Journal of Diabetes Science and Technology
Volume 4, Issue 6, November 2010

SYMPOSIUM

The Nature of Amyloid-like Glucagon Fibrils

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Abstract

Protein aggregation and formation of amyloid fibrils is a phenomenon usually associated with proteotoxicity and degenerative diseases, such as type 2 diabetes, Alzheimer's disease, and prion diseases. However, several protein and peptide hormones are known to have a high propensity to form amyloid-like fibrils *in vitro* raising concerns about safety and stability of pharmaceutical protein solutions. Comprehensive understanding of the aggregation mechanisms is an important prerequisite to the design of strategies to prevent fibril formation. Detailed kinetic, spectroscopic, and morphological studies have revealed that glucagon can form several types of fibrils that differ at the level of molecular packing of the peptide. Each type forms through distinct nucleation-dependent aggregation pathways influenced by solution conditions and can be self-propagated by seeding. An increasing number of functional amyloid-like structures have been discovered in nature, and it has recently been proposed that an amyloid-like state of glucagon may be utilized by the pancreatic α-cells as *in vivo* storage form. This article reviews the current state of our knowledge about the nature of the different types of amyloid-like glucagon fibrils, the mechanisms by which they form, and discusses implications for formulation strategies and the safety of glucagon pharmaceuticals.

J Diabetes Sci Technol 2010;4(6):1357-1367

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Abbreviations: (Aβ) amyloid-β-peptide, (CD) circular dichroism, (CyD) cyclodextrin, (EM) electron microscopy, (HP-βCyD) hydroxypropyl-β-cyclodextrin, (M-βCyD) methyl-β-cyclodextrin, (NMR) nuclear magnetic resonance, (QSA) quantitative seeding assay, (ThT) thioflavin T, (T_m^{app}) apparent thermal dissociation midpoint, (Trp) tryptophan, ($t_{threshold}$) threshold time

Keywords: aggregation, amyloid, cyclodextrins, drug formulation, excipients, fibrils, glucagon

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