Structural and Functional Insights into Hemoglobin Glycation

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Abstract

In biological systems, electrophiles such as α-dicarbonyls are capable of covalently modifying nucleophilic amino acid residues to form deleterious products (Advanced Glycation Endproducts, AGEs) non enzymatically. Glycated proteins cause metabolic disorders. Hemoglobin (Hb) is a major cargo protein present in RBC and is highly prone to glycation. The glycation-induced structural modifications in hemoglobin have been proposed to be associated with loss of their function, development of oxidative stress and aging related complications in diabetes. Yet, the effects of glycation on the molecular features of hemoglobin are unknown. Considering the physiological significance of glycation, the present study was focused on determining the specific AGEs (MGH1) mediated structural and functional changes in Hb based on the combination of both crystallographic and biophysical analyses. Here, we present the crystal structures of glycated hemoglobin. The 3D structure reveals covalently bound AGE adducts on the side chains of arginine (R40MGH1 & R31MGH1) residues, and these glycation sites have also been confirmed by mass spectrometry analysis. Glycated hemoglobin structures exhibit altered quaternary conformation, stabilizing relaxed, high affinity states (R, R2, RR2) with significant changes at the α1β2 interface. Biophysical analyses show changes in UV spectral bands and a decrease in α-helical content. Structural analyses revealed relaxed state-like heme geometry and intermediate α/β-cleft conformations, disrupting allosteric regulation.

Keywords: Glycation, Hemoglobin, Advanced Glycation Endproducts, Structure determination, Structure-Function analysis.