Ligand Binding in Hemoglobin: the Work of Quentin H. Gibson

Oxygen Binding and Subunit Interaction of Hemoglobin in Relation to the Two-state Model

Ligand Recombination to the α and β Subunits of Human Hemoglobin

Quentin Howieson Gibson was born in Aberdeen, Scotland in 1918. He attended Queen's University Belfast and received his M.B., Ch.B. degree in 1941, his M.D. in 1944, and his Ph.D. in 1946. After graduating, he became a lecturer in the Department of Physiology at the University of Sheffield and worked his way up to become Professor and Head of the Department of Biochemistry by 1955.

In 1963, Gibson came to the U.S. and joined the faculty of the Graduate School of Medicine at the University of Pennsylvania as a Professor of Physiology. He remained at Penn until 1965 when he became the Greater Philadelphia Professor of Biochemistry, Molecular and Cell Biology at Cornell University. In 1996, Gibson joined the Department of Biochemistry and Cell Biology at Rice University.

Gibson is probably best known for his research on the structure and function of hemoglobin. The hemoglobin molecule consists of four globular protein subunits, each of which contains a heme group that can bind to one molecule of oxygen. The binding of oxygen to hemoglobin is cooperative, the first bound oxygen alters the shape of the molecule to increase the binding affinity of the additional subunits. Conversely, hemoglobin's oxygen binding capacity is decreased in the presence of carbon monoxide because both gases compete for the same binding sites on hemoglobin, carbon monoxide binding preferentially in place of oxygen.

Gibson started his hemoglobin studies in graduate school, submitting a thesis titled “Methaemoglobin,” in which he studied the form of hemoglobin where the iron in the heme group is in the Fe³⁺ state rather than the Fe²⁺ state and is thus unable to carry oxygen. He followed this up with research on familial idiopathic methemoglobinemia, a hereditary hematological disease in which hemoglobin is unable to bind to oxygen, causing dyspnea and fatigue after physical exertion. He was able to identify the pathway involved in the reduction of methemoglobin (1), thereby describing the first hereditary disorder involving an enzyme deficiency. As a result, the disease was named “Gibson's syndrome.” Since then, Gibson has made numerous additional contributions to the study of hemoglobin, some of which are detailed in the two Journal of Biological Chemistry (JBC) Classics reprinted here.
In the first Classic, Gibson and Stuart J. Edelstein look at the oxygen binding and subunit interaction in hemoglobin. In 1965, Jacques Monod, Jeffries Wyman, and Jean-Pierre Changeux proposed a model which stated that proteins that exhibit cooperativity can exist in only two conformational states, and the equilibrium between these two states is modified by binding of a ligand, oxygen in the case of hemoglobin (2). This became known as the “concerted” or the “MWC” model, for Monod, Wyman, and Changeux. (More information on Wyman’s research on protein chemistry and allosterism can be found in his JBC Classic (3).)

By the mid-1980s, several groups had found evidence that challenged this model as it related to the mechanistic basis of ligand binding by hemoglobin. For example, Frederick C. Mills and Gary K. Ackers reported that the subunit interactions of hemoglobin decreased on binding of the fourth molecule of oxygen to hemoglobin (4). The effect, which they called “quaternary enhancement,” was incompatible with the two-state MWC allosteric model. In the first Classic, Gibson and Edelstein measured the free energy of binding of the fourth oxygen molecule and compared their result of $\Delta G = -8.6 \text{ kcal/mol}$ with Mills and Acker’s result of $\Delta G = -9.3 \text{ kcal/mol}$. Gibson’s smaller value was consistent with other values found in the literature, and it also allowed reasonable representation of the equilibrium curve using the two-state model without invoking quaternary enhancement.

In the second JBC Classic, Gibson looks at ligand binding in human hemoglobin. This paper was an extension of an analysis Gibson had done the previous year on ligand rebinding to sperm whale myoglobin (5). In the paper reprinted here, Gibson and his colleagues explored the rebinding of CO, O2, NO, methyl, ethyl, n-propyl, and n-butyl isocyanide to the isolated $\alpha$- and $\beta$-chains of hemoglobin as well as the intact molecule. From these experiments the researchers were able to determine the differences between the overall rate constants of the two hemoglobin subunits as well as the differences in binding of the various ligands.

In recognition of his contributions to science, Gibson has earned many honors including memberships in the Royal Society of London, the National Academy of Sciences, and the American Association for the Advancement of Science. He served as an Associate Editor for the JBC from 1975 to 1994.

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REFERENCES