Title: How Does Hemoglobin Regulate its O₂-Affinity and Cooperativity?

Abstract:

Human hemoglobin (Hb) is an efficient O₂-transporter in the blood. This red tetramer hemoproteins binds four O₂/tetramer at an arterial O₂-pressure of 100 Torr (in the lung) and releases them at a venous O₂-pressure of <40 Torr (in the capillary) at 37°C, in order to deliver O₂ to the tissues, by reversibly changing its O₂-affinity depending on the O₂-pressure of the environment (the cooperativity). The current widely-accepted hypothesis of the mechanism of the cooperativity of Hb was proposed by Perutz [1], that was based upon the stereoechemical molecular structures of deoxy- and oxy-Hb, which he had determined by X-ray crystallography. Deoxy-Hb has a more rigid tetramer structures (the T-quaternary structure), which constrains the coordination structure of the heme group, leading to a low O₂-affinity state. As four O₂ bind successively to Hb, its structure changes to a less rigid R-quaternary state, in which all the structural constraints are removed, resulted in the unconstrained coordination structure of the heme groups with a high O₂-affinity.

However, we found that the O₂-affinity of either deoxy- or oxy-Hb can be reduced as much as >10³-folds by heterotropic effectors such as 2,3-BPG, IHP, and BZF without detectable changes in the T-/R-quaternary/tertiary structure as well as the coordination structures of the heme group [2-4]. Thus, we were not able to find the casual correlation between T-/R-quaternary structures and the low/high O₂-affinities, as proposed by Perutz [1].

In Hb, the apparent O₂-affinity is controlled by regulating the physical barrier of globin against the migration of O₂ through protein matrix from the “caged” state to solvent [5-7]. The physical barrier is lowered by the heterotropic effector-linked, high-frequency thermal fluctuations [8], which make the protein barrier more and more transparent to small ligands like O₂. Thus, the apparent O₂-affinity of Hb is controlled by protein-structural dynamics rather than the static T-/R-quaternary/tertiary structural changes of Hb [4].