All living things have a metabolism, which is a set of chemical reactions. For these chemical reactions to happen, some chemicals must enter the organism and others must leave it. The first article in this series explained why it matters whether a substance dissolves in water or fat. This article describes the role of various proteins in the transport of oxygen and carbon dioxide in the bloodstream.

Blood is thicker than water. Blood is also far better than water at transporting oxygen and carbon dioxide. Oxygen (O₂) and carbon dioxide (CO₂) are nonpolar molecules. For this reason, these gases dissolve well in lipids (fats and oily substances) but poorly in water. Thus, they give us a good example of the dilemma of transport, which I described in the first article in this series:

- Lipid-soluble substances can easily pass through the cell membrane to enter or leave a cell, but they are hard to transport in the blood.
- Water-soluble substances can be easily transported in the blood, but it is hard for them to enter or leave cells.

Oxygen and carbon dioxide can easily enter or leave your cells; but how can oxygen get to your cells, and how can carbon dioxide get taken away from your cells? To solve the problems raised by the dilemma of transport, the body makes proteins. Red blood cells have 3 important proteins that make it possible for the blood to transport enough oxygen and carbon dioxide to serve the body’s needs:

- The red pigment hemoglobin
- An enzyme called carbonic anhydrase 1
- A membrane transport protein called solute carrier family 4 member 1 (SLC4A1)

The heart works hard to pump blood so that the blood circulates through the body. This energy-consuming process is an example of active transport. The flow of gases into and out of the bloodstream—and into and out of red blood cells—is an example of passive transport. Passive transport means a net flow of a substance from an area of higher concentration to an area of lower concentration, or a net flow that is “downhill” relative to a voltage gradient.

In this article, I will explain 3 important things:
- Why red blood cells play such an important role in transporting oxygen and carbon dioxide
- How your blood pH affects your respiratory rate
- Why carbon dioxide plays an important role in maintaining a stable pH within the body

OXYGEN AND CARBON DIOXIDE DISSOLVE POORLY IN WATER

As I explained in the first article in this series, water is a polar molecule. Polarity means that the molecule has a lopsided distribution of electrical charge (ie, it has a dipole or multipole moment). A negative pole of one polar molecule will be attracted to a positive pole of a nearby polar molecule. For this reason, water molecules are strongly attracted to one another. That is why water is liquid at room temperature, even though its molecular weight is only about 18 atomic mass units.

Oxygen and carbon dioxide are gases at room temperature, even though their molecular weights are higher than water’s (roughly 32 and 44 atomic mass units, respectively). Water’s polarity also explains why water is such a good solvent for ions (eg, salt) and polar molecules (eg, sugar). However, water is a poor solvent for nonpolar molecules, including oxygen and carbon dioxide. For this reason, the watery portion of the blood can hold only a small amount of oxygen and carbon dioxide—not enough to meet the body’s needs for gas transport.

Nevertheless, blood can carry a lot of oxygen because red blood cells contain hemoglobin, which serves as a transport protein for oxygen. Blood can carry a lot of carbon dioxide partly because some carbon dioxide binds to hemoglobin but mainly because the carbonic anhydrase enzyme in red blood
cells speeds up the conversion of carbon dioxide to bicarbonate anion ($\text{HCO}_3^-$), which dissolves easily in water.

WHAT IS HEMOGLOBIN?

Hemoglobin is the red pigment in our red blood cells (erythrocytes). Hemoglobin is a metalloprotein, meaning it contains metal ions. Each hemoglobin molecule consists of 4 protein subunits and 4 molecules of heme (Figure 1). Heme consists of a porphyrin ring that surrounds an electrically charged atom of iron ($\text{Fe}^{2+}$).4

When the hemoglobin molecule encounters a molecule of oxygen, a reduction-oxidation (redox) reaction takes place.4 The $\text{Fe}^{2+}$ atom is oxidized (ie, loses an electron) to become $\text{Fe}^{3+}$. The oxygen molecule is reduced (ie, gains an electron) to become a superoxide anion ($\text{O}_2^-$). The superoxide anion then forms a complex with the $\text{Fe}^{3+}$. As each hemoglobin molecule contains 4 iron atoms, it can carry up to 4 molecules of oxygen. The oxygenated form of hemoglobin is called oxyhemoglobin. The hemoglobin in the red blood cells increases the blood's ability to carry oxygen by about 70-fold. Hemoglobin can also carry some carbon dioxide and some nitric oxide.

WHY HEMOGLOBIN IS A TRANSPORT PROTEIN

Hemoglobin is useful as an oxygen-transport protein because it can pick up oxygen in areas where oxygen is plentiful (ie, where the partial pressure of oxygen [$\text{PO}_2$] is high) and release the oxygen in areas where oxygen is scarce (where the $\text{PO}_2$ is low). You can see this effect if you look at a graph of the oxygen saturation curve for hemoglobin (Figure 2).

Although hemoglobin binds a lot of oxygen when it is in an area of high oxygen tension (high $\text{PO}_2$), hemoglobin cannot hold as much oxygen in an area of low oxygen tension (low $\text{PO}_2$). As a result, the hemoglobin can pick up oxygen in the lungs and release it in other parts of the body, such as the skeletal muscles.

Figure 2. This graph shows the oxygen saturation curve for normal hemoglobin, as tested in vitro at a pH of 7.6 (top curve), 7.4, and 7.2 (bottom curve). Normal pH is very close to 7.4. The oxygen saturation curve for hemoglobin in vitro is sigmoidal (S-shaped) because the first molecule of oxygen that binds to hemoglobin alters the conformation (3-dimensional shape) of the hemoglobin molecule.4 This conformational change makes it easier for the hemoglobin molecule to bind the other 3 oxygen molecules. Note that hemoglobin has a higher affinity for oxygen at a higher pH. Thus, it would pick up even more oxygen in the high-pH environment of the lungs and release more oxygen in the low-pH environment of the rest of the body. People with sickle-cell anemia have abnormal hemoglobin. The oxygen saturation curve for their hemoglobin would be shifted to the right (lower affinity for oxygen).

Hemoglobin molecules exist in 2 basic conformations (3-dimensional shapes). Deoxygenated hemoglobin is in a “taut” or “tense” (T) state. Once the hemoglobin molecule has picked up at least 2 oxygen molecules, it can transition to
the “relaxed” (R) state, which makes it easier for the hemoglobin molecule to absorb the other 2 oxygen molecules.\(^5\) (This explains why hemoglobin’s oxygen-dissociation curve is sigmoidal [S-shaped]). The binding of hydrogen ions (H\(^+\)), chloride anions (Cl\(^-\)), carbon dioxide, and organic and inorganic phosphates to sites other than the heme groups can affect the transition between the T and R states. As a result, they can help to regulate the function of hemoglobin. Note that hemoglobin’s oxygen-dissociation curve gets shifted to the right by conditions found in exercising muscles (eg, low pH and high temperature). This right shift allows the hemoglobin to deliver oxygen most efficiently where it is needed the most.

People with sickle-cell disease have abnormal hemoglobin that has a lower affinity for oxygen. As a result, the oxygen saturation curve is shifted to the right. On the plus side, this rightward shift allows the blood to unload more oxygen in poorly vascularized tissue. As a result, the patient’s heart will not have to work harder to compensate for the low oxygen-carrying capacity of the blood. The downside is that the venous blood in these patients can become severely deoxygenated. As a result, the abnormal hemoglobin molecules will be more prone to bind together into stiff polymers, causing the red blood cells to become abnormally stiff and sickle-shaped. These stiff, abnormally shaped red blood cells can clog tiny blood vessels and cause severe organ damage.\(^6\) Because of the short life span of their red blood cells, these patients often have a shortage of red blood cells (anemia).

Unfortunately, hemoglobin has a higher affinity for carbon monoxide (CO) than for oxygen. When carbon monoxide binds to hemoglobin, it forms a stable complex called carboxyhemoglobin. As a result, the hemoglobin cannot bind to oxygen. This is why carbon monoxide poisoning can be deadly. Hyperbaric oxygen (pure oxygen supplied at more than atmospheric pressure) is often used to treat carbon monoxide poisoning.\(^7\)

**WHY DISSOLVED CARBON DIOXIDE LOWERS pH**

Hydrogen ions (H\(^+\)) have an important effect on the oxygen saturation curve of hemoglobin. Some of these hydrogen ions are generated by the carbon dioxide that is dissolved in the bodily fluids. When carbon dioxide dissolves in water, some of the carbon dioxide molecules react with a water molecule to form a bicarbonate anion (HCO\(_3^-\)) and a hydrogen ion (H\(^+\)).

\[
\text{CO}_2 + \text{H}_2\text{O} \xrightarrow{\text{carbonic anhydrase}} \text{HCO}_3^- + \text{H}^+
\]

The double-ended arrow indicates that this reaction is reversible. Hydrogen ions are sometimes called protons. Most hydrogen ions consist of a single proton. However, some hydrogen ions have 1 or even 2 neutrons attached to the proton.

Normally, you would expect the pH of pure water to be 7.0, which is neutral (see sidebar). But if you expose pure water to atmospheric air, the pH will drop to approximately 5.8 because of the hydrogen ions released by this reaction. This pH is actually a bit higher than you might expect, given the amount of carbon dioxide that has reacted with the water. That’s because some of the hydrogen ions bind to bicarbonate anions to form carbonic acid.

\[
\text{HCO}_3^- + \text{H}^+ \xrightarrow{\text{bicarbonate}} \text{H}_2\text{CO}_3
\]

Again, the double-ended arrow indicates that the reaction is reversible. Carbonic acid is a diprotic acid, meaning it can give up as many as 2 hydrogen ions. However, it is a weak acid. Only a small percentage of the carbonic acid molecules in a water solution will give up even 1 proton, to yield a bicarbonate ion (HCO\(_3^-\)). An even smaller percentage of carbonic acid molecules will give up both protons, to become a carbonate anion (CO\(_3^{2-}\)). The bicarbonate and carbonate anions can act as a buffer. If you add additional hydrogen ions to a bicarbonate solution, many of those hydrogen ions will react with the bicarbonate to yield water and carbon dioxide, which may leave the solution as a gas. This is why you get bubbles of carbon dioxide when you add an acid, such as vinegar, to baking soda (sodium bicarbonate).

**CARBON DIOXIDE MAKES HEMOGLOBIN RELEASE MORE OXYGEN**

This conversion of dissolved carbon dioxide to bicarbonate is normally so slow that it would have no useful effect on gas transport in the body. However, red blood cells contain an enzyme called carbonic anhydrase 1, which speeds up the reaction about a millionfold. This reaction has several effects.

- It decreases the carbon dioxide concentration within the red blood cells. As a result, it creates a concentration gradient that allows more carbon dioxide to flow “downhill” from the surrounding tissue into the red blood cells.\(^8\)
- It generates hydrogen ions, which can then bind to hemoglobin. The hydrogen ions help to convert the hemoglobin to the tense state, so that it releases more oxygen.\(^5\)
- It generates bicarbonate ions. As the concentration of bicarbonate ions inside the red blood cell rises, the bicarbonate ions start to flow out of the red blood cell through the
SLC4A1 transporter. SLC4A1 is an antiporter; it passively allows bicarbonate anions to leave the cell, but it uses the resulting energy to import a chloride anion. The chloride anions then bind to the hemoglobin, contributing to the tense state, so that the hemoglobin releases more oxygen.10

These effects explain a phenomenon called the Bohr effect, which is that low pH and high PCO₂ both cause the oxygen saturation curve of hemoglobin to shift to the right (Figure 2). Thus, the blood can release even more oxygen in low-oxygen areas where there is a lot of carbon dioxide and/or a lot of lactic acid (eg, in exercising skeletal muscle).

**CARBON DIOXIDE TRANSPORT**

Because carbon dioxide is poorly soluble in water, only a tiny amount of the carbon dioxide in the blood that is being returned from the rest of the body to the lungs is in the form of dissolved carbon dioxide. About 80% of it is in the form of bicarbonate ions that are produced in the red blood cells and released into the plasma.8 A small amount of carbon dioxide is bound directly to the protein portion of hemoglobin, to form carbaminohemoglobin.10

When the deoxygenated, carbon dioxide–rich blood returns to the lungs, it releases carbon dioxide and absorbs oxygen. Some of this gas exchange is the result of simple diffusion. As there is more carbon dioxide in the returning blood than in the air in the lungs, there will be a net flow of carbon dioxide from the blood to the air spaces of the lungs. As there is more oxygen in the air spaces in the lungs than in the blood returning from the rest of the body, there also will be a net flow of oxygen from the atmosphere to the blood.

In addition, this gas exchange is increased because of chemical changes in the blood. These chemical changes are basically a reversal of the changes I described above.

- Carbonic anhydrase 1 will speed up the reaction of bicarbonate anions and hydrogen ions to yield water and carbon dioxide; the carbon dioxide can then diffuse out of the red blood cell and out of the bloodstream.
- As the bicarbonate level inside the red blood cell drops, there will be a net flow of bicarbonate back into the red blood cell and a net flow of chloride out of the red blood cell, through the SLC4A1 antiporter.
- As the concentration of hydrogen ions and chloride ions in the red blood cell decreases, the hemoglobin is able to transition to the relaxed state so that it can pick up more oxygen (Bohr effect).
- As oxygen diffuses into red blood cells, it tends to displace the carbon dioxide that was bound to the hemoglobin (Haldane effect). This carbon dioxide can then diffuse out of the cell and out of the bloodstream.

**CARBON DIOXIDE AND pH BALANCE**

If oxygen stopped entering your bloodstream, you would quickly die. Yet low oxygen levels, as detected by oxygen sensors in your body, have only a small effect on your drive to breathe. This is why pilots flying at high altitudes in an unpressurized airplane would often pass out before they felt respiratory distress. (For this reason, federal aviation regulations require pilots to use supplemental oxygen during high-altitude flights.) Instead, your breathing rate is controlled mainly by the pH of your bodily fluids, which in turn is controlled mainly by the amount of carbon dioxide in your tissue. High PCO₂ in bodily fluids would result in low blood pH and thus a high drive to breathe. In people who have abnormally low blood pH because of excess acids produced by metabolism (metabolic acidosis), such as in cases of diabetic ketoacidosis or kidney failure, the strong drive to breathe can produce deep and labored breathing, which is called Kussmaul respiration.11

If you cannot get rid of enough carbon dioxide, your blood pH will be low. If your blood pH drops below 7.35 because of suppressed or impaired ventilation, the condition is called respiratory acidosis. On the other hand, if you hyperventilate, you can end up with abnormally low levels of carbon dioxide in the blood. This would raise the blood pH. If you hyperventilate to the point that your blood pH rises above 7.45, you would be in respiratory alkalosis.

During the course of a normal day, large amounts of acidic and alkaline substances enter the bloodstream. Yet the pH of the blood is supposed to remain steady at almost exactly 7.4. To maintain this steady pH, the body relies on a buffer. A buffer is a solution that resists changes in pH when acids or alkalis are added to it. Buffers are usually made out of a combination of a weak acid (eg, carbonic acid [H₂CO₃]) and its conjugate base (ie, bicarbonate anion [HCO₃⁻]). Look at what would happen if you added some strong acid (eg, hydrochloric acid) or a strong base (eg, sodium hydroxide) to the blood:

- **Add hydrochloric acid**: HCl + HCO₃⁻ →H₂CO₃ + Cl⁻; the bicarbonate ions will mop up hydrogen ions from the hydrochloric acid. As a result, there would be little or no drop in pH.
- **Add sodium hydroxide**: 2NaOH + H₂CO₃ →Na₂CO₃ + 2H₂O; the carbonic acid will dissociate to release protons to bind with the hydroxide ions (OH⁻). As a result, there will be an increase in bicarbonate and carbonate anions but little or no rise in pH.

Thus, the buffering capacity of your blood can keep your blood pH stable, despite the acids and alkalis that enter and leave your bloodstream during the course of a normal day. Adding even a strong acid or a strong base to a buffered solution will cause little change in pH until the solution’s buffering capacity is exhausted. If, however, you exceed the buffering
capacity of your blood and start to have an abnormal rise or fall in pH, your autonomic nervous system will adjust your breathing rate down or up to compensate.

ANEMIA IMPAIRS OXYGEN TRANSPORT
Your hemoglobin clearly plays an important role in transporting oxygen and carbon dioxide in your bloodstream. However, your red blood cells are responsible for carrying the hemoglobin. Hemoglobin is so reactive that it would cause problems if it were loose in the bloodstream. That's why diseases that cause hemolysis (destruction of red blood cells) can cause serious problems, such as clotting and inflammation. Hemolysis can also lead to anemia. Anemia is a general term for any problem that involves a shortage of red blood cells or a shortage of hemoglobin within the red blood cells.

Hemoglobin clearly plays an important role in carrying oxygen and carbon dioxide. Future articles in this series will give more details about gas exchange and circulation, as well as how the blood carries other substances, including lipids such as cholesterol.

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Laurie Endicott Thomas is the author of 5 books. Her book Thin Diabetes, Fat Diabetes: Prevent Type 1, Cure Type 2 (www.thindiabetes.com) explains how a severe shortage of insulin leads to problems with blood pH (diabetic ketoacidosis).

References