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Decreased Interactions between Calmodulin and a Mutant Huntingtin Model Might Reduce the Cytotoxic Level of Intracellular Ca^{2+}: A Molecular Dynamics Study

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Abstract: Mutant huntingtin (m-HTT) proteins and calmodulin (CaM) co-localize in the cerebral cortex with significant effects on the intracellular calcium levels by altering the specific calcium-mediated signals. Furthermore, the mutant huntingtin proteins show great affinity for CaM that can lead to a further stabilization of the mutant huntingtin aggregates. In this context, the present study focuses on describing the interactions between CaM and two huntingtin mutants from a biophysical point of view, by using classical Molecular Dynamics techniques. The huntingtin models consist of a wild-type structure, one mutant with 45 glutamine residues and the second mutant with nine additional key-point mutations from glutamine residues into proline residues (9P(EM) model). Our docking scores and binding free energy calculations show higher binding affinities of all HTT models for the C-lobe end of the CaM protein. In terms of dynamic evolution, the 9P(EM) model triggered great structural changes into the CaM protein's structure and shows the highest fluctuation rates due to its structural transitions at the helical level from α-helices to turns and random coils. Moreover, our proposed 9P(EM) model suggests much lower interaction energies when compared to the 45Qs-HTT mutant model, this finding being in good agreement with the 9P(EM)'s antagonistic effect hypothesis on highly toxic protein–protein interactions.

Keywords: calmodulin; calcium-binding protein; polyglutamine tract; polyglutamine disorders; Huntington's disease; molecular dynamics

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1. Introduction

The polyglutamine (polyQ) tract length of the mutant Huntingtin protein (m-HTT) is generally associated with the disease's onset and its severity. The physiological Huntingtin protein is expressed in almost all body tissues and has a molecular weight of 348 kDa. The polyQ tract is located at the protein's N-terminal domain, which is followed by the proline-rich domain (PRD) with a protective anti-aggregation role and a direct involvement in protein–protein interaction complexes [1]. Although the connection between Huntingtin's (HTT) structure and its function is not yet fully understood [2,3], the accumulation of insoluble aggregated N-terminal fragments of m-HTT together with their associated proteins, leads to loss of interruptions in the extended HTT sequence [4] and a wide range of cell pathologies related to gene modifiers [5–7].

The genetic defect in Huntington's disease (HD) is characterized by the expansion of the CAG trinucleotide repeats at the protein's N-terminal domain. For normal controls, which are considered as wild-type structures (wt-HTT), the polyQ tract (CAG trinucleotide translates the glutamine amino acid) consists of less than 35 CAG repeats, while the m-HTT is associated with a higher number of trinucleotide repeats [8].