3: Globular Proteins

Overview

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The previous chapter described the types of secondary and tertiary structures that are the bricks and mortar of protein architecture. By arranging these fundamental structural elements in different combinations, widely diverse proteins capable of various specialized functions can be constructed. Two important protein structures are globular proteins and fibrous proteins (or scleroproteins). As the name implies, globular proteins are spherical (or “globelike”) in overall shape. They are usually somewhat water-soluble, possessing many hydrophilic amino acids on their outer surface, facing the aqueous environment. More nonpolar amino acids face the interior of the protein, providing hydrophobic interactions to further stabilize the globular structure. This is in contrast to fibrous proteins, which form long rodlike filaments, are relatively inert or water-insoluble, and provide structural support in the extracellular environment. This chapter examines the relationship between structure and function for clinically important globular hemeproteins, such as hemoglobin and myoglobin. Fibrous structural proteins, such as collagen and elastin, are discussed in Chapter 4.

Globular Hemeproteins

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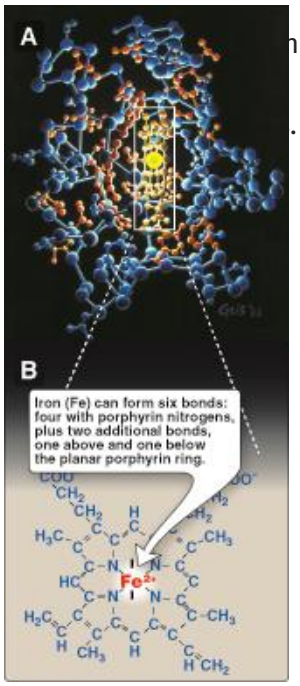
Hemeproteins are a group of specialized globular proteins that contain heme as a tightly bound prosthetic group (see p. 59 for a discussion of prosthetic groups). The function of the heme group is dictated by the three-dimensional structure of the protein. In the mitochondrial electron transport chain, the cytochrome protein structure allows for rapid and reversible oxidation–reduction electron transfer of the heme-coordinated iron, reversibly transitioning between its ferrous (Fe^{2+}) and ferric (Fe^{3+}) states (see p. 83). In the enzyme catalase, the heme group is structurally part of the enzyme's active site, which catalyzes the breakdown of hydrogen peroxide (see p. 163). The protein structure of hemoglobin can affect the alignment of the ferrous (Fe^{2+}) iron with respect to the plane of the heme prosthetic group. Changes in this alignment can affect the binding affinity and transport of oxygen by hemoglobin between the lungs and tissues.

Heme structure

Heme is a planar structure, comprised of a porphyrin ring with ferrous iron (Fe^{2+}) coordinated in the porphyrin ring center, as shown in Figure 3.1. The iron is held in the center of the heme molecule by bonds to four nitrogens of the porphyrin ring. The heme Fe^{2+} can form two additional bonds, one on each side of the planar porphyrin ring. In hemoglobin, one of these positions is coordinated to the side chain of a histidine residue of the globin molecule, whereas the other position is available to bind O_2 (Fig. 3.2).

FIGURE 3.1



nrome c). **B:** Structure of heme.

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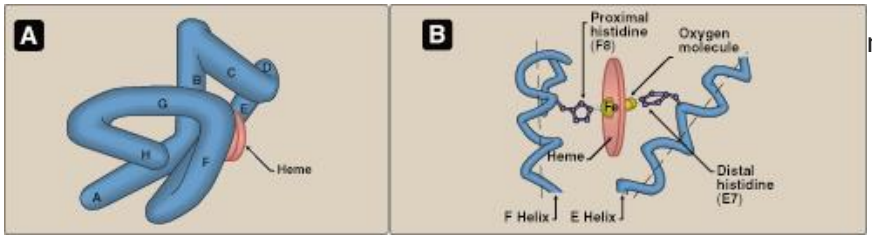
FIGURE 3.2



m of the oxygen-binding site of

Myoglobin structure and function

Myoglobin, a hemeprotein present in heart and skeletal muscle, functions both as an oxygen reservoir and as an oxygen carrier that increases the rate of oxygen transport within the muscle cell. Myoglobin consists of a single polypeptide chain that is structurally similar to the individual polypeptide chains of the tetrameric hemoglobin molecule. This homology makes myoglobin a useful model for interpreting some of the more complex properties of hemoglobin.

α-Helical content

Myoglobin is a compact molecule, with ~80% of its polypeptide chain folded into eight stretches of α-helix. These α-helical regions, labeled A to H in Figure 3.2A, are terminated either by the presence of proline, whose five-membered ring cannot be accommodated in an α-helix (see p. 16) or by β-bends and loops stabilized by hydrogen bonds and ionic bonds (see p. 19). (Note: Ionic bonds are also termed electrostatic interactions or salt bridges.)

Location of polar and nonpolar amino acid residues

The interior of the globular myoglobin molecule is composed almost entirely of nonpolar amino acids. Nonpolar amino acids are packed closely together, forming a structure stabilized by hydrophobic interactions between these clustered residues (see p. 19). In contrast, polar amino acids are located almost exclusively on the surface, where they can form hydrogen bonds, both with each other and with water.

Binding of the heme group

The heme prosthetic group of the myoglobin molecule sits in a crevice, which is lined with nonpolar amino acids. Notable exceptions are two histidine residues, which are basic amino acids (Fig. 3.2B). One of the two histidine residues, the proximal histidine (F8), binds directly to the Fe^{2+} of heme. The second, or distal histidine (E7), does not directly interact with the heme group but helps stabilize the binding of O_2 to Fe^{2+}. Thus, the protein, or globin, portion of myoglobin creates a special microenvironment for the heme that permits oxygenation, the reversible binding of one oxygen molecule. The simultaneous loss of electrons by Fe^{2+} (oxidation to the ferric [Fe^{3+}] form) occurs only rarely.

Hemoglobin structure and function

Hemoglobin is found exclusively in red blood cells (RBCs), where its main function is to transport O_2 from the lungs to the capillaries of the tissues. Hemoglobin A (HbA), the major hemoglobin in adults, is composed of four polypeptide chains (two α chains and two β chains) held together by noncovalent interactions (Fig. 3.3). Each chain (subunit) has stretches of α-helical structure and a hydrophobic heme-binding pocket similar to that described for myoglobin. However, the tetrameric hemoglobin molecule is structurally and functionally more complex than myoglobin. For example, hemoglobin can transport protons (H^+) and carbon dioxide (CO_2) from the tissues to the lungs and can carry four molecules of O_2 from the lungs to the cells of the body. Furthermore, the oxygen-binding properties of hemoglobin are regulated by interaction with allosteric effectors (see p. 30).

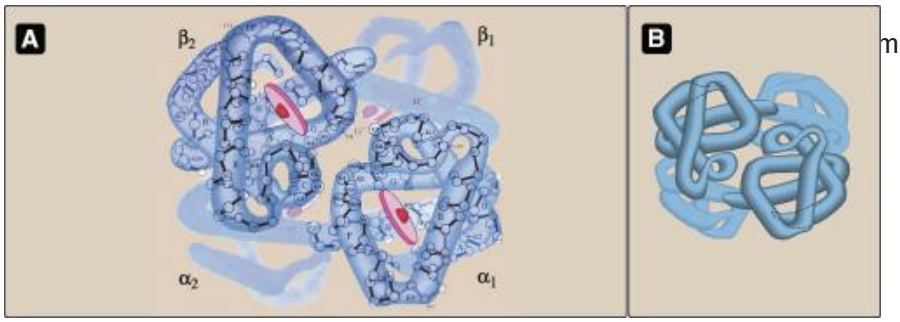
Quaternary structure

The hemoglobin tetramer can be envisioned as composed of two identical dimers, $\alpha\beta_1$ and $\alpha\beta_2$. The two polypeptide chains within each dimer are held tightly together primarily by hydrophobic interactions (Fig. 3.4). (Note: In this instance, hydrophobic amino acid residues are localized not only in the interior of the molecule but also in a region on the surface of each subunit. Multiple interchain hydrophobic interactions form strong associations between the α-subunit and the β-subunit in each of the dimers.) In contrast, the two dimers are held together primarily by polar bonds. The weaker interactions between the dimers allow them to move with respect to one other. This movement results in the two dimers occupying different relative positions in deoxyhemoglobin as compared with oxyhemoglobin (see Fig. 3.4).

T form

The deoxy form of hemoglobin is called the "T," or taut (tense) form. In the T form, the two αβ dimers interact through a network of ionic bonds and hydrogen bonds that constrain the movement of the polypeptide chains. The iron (Fe^{2+}) is pulled out of the heme planar structure. The T conformation is the low–oxygen-affinity form of hemoglobin.

FIGURE 3.3



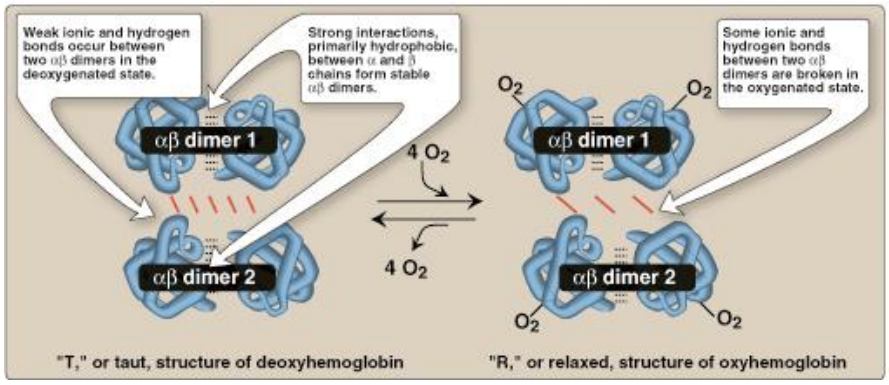
mplified drawing showing the α-helices.

Obtaining O_2 from the atmosphere solely by diffusion greatly limits the size of organisms. Circulatory systems overcome this, but transport molecules such as hemoglobin are also required because O_2 is only slightly soluble in aqueous solutions such as blood.

R form

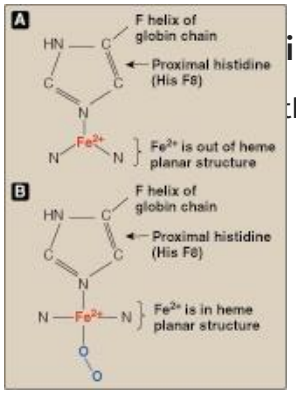
The binding of O_2 to hemoglobin causes the rupture of some of the polar bonds between the two αβ dimers, allowing movement of the Fe^{2+} with respect to the planar heme structure. Specifically, the binding of O_2 to the heme Fe^{2+} pulls the iron more directly into the plane of the heme ring structure (Fig. 3.5B). Because the iron is also linked to the proximal histidine (F8), the resulting movement of the globin chains alters the interface between the αβ dimers, leading to a structure called the "R," or relaxed form (see Fig. 3.4). The R conformation is the high–oxygen-affinity form of hemoglobin.

FIGURE 3.4



oxygenation and deoxygenation of

FIGURE 3.5



iron (Fe^{2+}).

the heme when oxygen (O_2) is not bound. **B:** Into the plane of the heme upon O_2 binding.

Oxygen binding to myoglobin and hemoglobin

Myoglobin can bind only one molecule of O_2, because it contains only one heme group. In contrast, hemoglobin can bind four molecules of O_2, one at each of its four heme groups. The degree of saturation (Y) of these oxygen-binding sites on all myoglobin or hemoglobin molecules can vary between zero (all sites are empty) and 100% (all sites are full), as shown in Figure 3.6. (Note: Pulse oximetry is a noninvasive, indirect method of measuring the oxygen saturation of arterial blood based on differences in light absorption by oxyhemoglobin and deoxyhemoglobin.)

Oxygen-dissociation curve

A plot of the degree of saturation (Y) measured at different partial pressures of oxygen (pO_2) is called the oxygen-dissociation curve. (Note: pO_2 may also be represented as PO_2.) The curves for myoglobin and hemoglobin show important differences (see Fig. 3.6). This graph illustrates that myoglobin has a higher oxygen affinity at all pO_2 values than does hemoglobin. The partial pressure of oxygen needed to achieve half saturation of the binding sites (P_{50}) is ~1 mm Hg for myoglobin and 26 mm Hg for hemoglobin. The higher the oxygen affinity (i.e., the more tightly O_2 binds), the lower the P_{50}.

Myoglobin

The oxygen-dissociation curve for myoglobin has a hyperbolic shape (see Fig. 3.6). This reflects the fact that myoglobin reversibly binds a single molecule of O_2. Thus, oxygenated (MbO_2) and deoxygenated (Mb) myoglobin exists in a simple equilibrium:

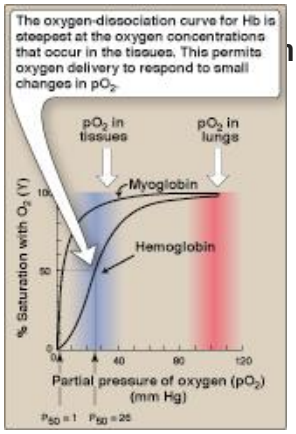
$$Mb + O_2 \rightleftarrows MbO_2$$

The equilibrium is shifted to the right or to the left as O_2 is added to or removed from the system. (Note: Myoglobin is designed to bind O_2 released by hemoglobin at the low pO_2 found in muscle. Myoglobin, in turn, releases O_2 within the muscle cell in response to oxygen demand.)

Hemoglobin

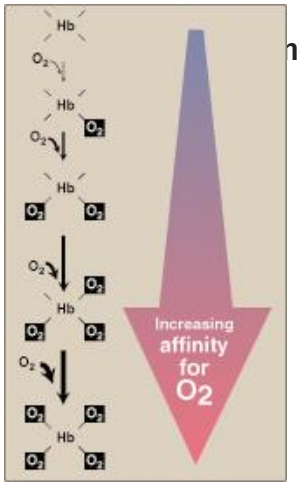
The oxygen-dissociation curve for hemoglobin is sigmoidal in shape (see Fig. 3.6), indicating that the subunits cooperate in binding O_2. Cooperative binding of O_2 by the four subunits of hemoglobin means that the binding of an oxygen molecule at one subunit increases the oxygen affinity of the remaining subunits in the same hemoglobin tetramer (Fig. 3.7). Although it is more difficult for the first oxygen molecule to bind to hemoglobin, the subsequent binding of oxygen molecules occurs with high affinity, as shown by the steep upward curve in the region near 20 to 30 mm Hg (see Fig. 3.6).

FIGURE 3.6



n curves for myoglobin and hemoglobin (Hb).

FIGURE 3.7



nds successive mole-cules of oxygen (O_2) with increasing affinity.

Allosteric effectors

The ability of hemoglobin to reversibly bind O_2 is affected by the pO_2, the pH of the environment, the partial pressure of carbon dioxide (pCO_2), and the concentration of 2,3-bisphosphoglycerate (2,3-BPG). These are collectively called allosteric ("other site") effectors, because their interaction at one site on the tetrameric hemoglobin molecule causes structural changes that affect the binding of O_2 to the heme iron at other sites on the molecule. (Note: The binding of O_2 to monomeric myoglobin is not influenced by allosteric effectors.)

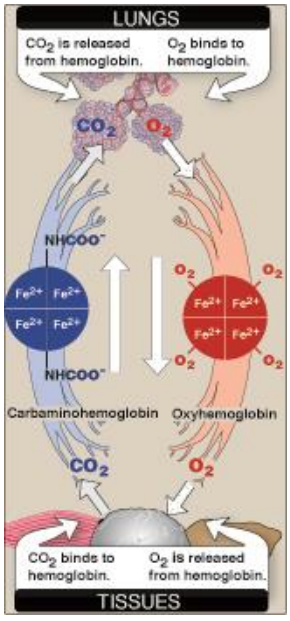
Oxygen

The sigmoidal oxygen-dissociation curve reflects specific structural changes that are initiated at one subunit and transmitted to other subunits in the hemoglobin tetramer. The net effect of this cooperativity is that the affinity of hemoglobin for the last oxygen molecule bound is ~300 times greater than its affinity for the first oxygen molecule bound. Oxygen, then, is an allosteric effector of hemoglobin. It stabilizes the R form.

Loading and unloading oxygen

The cooperative binding of O_2 allows hemoglobin to deliver more O_2 to the tissues in response to relatively small changes in the pO_2. This can be seen in Figure 3.6, which indicates pO_2 in the alveoli of the lung and the capillaries of the tissues. For example, in the lung, oxygen concentration is high, and hemoglobin becomes virtually saturated (or "loaded") with O_2. In contrast, in the peripheral tissues where the pO_2 is much lower than in the lungs, oxyhemoglobin releases (or "unloads") much of its O_2 for use in the oxidative metabolism of the tissues (Fig. 3.8).

FIGURE 3.8



and carbon dioxide by hemoglobin.

Significance of the sigmoidal oxygen-dissociation curve

The steep slope of the oxygen-dissociation curve over the range of oxygen concentrations that occur between the lungs and the tissues permits hemoglobin to carry and deliver O_2 efficiently from sites of high to sites of low pO_2. A molecule with a hyperbolic oxygen-dissociation curve, such as myoglobin, could not achieve the same degree of O_2 release within this range of pO_2. Instead, it would have maximum affinity for O_2 throughout this oxygen pressure range and, therefore, would deliver no O_2 to the tissues.

Bohr effect

The release of O_2 from hemoglobin is enhanced when the pH is lowered (proton concentration $[H^+]$ is increased) or when the hemoglobin is in the presence of an increased pCO_2. Both result in decreased oxygen affinity of hemoglobin and, therefore, a shift to the right in the oxygen-dissociation curve (Fig. 3.9). Both, then, stabilize the T (deoxy) form. This change in oxygen binding is called the Bohr effect. Conversely, raising the pH or lowering the concentration of CO_2 results in a greater oxygen affinity, a shift to the left in the oxygen-dissociation curve, and stabilization of the R (oxy) form.

Source of the protons that lower pH

The concentration of both H^+ and CO_2 in the capillaries of metabolically active tissues is higher than that observed in alveolar capillaries of the lungs, where CO_2 is released into the expired air. In the tissues, zinc-containing carbonic anhydrase converts CO_2 to carbonic acid:

$$CO_2 + H_2O \rightleftarrows H_2CO_3$$

which spontaneously ionizes to bicarbonate (the major blood buffer) and H^+:

$$H_2CO_3 \rightleftarrows HCO_3^- + H^+$$

The H^+ produced by this pair of reactions contributes to the lowering of pH. This differential pH gradient (i.e., lungs having a higher pH and tissues having a lower pH) favors the unloading of O_2 in the peripheral tissues and the loading of O_2 in the lung. Thus, the oxygen affinity of the hemoglobin molecule responds to small shifts in pH between the lungs and oxygen-consuming tissues, making hemoglobin a more efficient transporter of O_2.

Mechanism of the Bohr effect

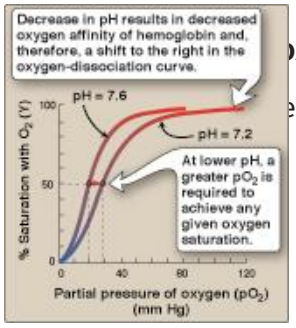
The Bohr effect reflects the fact that deoxyhemoglobin has a greater affinity for H^+ than does oxyhemoglobin. This is caused by ionizable functional groups such as specific histidine side chains that have a higher pK_a (see p. 7) in deoxyhemoglobin than in oxyhemoglobin. Therefore, an increase in the concentration of H^+ (resulting in a decrease in pH) causes these groups to become protonated (charged) and able to form ionic bonds (salt bridges). These bonds preferentially stabilize deoxyhemoglobin, producing a decrease in oxygen affinity. (Note: Hemoglobin, then, is an important blood buffer.)

The Bohr effect can be represented schematically as:

$$HbO_2 + H^+ \rightleftarrows HbH + O_2$$
Oxyhemoglobin Doxyhemoglobin

where an increase in H^+ concentration (or a lower pO_2) shifts the equilibrium to the right (favoring deoxyhemoglobin), whereas an increase in pO_2 (or a decrease in H^+ concentration) shifts the equilibrium to the left.

FIGURE 3.9



oxygen affinity of hemoglobin.

effectors of hemoglobin.

2,3-BPG effect on oxygen affinity

2,3-BPG is an important regulator of the binding of O_2 to hemoglobin. It is the most abundant organic phosphate in the RBCs, where its concentration is approximately that of hemoglobin. 2,3-BPG is synthesized from an intermediate of the glycolytic pathway (Fig. 3.10; see p. 32 for a discussion of 2,3-BPG synthesis in glycolysis).

2,3-BPG binding to deoxyhemoglobin

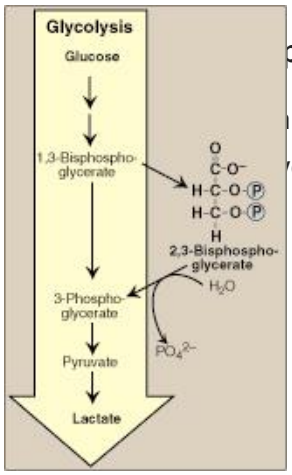
2,3-BPG decreases the oxygen affinity of hemoglobin by binding to deoxyhemoglobin but not to oxyhemoglobin. This preferential binding stabilizes the T conformation of hemoglobin. The effect of binding 2,3-BPG can be represented schematically as:

$$HbO_2 + \text{2,3-BPG} \rightleftarrows Hb - \text{2,3-BPG} + O_2$$
Oxyhemoglobin Doxyhemoglobin

2,3-BPG–binding site

One molecule of 2,3-BPG binds to a pocket, formed by the two β-globin chains, in the center of the deoxyhemoglobin tetramer (Fig. 3.11). This pocket contains several positively charged amino acids that form ionic bonds with the negatively charged phosphate groups of 2,3-BPG. (Note: Replacement of one of these amino acids can result in hemoglobin variants with abnormally high oxygen affinity that may be compensated for by increased RBC production [erythrocytosis].) Oxygenation of hemoglobin narrows the pocket and causes 2,3-BPG to be released.

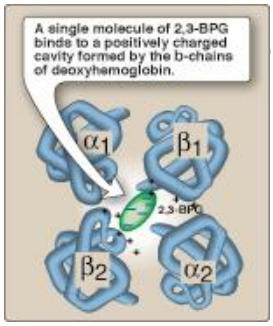
FIGURE 3.10



phosphoglycerate.

noryl group, PO_3^{2-}.) In older literature, 2,3-bisphosphoglycerate (2,3-BPG) may be referred ycerate (2,3-DPG).

FIGURE 3.11

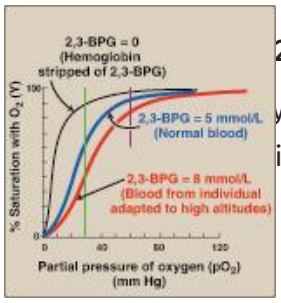


hosphoglycerate (2,3-BPG) by deoxyhemoglobin.

Oxygen-dissociation curve shift

Hemoglobin from which 2,3-BPG has been removed has high oxygen affinity. However the presence of 2,3-BPG significantly reduces the oxygen affinity of hemoglobin, shifting the oxygen-dissociation curve to the right (Fig. 3.12). This reduced affinity enables hemoglobin to release O_2 efficiently at the partial pressures found in the tissues.

FIGURE 3.12



2,3-bisphosphoglycerate (2,3-BPG) on the oxygen affinity of hemoglobin.

ygen in the tissues is indicated by the *green line*. Partial pressure of oxygen in the lungs icated by the *purple line*.

2,3-BPG levels in chronic hypoxia or anemia

The concentration of 2,3-BPG in the RBCs increases in response to chronic hypoxia, such as that observed in chronic obstructive pulmonary disease (COPD) like emphysema, or at high altitudes, where pO_2 is lower and circulating hemoglobin may have difficulty receiving sufficient O_2. Intracellular levels of 2,3-BPG are also elevated in chronic anemia, in which fewer than normal RBCs are available to supply the body's oxygen needs. Elevated 2,3-BPG levels lower the oxygen affinity of hemoglobin, permitting greater unloading of O_2 in the capillaries of tissues (see Fig. 3.12).

CLINICAL APPLICATION 3.1

2,3-BPG Offloads Oxygen to the Tissues

To illustrate the use of 2,3-BPG to offload oxygen to the tissues, consider two conditions: one individual living at sea level with 5 mmol/L 2,3-BPG, who travels to a high altitude where the pO_2 is lower, and another individual who lives at a high altitude and compensates by elevating their 2,3-BPG levels to 8 mmol/L. Hemoglobin in the lungs of the individual with 5 mmol/L 2,3-BPG will be fully saturated at sea level (Fig. 3.12). In the tissues, their hemoglobin is ~60% saturated (indicated by the *green line*), delivering ~40% of the bound oxygen to their tissues. At high altitudes with 5 mmol/L of 2,3-BPG, this same individual's hemoglobin will be only 90% saturated in the lungs (indicated by the *purple line*), so oxygen delivery to their tissues is only 30%. However, the individual living at a high altitude has adapted to have hemoglobin with 8 mmol/L of 2,3-BPG. The oxygen-binding curve shifts to the right. Oxygen saturation in the lungs is now only ~80% (indicated by the *purple line*) and oxygen saturation in the tissues is ~40% (indicated by the *green line*), providing a similar 40% delivery of the bound oxygen to the tissues by the increase in 2,3-BPG levels. The shift in O_2-binding affinity allowed a comparable 40%-oxygen delivery to the tissues.

2,3-BPG in transfused blood

2,3-BPG is essential for the normal oxygen transport function of hemoglobin. However, blood bank–stored blood gradually becomes depleted in 2,3-BPG. Consequently, stored blood displays an abnormally high oxygen affinity and fails to unload its bound O_2 properly in the tissues. Thus, hemoglobin deficient in 2,3-BPG would act as an oxygen "trap" rather than as an oxygen delivery system. Transfused RBCs are able to restore their depleted supplies of 2,3-BPG in 6 to 24 hours. However, severely ill patients may be compromised if transfused with large quantities of such 2,3-BPG–depleted blood. Stored blood, therefore, is treated with a "rejuvenation" solution that rapidly restores 2,3-BPG. (Note: Rejuvenation also restores ATP lost during storage.)

CO_2 binding

Most of the CO_2 produced in metabolism is hydrated and transported as bicarbonate ion (see Fig. 1.12 on p. 9). However, some CO_2 is carried as carbamate bound to the terminal amino groups of hemoglobin (forming carbaminohemoglobin as shown in Fig. 3.8), which can be represented schematically as follows:

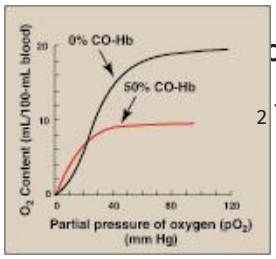
$$Hb - NH_2 + CO_2 \rightleftarrows Hb - NH - COO^- + H^+$$

The binding of CO_2 stabilizes the T, or deoxy, form of hemoglobin, resulting in a decrease in its oxygen affinity (see p. 30) and a right shift in the oxygen-dissociation curve. In the lungs, CO_2 dissociates from the hemoglobin and is released in the breath.

CO binding

Carbon monoxide (CO) binds tightly (but reversibly) to the hemoglobin iron, forming carboxyhemoglobin. When CO binds to one or more of the four heme sites, hemoglobin shifts to the R conformation, causing the remaining heme sites to bind O_2 with high affinity. This shifts the oxygen-dissociation curve to the left and changes the normal sigmoidal shape toward a hyperbola. As a result, the affected hemoglobin is unable to release O_2 to the tissues (Fig. 3.13). (Note: The affinity of hemoglobin for CO is 220 times greater than for O_2. Consequently, even minute concentrations of CO in the environment can produce toxic concentrations of carboxyhemoglobin in the blood. For example, increased levels of CO are found in the blood of tobacco smokers. CO toxicity appears to result from a combination of tissue hypoxia and direct CO-mediated damage at the cellular level.) CO poisoning is treated with 100% O_2 at high pressure (hyperbaric oxygen therapy), which facilitates the dissociation of CO from the hemoglobin. (Note: CO also inhibits Complex IV of the electron transport chain (see p. 84).) Nitric oxide gas (NO) also is carried by hemoglobin. NO is a potent vasodilator (see p. 166). It can be taken up (salvaged) or released from RBCs, thereby modulating NO availability and influencing blood vessel diameter.

FIGURE 3.13



onoxide (CO) on the oxygen affinity of hemoglobin.

2 for binding the heme iron. CO-Hb = carboxyhemoglobin (carbon monoxyhemoglobin).

Minor hemoglobins

It is important to remember that human HbA is just one member of a functionally and structurally related family of proteins, the hemoglobins (Fig. 3.14). Each of these oxygen-carrying proteins is a tetramer, composed of two α-globin (or α-like) polypeptides and two β-globin (or β-like) polypeptides. HbF is synthesized during fetal development, but is represented as <2% of the hemoglobin in adult blood. HbF is concentrated in RBCs known as F cells. HbA_2 is also synthesized in the adult, although at low levels compared with HbA. HbA can become modified by the covalent addition of a hexose (HbA_{1c}, see II.F.3. below).

Fetal hemoglobin

HbF is a tetramer consisting of two α chains identical to those found in HbA, plus two γ chains ($\alpha_2\gamma_2$; see Fig. 3.14). The γ chains are members of the β-globin gene family (see p. 36).

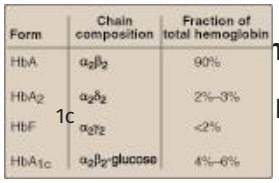
HbF synthesis during development

In the first month after conception, embryonic hemoglobins such as Hb Gower 1, composed of two α-like zeta (ζ) chains and two β-like epsilon (ε) chains ($\zeta_2\varepsilon_2$), are synthesized by the embryonic yolk sac. In the fifth week of gestation, the site of globin synthesis shifts, first to the liver and then to the marrow, and the primary product is HbF. HbF is the major hemoglobin found in the fetus and newborn, accounting for ~60% of the total hemoglobin in the RBCs during the last months of fetal life (Fig. 3.15). HbA synthesis starts in the bone marrow around the eighth month of pregnancy and gradually replaces HbF. Figure 3.15 shows the relative production of each type of hemoglobin chain during fetal and postnatal life.

2,3-BPG binding to HbF

Under physiologic conditions, HbF has a higher oxygen affinity than does HbA as a result of HbF weakly binding 2,3-BPG. (Note: The γ-globin chains of HbF lack some of the positively charged amino acids that are responsible for binding 2,3-BPG in the β-globin chains.) Because 2,3-BPG serves to reduce the oxygen affinity of hemoglobin, the weaker interaction between 2,3-BPG and HbF results in a higher oxygen affinity for HbF relative to HbA. In contrast, if both HbA and HbF are stripped of their 2,3-BPG, they then have a similar oxygen affinity. The higher oxygen affinity of HbF facilitates the transfer of O_2 from the maternal circulation across the placenta to the RBCs of the fetus.

FIGURE 3.14



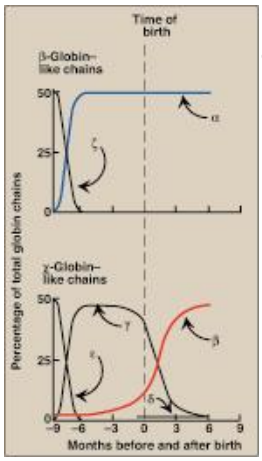
Form	Chain composition	Fraction of total hemoglobin
HbA	$\alpha_2\beta_2$	90%
HbA_2	$\alpha_2\delta_2$	2%–3%
HbF	$\alpha_2\gamma_2$	<2%
HbA_{1c}	$\alpha_2\beta_2$-glucose	4%–6%

ns found in adult blood.

1c

HbA (or HbA_1). (Note: The α chains in these hemoglobins are identical.) Hb = hemoglobin.

FIGURE 3.15



anges in globin production.

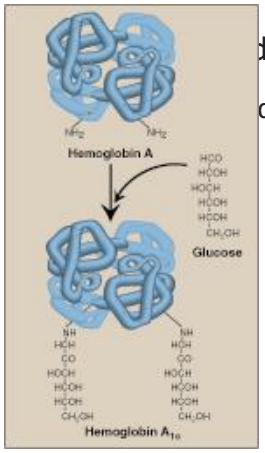
Hemoglobin A_2

HbA_2 is a minor component of normal adult hemoglobin, first appearing shortly before birth and, ultimately, constituting ~2% of the total hemoglobin. It is composed of two α-globin chains and two δ-globin chains ($\alpha_2\delta_2$; see Fig. 3.14).

Hemoglobin A_{1c}

Under physiologic conditions, sugar molecules, predominantly glucose, are added nonenzymatically to HbA in a process referred to as glycation. The extent of glycation is dependent on the plasma concentration of the hexose. The most abundant form of glycated hemoglobin is HbA_{1c}. In HbA_{1c}, glucose residues are attached to the amino groups of the N-terminal valines of the β-globin chains (Fig. 3.16). Increased amounts of HbA_{1c} are found in RBCs of patients with diabetes mellitus, because their HbA has contact with higher glucose concentrations during the 120-day lifetime of these cells (see p. 340 for a discussion of the use of HbA_{1c} levels in assessing average blood glucose levels in patients with diabetes).

FIGURE 3.16



dition of glucose to hemoglobin.

ddition of a sugar to a protein is referred to as glycation.

Globin Gene Organization

Listen

To understand diseases resulting from genetic alterations in the structure or synthesis of hemoglobin, it is necessary to grasp how the hemoglobin genes, which direct the synthesis of the different globin chains, are structurally organized into gene families, and also how they are expressed. Expression of a globin gene begins in RBC precursors, where the DNA sequence encoding the gene is transcribed. Two introns are spliced out to join together three exons into the mature mRNA for translation. A more detailed description of gene expression is presented in Unit VII, Chapters 30, 31, and 32.

α-Gene family

The genes coding for the α-globin and β-globin subunits of the hemoglobin chains occur in two separate gene clusters (or families) located on two different chromosomes (Fig. 3.17). The α-gene cluster on chromosome 16 contains two genes for the α-globin chains. It also contains the ζ gene that is expressed early in development as an α-globin–like component of embryonic hemoglobin. (Note: Globin gene families also contain globin-like genes that are not expressed, i.e., their genetic information is not used to produce globin chains. These are called pseudogenes.)