

Altered ligand rebinding kinetics due to distal side effects in hemoglobins chico (Lys E10 66 $\beta \rightarrow$ Thr).

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Abstract

Hb Chico is an unusual human hemoglobin variant that has lowered oxygen affinity, but unaltered cooperativity and anion sensitivity. Previous studies showed these features to be associated with distal-side heme pocket alterations that confer increased structural rigidity on the molecule and that increase water content in the β -chain heme pocket. We report here that the extent of nanosecond geminate rebinding of oxygen to the variant and its isolated β -chains is appreciably decreased. Structural alterations in this variant decrease its oxygen recombination rates without significantly altering rates of migration out of the heme pocket. Data analysis indicates that one or more barriers that impede rebinding of oxygen from docking sites in the heme pocket are increased, with less consequence for CO rebinding. Resonance Raman spectra show no significant alterations in spectral regions sensitive to interactions between the heme iron and the proximal histidine residue, confirming that the functional differences in the variant are due to distal-side heme pocket alterations. These effects are discussed in the context of a schematic representation of heme pocket wells and barriers that could aid the design of novel hemoglobins with altered ligand affinity without loss of the normal allosteric responses that facilitate unloading of oxygen to respiring tissues.