Proteins: Myoglobin & Hemoglobin

6

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BIOMEDICAL IMPORTANCE

The heme proteins myoglobin and hemoglobin maintain a supply of oxygen essential for oxidative metabolism. Myoglobin, a monomeric protein of red muscle, stores oxygen as a reserve against oxygen deprivation. Hemoglobin, a tetrameric protein of erythrocytes, transports O_2 to the tissues and returns CO_2 and protons to the lungs. Cyanide and carbon monoxide kill because they disrupt the physiologic function of the heme proteins cytochrome oxidase and hemoglobin, respectively. The secondary-tertiary structure of the subunits of hemoglobin resembles myoglobin. However, the tetrameric structure of hemoglobin permits cooperative interactions that are central to its function. For example, 2,3-bisphosphoglycerate (BPG) promotes the efficient release of O_2 by stabilizing the quaternary structure of deoxyhemoglobin. Hemoglobin and myoglobin illustrate both protein structure-function relationships and the molecular basis of genetic diseases such as sickle cell disease and the thalassemias.

HEME & FERROUS IRON CONFER THE ABILITY TO STORE & TO TRANSPORT OXYGEN

Myoglobin and hemoglobin contain **heme,** a cyclic tetrapyrrole consisting of four molecules of pyrrole linked by α-methylene bridges. This planar network of conjugated double bonds absorbs visible light and colors heme deep red. The substituents at the β-positions of heme are methyl (M), vinyl (V), and propionate (Pr) groups arranged in the order M, V, M, V, M, Pr, Pr, M (Figure 6–1). One atom of ferrous iron (Fe_2^+) resides at the center of the planar tetrapyrrole. Other proteins with metal-containing tetrapyrrole prosthetic groups include the cytochromes (Fe and Cu) and chlorophyll (Mg) (see Chapter 12). Oxidation and reduction of the Fe and Cu atoms of cytochromes is essential to their biologic function as carriers of electrons. By contrast, oxidation of the Fe_2^+ of myoglobin or hemoglobin to Fe_3^+ destroys their biologic activity.

Myoglobin Is Rich in α Helix

Oxygen stored in red muscle myoglobin is released during O_2 deprivation (eg, severe exercise) for use in muscle mitochondria for aerobic synthesis of ATP (see Chapter 12). A 153-aminoacyl residue polypeptide (MW 17,000), myoglobin folds into a compact shape that measures 4.5 × 3.5 × 2.5 nm (Figure 6–2). Unusually high proportions, about 75%, of the residues are present in eight right-handed, 7–20 residue α helices. Starting at the amino terminal, these are termed helices A–H. Typical of globular proteins, the surface of myoglobin is polar, while—with only two exceptions—the interior contains only nonpolar residues such as Leu, Val, Phe, and Met. The exceptions are His E7 and His F8, the seventh and eighth residues in helices E and F, which lie close to the heme iron where they function in O_2 binding.

Histidines F8 & E7 Perform Unique Roles in Oxygen Binding

The heme of myoglobin lies in a crevice between helices E and F oriented with its polar propionate groups facing the surface of the globin (Figure 6–2). The remainder resides in the nonpolar interior. The fifth coordination position of the iron is linked to a ring nitrogen of the **proximal histidine,** His F8. The **distal histidine,** His E7, lies on the side of the heme ring opposite to His F8.

The Iron Moves Toward the Plane of the Heme When Oxygen Is Bound

The iron of unoxygenated myoglobin lies 0.03 nm (0.3 Å) outside the plane of the heme ring, toward His F8. The heme therefore "puckers" slightly. When O_2 occupies the sixth coordination position, the iron moves to within 0.01 nm (0.1 Å) of the plane of the heme ring. Oxygenation of myoglobin thus is accompanied by motion of the iron, of His F8, and of residues linked to His F8.

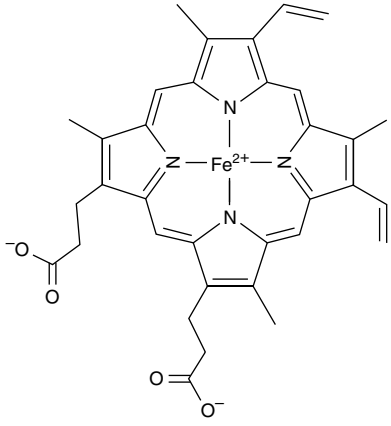


Figure 6–1. Heme. The pyrrole rings and methylene bridge carbons are coplanar, and the iron atom (Fe_2^+) resides in almost the same plane. The fifth and sixth coordination positions of Fe_2^+ are directed perpendicular to—and directly above and below—the plane of the heme ring. Observe the nature of the substituent groups on the β carbons of the pyrrole rings, the central iron atom, and the location of the polar side of the heme ring (at about 7 o'clock) that faces the surface of the myoglobin molecule.

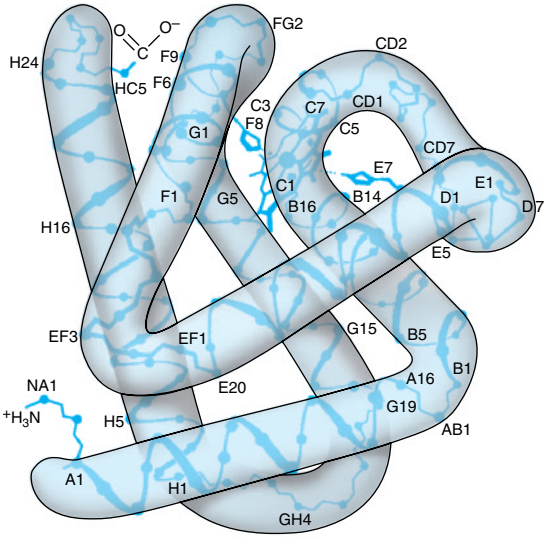


Figure 6–2. A model of myoglobin at low resolution. Only the α-carbon atoms are shown. The α-helical regions are named A through H. (Based on Dickerson RE in: The Proteins, 2nd ed. Vol 2. Neurath H [editor]. Academic Press, 1964. Reproduced with permission.)

Apomyoglobin Provides a Hindered Environment for Heme Iron

When O_2 binds to myoglobin, the bond between the first oxygen atom and the Fe_2^+ is perpendicular to the plane of the heme ring. The bond linking the first and second oxygen atoms lies at an angle of 121 degrees to the plane of the heme, orienting the second oxygen away from the distal histidine (Figure 6–3, left). Isolated heme binds carbon monoxide (CO) 25,000 times more strongly than oxygen. Since CO is present in small quantities in the atmosphere and arises in cells from the catabolism of heme, why is it that CO does not completely displace O_2 from heme iron? The accepted explanation is that the apoproteins of myoglobin and hemoglobin create a **hindered environment.** While CO can bind to isolated heme in its preferred orientation, ie, with all three atoms (Fe, C, and O) perpendicular to the plane of the heme, in myoglobin and hemoglobin the distal histidine sterically precludes this orientation. Binding at a less favored angle reduces the strength of the heme-CO bond to about 200 times that of the heme-O_2 bond (Figure 6–3, right) at which level the great excess of O_2 over CO normally present dominates. Nevertheless, about 1% of myoglobin typically is present combined with carbon monoxide.

THE OXYGEN DISSOCIATION CURVES FOR MYOGLOBIN & HEMOGLOBIN SUIT THEIR PHYSIOLOGIC ROLES

Why is myoglobin unsuitable as an O_2 transport protein but well suited for O_2 storage? The relationship between the concentration, or partial pressure, of O_2 (P_{O_2}) and the quantity of O_2 bound is expressed as an O_2 saturation isotherm (Figure 6–4). The oxygen-

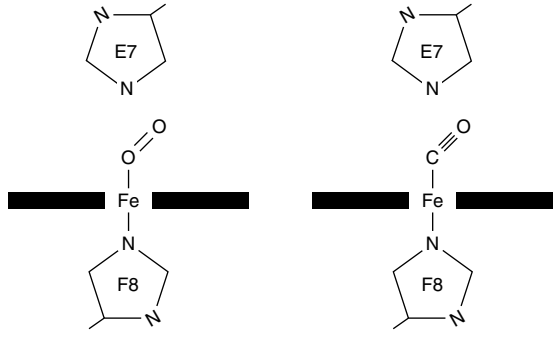


Figure 6–3. Angles for bonding of oxygen and carbon monoxide to the heme iron of myoglobin. The distal E7 histidine hinders bonding of CO at the preferred (180 degree) angle to the plane of the heme ring.

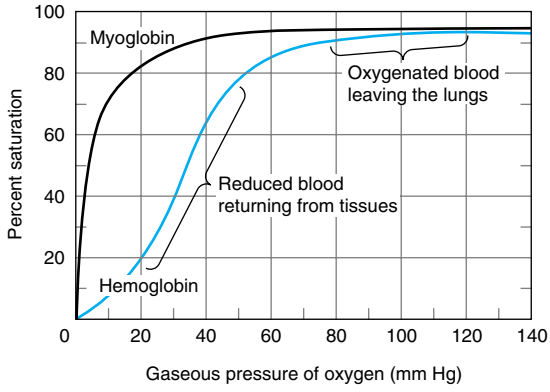


Figure 6–4. Oxygen-binding curves of both hemoglobin and myoglobin. Arterial oxygen tension is about 100 mm Hg; mixed venous oxygen tension is about 40 mm Hg; capillary (active muscle) oxygen tension is about 20 mm Hg; and the minimum oxygen tension required for cytochrome oxidase is about 5 mm Hg. Association of chains into a tetrameric structure (hemoglobin) results in much greater oxygen delivery than would be possible with single chains. (Modified, with permission, from Scriver CR et al [editors]: The Molecular and Metabolic Bases of Inherited Disease, 7th ed. McGraw-Hill, 1995.)

binding curve for myoglobin is hyperbolic. Myoglobin therefore loads O_2 readily at the P_{O_2} of the lung capillary bed (100 mm Hg). However, since myoglobin releases only a small fraction of its bound O_2 at the P_{O_2} values typically encountered in active muscle (20 mm Hg) or other tissues (40 mm Hg), it represents an ineffective vehicle for delivery of O_2. However, when strenuous exercise lowers the P_{O_2} of muscle tissue to about 5 mm Hg, myoglobin releases O_2 for mitochondrial synthesis of ATP, permitting continued muscular activity.

THE ALLOSTERIC PROPERTIES OF HEMOGLOBINS RESULT FROM THEIR QUATERNARY STRUCTURES

The properties of individual hemoglobins are consequences of their quaternary as well as of their secondary and tertiary structures. The quaternary structure of hemoglobin confers striking additional properties, absent from monomeric myoglobin, which adapts it to its unique biologic roles. The **allosteric** (Gk *allos* "other," *steros* "space") properties of hemoglobin provide, in addition, a model for understanding other allosteric proteins (see Chapter 11).

Hemoglobin Is Tetrameric

Hemoglobins are tetramers comprised of pairs of two different polypeptide subunits. Greek letters are used to designate each subunit type. The subunit composition of the principal hemoglobins are $\alpha_2\beta_2$ (HbA; normal adult hemoglobin), $\alpha_2\gamma_2$ (HbF; fetal hemoglobin), α_2S_2 (HbS; sickle cell hemoglobin), and $\alpha_2\delta_2$ (HbA_2; a minor adult hemoglobin). The primary structures of the β, γ, and δ chains of human hemoglobin are highly conserved.

Myoglobin & the β Subunits of Hemoglobin Share Almost Identical Secondary and Tertiary Structures

Despite differences in the kind and number of amino acids present, myoglobin and the β polypeptide of hemoglobin A have almost identical secondary and tertiary structures. Similarities include the location of the heme and the eight helical regions and the presence of amino acids with similar properties at comparable locations. Although it possesses seven rather than eight helical regions, the α polypeptide of hemoglobin also closely resembles myoglobin.

Oxygenation of Hemoglobin Triggers Conformational Changes in the Apoprotein

Hemoglobins bind four molecules of O_2 per tetramer, one per heme. A molecule of O_2 binds to a hemoglobin tetramer more readily if other O_2 molecules are already bound (Figure 6–4). Termed **cooperative binding,** this phenomenon permits hemoglobin to maximize both the quantity of O_2 loaded at the P_{O_2} of the lungs and the quantity of O_2 released at the P_{O_2} of the peripheral tissues. Cooperative interactions, an exclusive property of multimeric proteins, are critically important to aerobic life.

P_{50} Expresses the Relative Affinities of Different Hemoglobins for Oxygen

The quantity P_{50}, a measure of O_2 concentration, is the partial pressure of O_2 that half-saturates a given hemoglobin. Depending on the organism, P_{50} can vary widely, but in all instances it will exceed the P_{O_2} of the peripheral tissues. For example, values of P_{50} for HbA and fetal HbF are 26 and 20 mm Hg, respectively. In the placenta, this difference enables HbF to extract oxygen from the HbA in the mother's blood. However, HbF is suboptimal postpartum since its high affinity for O_2 dictates that it can deliver less O_2 to the tissues.

The subunit composition of hemoglobin tetramers undergoes complex changes during development. The

human fetus initially synthesizes a $\zeta_2\varepsilon_2$ tetramer. By the end of the first trimester, ζ and γ subunits have been replaced by α and ε subunits, forming HbF ($\alpha_2\gamma_2$), the hemoglobin of late fetal life. While synthesis of β subunits begins in the third trimester, β subunits do not completely replace γ subunits to yield adult HbA ($\alpha_2\beta_2$) until some weeks postpartum (Figure 6–5).

Oxygenation of Hemoglobin Is Accompanied by Large Conformational Changes

The binding of the first O_2 molecule to deoxyHb shifts the heme iron towards the plane of the heme ring from a position about 0.6 nm beyond it (Figure 6–6). This motion is transmitted to the proximal (F8) histidine and to the residues attached thereto, which in turn causes the rupture of salt bridges between the carboxyl terminal residues of all four subunits. As a consequence, one pair of α/β subunits rotates 15 degrees with respect to the other, compacting the tetramer (Figure 6–7). Profound changes in secondary, tertiary, and quaternary structure accompany the high-affinity O_2-induced transition of hemoglobin from the low-affinity **T (taut) state** to the **R (relaxed) state.** These changes significantly increase the affinity of the remaining unoxygenated hemes for O_2, as subsequent binding events require the rupture of fewer salt bridges (Figure 6–8). The terms T and R also are used to refer to the low-affinity and high-affinity conformations of allosteric enzymes, respectively.

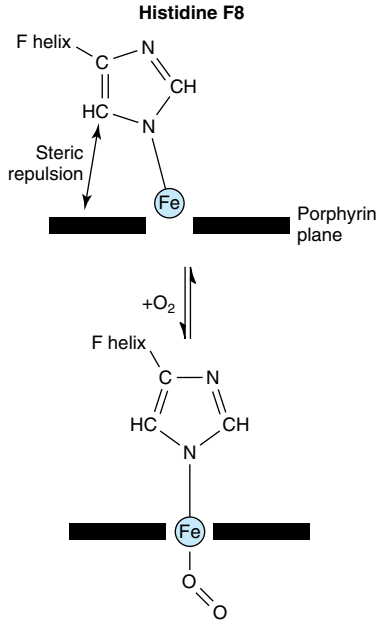


Figure 6–6. The iron atom moves into the plane of the heme on oxygenation. Histidine F8 and its associated residues are pulled along with the iron atom. (Slightly modified and reproduced, with permission, from Stryer L: *Biochemistry,* 4th ed. Freeman, 1995.)

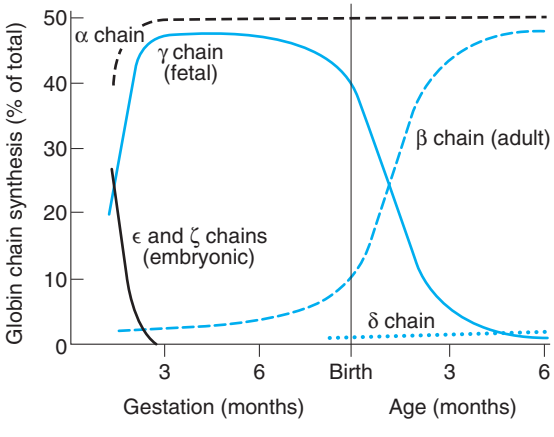


Figure 6–5. Developmental pattern of the quaternary structure of fetal and newborn hemoglobins. (Reproduced, with permission, from Ganong WF: *Review of Medical Physiology,* 20th ed. McGraw-Hill, 2001.)

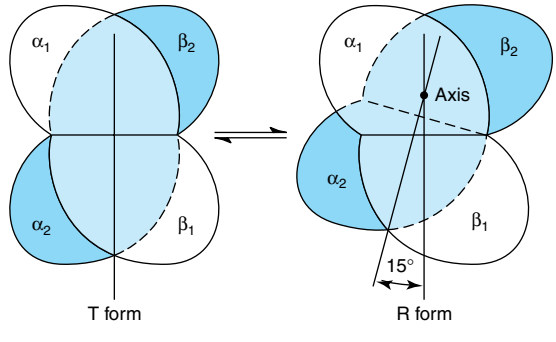


Figure 6–7. During transition of the T form to the R form of hemoglobin, one pair of subunits (α_2/β_2) rotates through 15 degrees relative to the other pair (α_1/β_1). The axis of rotation is eccentric, and the α_2/β_2 pair also shifts toward the axis somewhat. In the diagram, the unshaded α_1/β_1 pair is shown fixed while the colored α_2/β_2 pair both shifts and rotates.

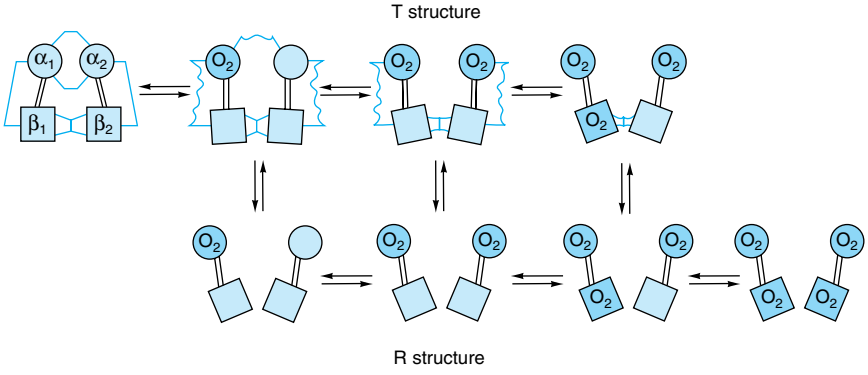


Figure 6–8. Transition from the T structure to the R structure. In this model, salt bridges (thin lines) linking the subunits in the T structure break progressively as oxygen is added, and even those salt bridges that have not yet ruptured are progressively weakened (wavy lines). The transition from T to R does not take place after a fixed number of oxygen molecules have been bound but becomes more probable as each successive oxygen binds. The transition between the two structures is influenced by protons, carbon dioxide, chloride, and BPG; the higher their concentration, the more oxygen must be bound to trigger the transition. Fully oxygenated molecules in the T structure and fully deoxygenated molecules in the R structure are not shown because they are unstable. (Modified and redrawn, with permission, from Perutz MF: Hemoglobin structure and respiratory transport. Sci Am [Dec] 1978;239:92.)

After Releasing O_2 at the Tissues, Hemoglobin Transports CO_2 & Protons to the Lungs

In addition to transporting O_2 from the lungs to peripheral tissues, hemoglobin transports CO_2, the byproduct of respiration, and protons from peripheral tissues to the lungs. Hemoglobin carries CO_2 as carbamates formed with the amino terminal nitrogens of the polypeptide chains.

$$CO_2 + Hb{-}NH_3^+ = 2H^+ + Hb{-}\overset{H}{N}{-}\overset{O}{\overset{\|}{C}}{-}O^-$$

Carbamates change the charge on amino terminals from positive to negative, favoring salt bond formation between the α and β chains.

Hemoglobin carbamates account for about 15% of the CO_2 in venous blood. Much of the remaining CO_2 is carried as bicarbonate, which is formed in erythrocytes by the hydration of CO_2 to carbonic acid (H_2CO_3), a process catalyzed by carbonic anhydrase. At the pH of venous blood, H_2CO_3 dissociates into bicarbonate and a proton.

$$CO_2 + H_2O \xrightleftharpoons{\text{CARBONIC ANHYDRASE}} H_2CO_3 \xrightleftharpoons{\text{(Spontaneous)}} HCO_3^- + H^+$$

Carbonic acid

Deoxyhemoglobin binds one proton for every two O_2 molecules released, contributing significantly to the buffering capacity of blood. The somewhat lower pH of peripheral tissues, aided by carbamation, stabilizes the T state and thus enhances the delivery of O_2. In the lungs, the process reverses. As O_2 binds to deoxyhemoglobin, protons are released and combine with bicarbonate to form carbonic acid. Dehydration of H_2CO_3, catalyzed by carbonic anhydrase, forms CO_2, which is exhaled. Binding of oxygen thus drives the exhalation of CO_2 (Figure 6–9).This reciprocal coupling of proton and O_2 binding is termed the **Bohr effect.** The Bohr effect is dependent upon **cooperative interactions between the hemes of the hemoglobin tetramer.** Myoglobin, a monomer, exhibits no Bohr effect.

Protons Arise From Rupture of Salt Bonds When O_2 Binds

Protons responsible for the Bohr effect arise from rupture of salt bridges during the binding of O_2 to T state

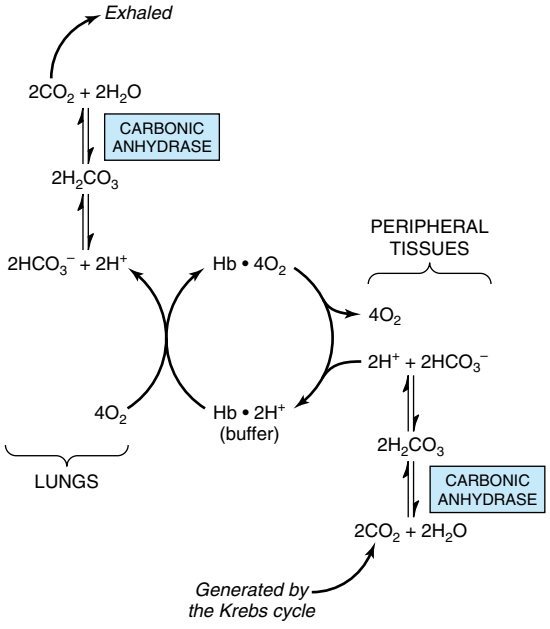
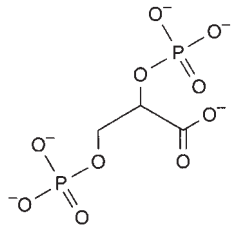


Figure 6–9. The Bohr effect. Carbon dioxide generated in peripheral tissues combines with water to form carbonic acid, which dissociates into protons and bicarbonate ions. Deoxyhemoglobin acts as a buffer by binding protons and delivering them to the lungs. In the lungs, the uptake of oxygen by hemoglobin releases protons that combine with bicarbonate ion, forming carbonic acid, which when dehydrated by carbonic anhydrase becomes carbon dioxide, which then is exhaled.

hemoglobin. Conversion to the oxygenated R state breaks salt bridges involving β-chain residue His 146. The subsequent dissociation of protons from His 146 drives the conversion of bicarbonate to carbonic acid (Figure 6–9). Upon the release of O_2, the T structure and its salt bridges re-form. This conformational change increases the pK_a of the β-chain His 146 residues, which bind protons. By facilitating the re-formation of salt bridges, an increase in proton concentration enhances the release of O_2 from oxygenated (R state) hemoglobin. Conversely, an increase in P_{O_2} promotes proton release.

2,3-Bisphosphoglycerate (BPG) Stabilizes the T Structure of Hemoglobin

A low P_{O_2} in peripheral tissues promotes the synthesis in erythrocytes of 2,3-bisphosphoglycerate (BPG) from the glycolytic intermediate 1,3-bisphosphoglycerate.



The hemoglobin tetramer binds one molecule of BPG in the central cavity formed by its four subunits. However, the space between the H helices of the β chains lining the cavity is sufficiently wide to accommodate BPG only when hemoglobin is in the T state. BPG forms salt bridges with the terminal amino groups of both β chains via Val NA1 and with Lys EF6 and His H21 (Figure 6–10). BPG therefore stabilizes deoxygenated (T state) hemoglobin by forming additional salt bridges that must be broken prior to conversion to the R state.

Residue H21 of the γ subunit of fetal hemoglobin (HbF) is Ser rather than His. Since Ser cannot form a salt bridge, BPG binds more weakly to HbF than to HbA. The lower stabilization afforded to the T state by BPG accounts for HbF having a higher affinity for O_2 than HbA.

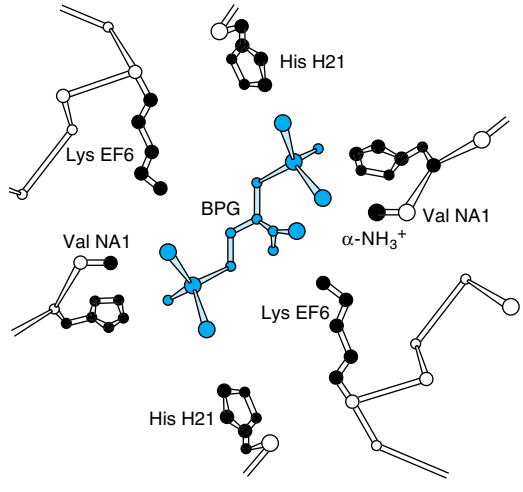


Figure 6–10. Mode of binding of 2,3-bisphosphoglycerate to human deoxyhemoglobin. BPG interacts with three positively charged groups on each β chain. (Based on Arnone A: X-ray diffraction study of binding of 2,3-diphosphoglycerate to human deoxyhemoglobin. Nature 1972;237:146. Reproduced with permission.)

Adaptation to High Altitude

Physiologic changes that accompany prolonged exposure to high altitude include an increase in the number of erythrocytes and in their concentrations of hemoglobin and of BPG. Elevated BPG lowers the affinity of HbA for O_2 (decreases P_{50}), which enhances release of O_2 at the tissues.

NUMEROUS MUTANT HUMAN HEMOGLOBINS HAVE BEEN IDENTIFIED

Mutations in the genes that encode the α or β subunits of hemoglobin potentially can affect its biologic function. However, almost all of the over 800 known mutant human hemoglobins are both extremely rare and benign, presenting no clinical abnormalities. When a mutation does compromise biologic function, the condition is termed a **hemoglobinopathy.** The URL http://globin.cse.psu.edu/ (Globin Gene Server) provides information about—and links for—normal and mutant hemoglobins.

Methemoglobin & Hemoglobin M

In methemoglobinemia, the heme iron is ferric rather than ferrous. Methemoglobin thus can neither bind nor transport O_2. Normally, the enzyme methemoglobin reductase reduces the Fe_3^+ of methemoglobin to Fe_2^+. Methemoglobin can arise by oxidation of Fe_2^+ to Fe_3^+ as a side effect of agents such as sulfonamides, from hereditary hemoglobin M, or consequent to reduced activity of the enzyme methemoglobin reductase.

In hemoglobin M, histidine F8 (His F8) has been replaced by tyrosine. The iron of HbM forms a tight ionic complex with the phenolate anion of tyrosine that stabilizes the Fe_3^+ form. In α-chain hemoglobin M variants, the R-T equilibrium favors the T state. Oxygen affinity is reduced, and the Bohr effect is absent. β-Chain hemoglobin M variants exhibit R-T switching, and the Bohr effect is therefore present.

Mutations (eg, hemoglobin Chesapeake) that favor the R state increase O_2 affinity. These hemoglobins therefore fail to deliver adequate O_2 to peripheral tissues. The resulting tissue hypoxia leads to **polycythemia,** an increased concentration of erythrocytes.

Hemoglobin S

In HbS, the nonpolar amino acid valine has replaced the polar surface residue Glu6 of the β subunit, generating a hydrophobic **"sticky patch"** on the surface of the β subunit of both oxyHbS and deoxyHbS. Both HbA and HbS contain a complementary sticky patch on their surfaces that is exposed only in the deoxygenated, R state. Thus, at low P_{O_2}, deoxyHbS can polymerize to form long, insoluble fibers. Binding of deoxyHbA terminates fiber polymerization, since HbA lacks the second sticky patch necessary to bind another Hb molecule (Figure 6–11). These twisted helical fibers distort the erythrocyte into a characteristic sickle shape, rendering it vulnerable to lysis in the interstices of the splenic sinusoids. They also cause multiple secondary clinical effects. A low P_{O_2} such as that at high altitudes exacerbates the tendency to polymerize.

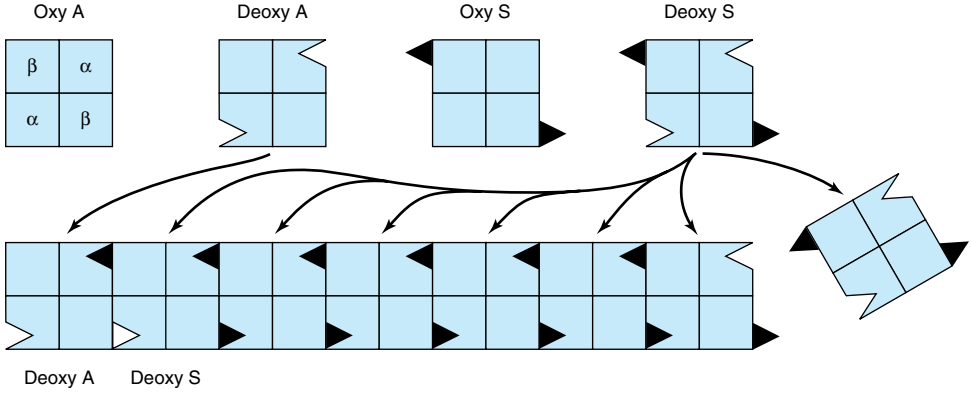


Figure 6–11. Representation of the sticky patch (▲) on hemoglobin S and its "receptor" (△) on deoxyhemoglobin A and deoxyhemoglobin S. The complementary surfaces allow deoxyhemoglobin S to polymerize into a fibrous structure, but the presence of deoxyhemoglobin A will terminate the polymerization by failing to provide sticky patches. (Modified and reproduced, with permission, from Stryer L: *Biochemistry,* 4th ed. Freeman, 1995.)

BIOMEDICAL IMPLICATIONS

Myoglobinuria

Following massive crush injury, myoglobin released from damaged muscle fibers colors the urine dark red. Myoglobin can be detected in plasma following a myocardial infarction, but assay of serum enzymes (see Chapter 7) provides a more sensitive index of myocardial injury.

Anemias

Anemias, reductions in the number of red blood cells or of hemoglobin in the blood, can reflect impaired synthesis of hemoglobin (eg, in iron deficiency; Chapter 51) or impaired production of erythrocytes (eg, in folic acid or vitamin B_{12} deficiency; Chapter 45). Diagnosis of anemias begins with spectroscopic measurement of blood hemoglobin levels.

Thalassemias

The genetic defects known as thalassemias result from the partial or total absence of one or more α or β chains of hemoglobin. Over 750 different mutations have been identified, but only three are common. Either the α chain (alpha thalassemias) or β chain (beta thalassemias) can be affected. A superscript indicates whether a subunit is completely absent (α^0 or β^0) or whether its synthesis is reduced (α^+ or β^+). Apart from marrow transplantation, treatment is symptomatic.

Certain mutant hemoglobins are common in many populations, and a patient may inherit more than one type. Hemoglobin disorders thus present a complex pattern of clinical phenotypes. The use of DNA probes for their diagnosis is considered in Chapter 40.

Glycosylated Hemoglobin (HbA_{1c})

When blood glucose enters the erythrocytes it glycosylates the ε-amino group of lysine residues and the amino terminals of hemoglobin. The fraction of hemoglobin glycosylated, normally about 5%, is proportionate to blood glucose concentration. Since the half-life of an erythrocyte is typically 60 days, the level of glycosylated hemoglobin (HbA_{1c}) reflects the mean blood glucose concentration over the preceding 6–8 weeks. Measurement of HbA_{1c} therefore provides valuable information for management of diabetes mellitus.

SUMMARY

- Myoglobin is monomeric; hemoglobin is a tetramer of two subunit types ($\alpha_2\beta_2$ in HbA). Despite having different primary structures, myoglobin and the subunits of hemoglobin have nearly identical secondary and tertiary structures.
- Heme, an essentially planar, slightly puckered, cyclic tetrapyrrole, has a central Fe_2^+ linked to all four nitrogen atoms of the heme, to histidine F8, and, in oxyMb and oxyHb, also to O_2.
- The O_2-binding curve for myoglobin is hyperbolic, but for hemoglobin it is sigmoidal, a consequence of cooperative interactions in the tetramer. Cooperativity maximizes the ability of hemoglobin both to load O_2 at the P_{O_2} of the lungs and to deliver O_2 at the P_{O_2} of the tissues.
- Relative affinities of different hemoglobins for oxygen are expressed as P_{50}, the P_{O_2} that half-saturates them with O_2. Hemoglobins saturate at the partial pressures of their respective respiratory organ, eg, the lung or placenta.
- On oxygenation of hemoglobin, the iron, histidine F8, and linked residues move toward the heme ring. Conformational changes that accompany oxygenation include rupture of salt bonds and loosening of quaternary structure, facilitating binding of additional O_2.
- 2,3-Bisphosphoglycerate (BPG) in the central cavity of deoxyHb forms salt bonds with the β subunits that stabilize deoxyHb. On oxygenation, the central cavity contracts, BPG is extruded, and the quaternary structure loosens.
- Hemoglobin also functions in CO_2 and proton transport from tissues to lungs. Release of O_2 from oxyHb at the tissues is accompanied by uptake of protons due to lowering of the pK_a of histidine residues.
- In sickle cell hemoglobin (HbS), Val replaces the β6 Glu of HbA, creating a "sticky patch" that has a complement on deoxyHb (but not on oxyHb). DeoxyHbS polymerizes at low O_2 concentrations, forming fibers that distort erythrocytes into sickle shapes.
- Alpha and beta thalassemias are anemias that result from reduced production of α and β subunits of HbA, respectively.

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