INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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SHORT ABSTRACT

The aggregation of human islet amyloid polypeptide (hIAPP) stands at the nexus of Type II Diabetes (T2D) pathogenesis. In order to counteract the advancement of this disease, a possible therapeutic avenue is to curb the misfolding and aggregation of hIAPP. Within this thesis, we embark on the intricate journey of hIAPP aggregation, coupled with the myriad classes of compounds harboring the potential to impede this process. In Chapter I, a foundation is laid through the introduction of hIAPP and an array of different categories of inhibitors, each contributing to the modulation of hIAPP aggregation. A brief discussion of the molecular dynamics simulation methodology, which is a vital framework underpinning our study is followed. Thereafter, Chapter II takes the helm into venturing the different conformational states of an amyloid prone fragment of hIAPP, $hIAPP_{20-29}$, via Markov State Modelling. Here, the transition pathway between the metastable states is analysed, which are crucial for the misfolding of hIAPP. Chapter III explores the influence of two small biological molecules on hIAPP aggregation. In Part (a), we have explored the effect of norepinephrine, which is a common neurotransmitter, on the amyloidogenesis of hIAPP. In Part (b), a new aspect of adenosine triphosphate (ATP), other than being the energy source for biochemical processes, is inquired. This chapter, thus, enlighten us about the diversity of the molecular structures that can modulate the aggregation of hIAPP and the effect of these structures on the activity of the inhibitors. Chapter IV turns the discourse towards peptides and peptidomimetics, probing their roles in shaping the aggregation narrative. Two such inhibitors are investigated, both of which are extracted from the amyloid core region of hIAPP, i.e., $N_{22}FGAIL_{27}$. In Part (a), this hIAPP fragment is replaced with all D-amino acids, and is used to prohibit the self-assembly of full-length hIAPP. In Part (b), a conformationally restricted element, aminobenzoic acid is incorporated into NFGAIL, by replacing Ile26 and/or Gly24 residues. Here, three different isomers of aminobenzoic acid is used, i.e., (β, γ, δ). β- and γ- containing peptidomimetics successfully prevent the aggregation of hIAPP, but δ- peptidomimetics promote it, highlighting the contrasting behaviour of the isomers. Hence, in this chapter, we have conveyed the effect of stereochemistry of the amino acid residues or modified organic moieties on the inhibitory potential of peptides or peptidomimetics. A novel dimension unfurls in Chapter V, where the alliance between boron nitride nanomaterials and hIAPP aggregation is explored. The curvature of the nanomaterials is observed to have an impact on their interaction site with hIAPP.

Finally, Chapter VI unfurls a tapestry of conclusions, weaving together the diverse threads from our journey. In unity, this thesis stands as an ardent exploration, deciphering the aggregation pathway of hIAPP and unveiling a constellation of agents poised to intervene. The information regarding the structure and activity of the various inhibitors provides a holistic comprehension of the crucial molecular scaffolds and properties required to design drugs for combatting T2D's relentless advance.