloidosis; also known as Primary systemic amyloidosis (PSA)	Immunoglobulin light chains	Systemic
Amyloid heavy chain (AH) amyloidosis	Immunoglobulin heavy chains	Systemic
Dialysis-related amyloidosis	β2-microglobulin (β2m)	Systemic
Corneal amyloidosis associated with trichiasis	Variation of lactoferrin (LF)	Local
Hereditary lattice corneal dystrophy	Mainly C-terminal fragments of kerato-epithelin	Local
AA amyloidosis or Secondary amyloidosis (associated with inflammatory disorders such as tuberculosis, rheumatoid arthritis, bronchiectasis, ulcerative colitis, Crohn's disease, renal cell carcinoma, ankylosing spondylitis, nephritic syndrome, chronic osteomyelitis, Hodgkin disease, familial Mediterranean fever)	Serum amyloid A (SAA) protein	Systemic
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	Mutations in the *Notch3* gene	Neurodegenerative or Systemic
ApoA-II amyloidosis	Apolipoprotein A-II (ApoA2)	Systemic
ApoA-IV amyloidosis	N-terminal fragment of apolipoprotein A-IV (ApoA4)	Systemic
Fibrinogen amyloidosis	Variants of fibrinogen α-chain	Systemic
Lysozyme amyloidosis	Mutants of lysozyme	Systemic

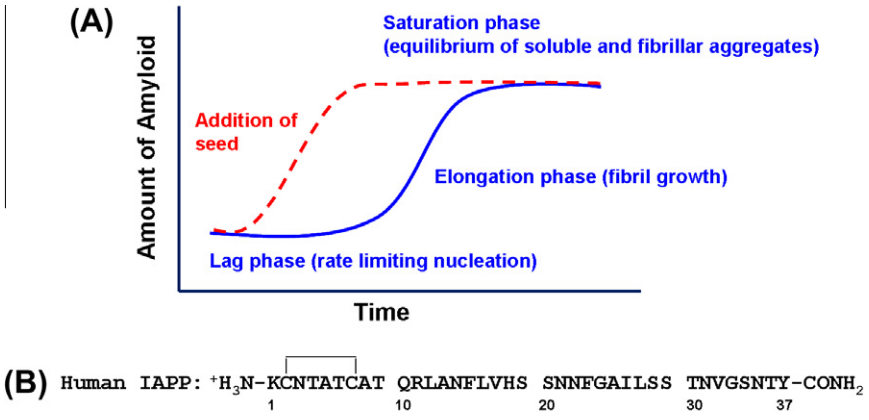

Fig. 1. Amyloid formation by IAPP. (A) Schematic diagram of amyloid formation (solid blue curve). During the lag phase monomers associate to form oligomeric species which then assemble to nucleate an exponential growth phase. Secondary nucleation and off-pathway steps such as formation of amorphous aggregates are omitted for clarity. Amyloid formation can be accelerated by the addition of small amounts of preformed fibrils (dashed red curve). (B) The primary sequence of human IAPP. The peptide has a free N-terminus, an amidated C-terminus and an intramolecular disulfide bond between residues 2 and 7.

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