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Effect of N-terminus of Human Islet Amyloid Polypeptide on Amyloidogenicity and Cytotoxicity

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Abstract

Islet amyloid polypeptide (IAPP, also known as amylin) is a 37 residue neuropancreatic polypeptide hormone, which helps to regulate satiety, control gastric emptying, suppress glucagon release and maintain glucose homeostasis by suppressing insulin-mediated glucose uptake. IAPP forms amyloid in the islets of Langerhans in type-2 diabetes, a process which contributes to β-cell dysfunction and death. In spite of the importance of islet amyloid formation, the feature that controls the amyloidogenicity and cytotoxicity of amylin has not been understood. The role of the N-terminus region of amylin in amyloid formation is largely unexplored and no analysis of N-terminal mutants has been reported. We examined the des-Lys-1 variant of human amylin (h-amylin), the amylin without the first Lys residue. The des-Lys-1 is a variant which is likely produced *in vivo*. Lys-1 is a region of high charge density in the h-amylin amyloid fiber. The des-Lys-1 polypeptide forms amyloid on the same time scale as wild-type h-amylin in PBS but does so more rapidly in Tris. The des-Lys-1 variant is somewhat less toxic to cultured INS cells than wild type h-amylin. We also examined K1E and K1I variants of the h-amylin to understand the effect of the N-terminus of the h-amylin on amyloidogenicity and cytotoxicity. The positive charged Lys-1 is replaced by a negative charged Glu in K1E h-amylin and by a neutral amino acid, Ile, in K1I h-amylin. The K1E replacement reduces the net charge by 2 units but amyloid formation in PBS occurs on the time scale similar to that of wild type h-amylin. A Lys-1 to Glu replacement has a weak effect on the amyloid formation but does reduce toxicity relative to that of h-amylin. The K1I replacement decreases the net charge by 1 unit and the Lys-1 to Ile substitution shows similar tendency of amyloidogenicity and cytotoxicity to the Lys-1 to Glu substitution. The analysis of the des-Lys-1, K1E and K1I variants of h-amylin provides evidence that the variants have a modest effect on the amyloid formation in PBS but reduces toxicity relative to that of wild type h-amylin. This analysis also demonstrates that there is not a direct 1:1 direct relationship between the charged residue of the polypeptide and the rate of amyloid formation. The dependence of the time scale of amyloid formation by wild type h-amylin, des-Lys-1, K1E and K1I h-amylin variants on the choice of buffer highlights the difficulties in objectively defining the amyloidogenicity of a polypeptide because the rate of amyloid formation is dependent upon solution conditions. The observed buffer-dependent effects reveal the importance of studying amyloid formation under different conditions.

Biography:

Kyung-Hoon Lee is a PHD Graduate from the University of Chauhan and presently working as an Assistant Professor in Department of Biology at Chowan University.

Speaker Publications:

1. "Analysis of Baboon IAPP Provides Insight into Amyloidogenicity and Cytotoxicity of Human IAPP" Biophysical Journal
Volume 118, Issue 5, 10 March 2020, Pages 1142-1151
2. "Analysis of Prairie Vole Amylin Reveals the Importance of the N-Terminus and Residue 22 in Amyloidogenicity and Cytotoxicity" Journal of Bio Chemistry
Volume 23, Issue 1, January 2019, Pages 1-6
3. "Amyloidogenicity and cytotoxicity of des-Lys-1 human amylin provides insight into amylin self-assembly and highlights the difficulties of defining amyloidogenicity"; rotein Engineering, Design and Selection, Volume 32, Issue 2, February 2019, Pages 87–93

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