An investigation into the role of turn-supporting motif in polyglutamine binding peptide (QBP1) in Huntingtin aggregation inhibition

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Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by cognitive decline, motor dysfunction, and neuropsychiatric disturbances. The most prominent HD symptoms are related to chorea's, which is an involuntary and sudden muscle movement. It is caused by the expansion of the CAG tract from a threshold limit (>36) in the exon 1 region (HDx1) of the huntingtin gene IT-15, which results in the transformation of ubiquitously expressed huntingtin protein into the pathogenic huntingtin protein. It is imperative to devise strategies that could inhibit huntingtin aggregation. Polyglutamine binding peptide 1 (QBP1) Ac-SNWKWWPGIFD-am is a potent therapeutic peptide known to bind with pathogenic polyQ regions and prevent their transition monomeric protein to amyloid-like structures. QBP1 peptides harbor a Pro-Gly dipeptide motif, a characteristic feature of potential β-turn regions. This study shows that this turn-supporting dipeptide motif is essential for QBP1-mediated inhibition of huntingtin aggregation by using single amino-acid substitutions to generate analogs that could support, introduce, or eliminate the β-turn. Besides, this study identified, somewhat serendipitously, a minimal QBP1 analog that induces an α-helical conformation in the Trx-HDx1 protein.

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