NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Presents

Caught Red-Handed!

Hemoglobin, Carbon Monoxide, and a Butcher's Knife

by

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Part I – The Brooklyn Butcher?**

In December of 1926, John Taft was caught disposing of the dismembered body of Ms. Frannie Beauregard off the Brooklyn waterfront on a Tuesday at midnight. Taft, a 27-year-old longshoreman, was arrested and charged with murder after a patrolman confronted him near India Wharf. He was found to be in possession of the bright red torso of Ms. Beauregard, his neighbor. After searching his nearby apartment, the investigators found the victim's lower extremities and several knives. Taft, soon dubbed the "Brooklyn Butcher," claimed that he and the victim had an argument and he had then fallen asleep. After waking up with a splitting headache, he found his neighbor dead on the floor and then began to dismember the body. When speaking to police, he claimed he woke up feeling dizzy, disoriented, and nauseous. When examining Ms. Beauregard's body, the medical examiner, Dr. Charles Norwood, hypothesized that her death came not at the hands of Mr. Taft, but from a cause less gruesome; he believed her death to be the result of carbon monoxide poisoning.

Questions

1. Describe the protein hemoglobin and its function in transport of gasses (oxygen and carbon dioxide) in the body.

2. Provide at least five signs or symptoms of carbon monoxide poisoning.

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*These four undergraduate students contributed equally to the creation of this case study and are listed in alphabetical order.

**The storyline in this case study is a work of fiction, but closely follows a true story as relayed in Chapter 6 of *The Poisoner's Handbook: Murder and the Birth of Forensic Medicine in Jazz Age New York* by Deborah Blum (2010). Also see the corresponding film version, *The Poisoner's Handbook* (2013), an episode in the PBS series *American Experience.*

Part II – Hemoglobin Function

Adult hemoglobin is a protein that contains two alpha chains and two beta chains, each of which contains a heme subgroup that binds oxygen. When all four binding sites are occupied by oxygen, the hemoglobin is referred to as oxyhemoglobin (OHb). However, when oxygen is not bound to the sites, it is called deoxyhemoglobin. The configuration of both the heme group and the hemoglobin molecule itself change upon binding to oxygen, resulting in a conformational change. Oxygen binding to hemoglobin is cooperative, meaning that each additional oxygen molecule has a higher affinity for the heme group than the previous one (the molecule always has a higher affinity for the fourth oxygen vs. the first). Once oxygen binds to the heme, a conformational change in the heme portion begins to occur, "opening up" the molecule and making it easier for subsequent oxygen molecules to bind. This relationship is reversed as oxygen is released from hemolglobin (harder to release the first O_2 vs. the fourth O_2). Oxyhemoglobin is the relaxed state (conformation) of the molecule (R state; sometimes called the loose or L state), while deoxyhemoglobin is the tensed, or taut, state (T state). When hemoglobin has a greater affinity for oxygen it is in the relaxed state. When it has a decreased affinity for oxygen it is in the tensed state. Watch the following two videos for a better understanding.

- ***Video 1: Animation of the T to R Transition of Hemoglobin.*** Red indicates oxygenated, whereas blue represents deoxygenated state of hemoglobin. The heme group is shown in ball and stick representation, and the histidine is shown in the bottom center of the movie. The video first focuses on a heme group, and then zooms out to depict the structure of the tetramer. *Credit:* Janet Iwasa, CC BY-NC-ND 3.0 US, <https://biochem.web.utah.edu/iwasa/projects/hemoglobin.html>.
- ***Video 2: Conformational Changes Lead to Changes in the Affinity of Hemoglobin for Oxygen.*** This animation illustrates the requirement of two bound oxygens for T to R transition. *Credit:* Janet Iwasa, CC BY-NC-ND 3.0 US, <https://biochem.web.utah.edu/iwasa/projects/hemoglobin.html>.

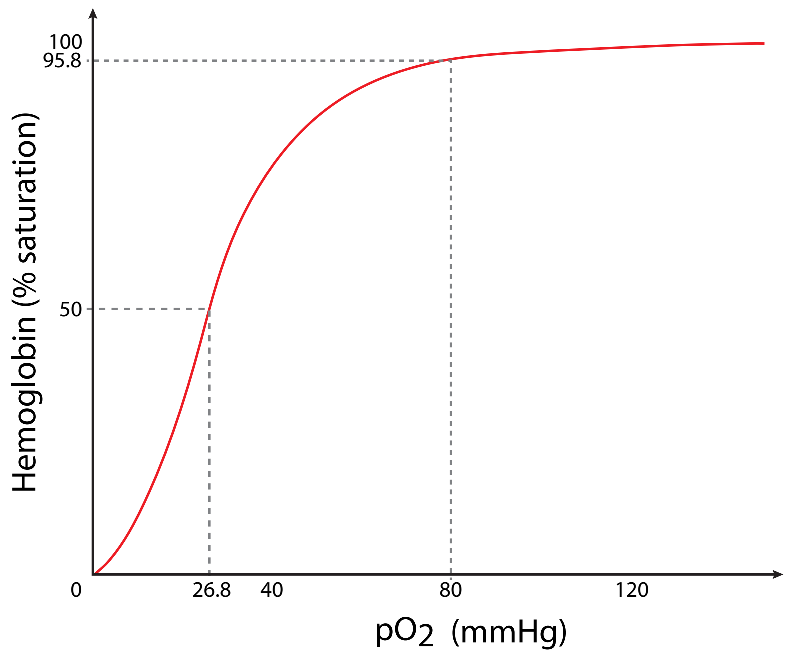
The specific details are complex, but in general, hemoglobin and oxyhemoglobin absorb different wavelengths of light. Due to conformational changes, oxyhemoglobin appears more bright reddish, whereas deoxyhemoglobin appears more maroon, or dark red, in color. These color changes are due in part to the way in which the molecule absorbs light, based on its configuration. Basically, oxyhemoglobin absorbs less red light, and thus reflects it, whereas deoxyhemoglobin absorbs more red light and thus appears less red.

Question

3. Draw a model or cartoon schematic of adult hemoglobin. Make sure to include the four chains and the heme groups. Also, note where in the structure oxygen would bind.

The oxygen-hemoglobin saturation curve, also called the oxygen dissociation curve, displays the relationship between the hemoglobin binding sites occupied by oxygen and the partial pressure of oxygen (see below graph). This curve allows one to estimate the affinity of hemoglobin for oxygen over a range of O_2 partial pressures (pO_2). At sea level, the partial pressure of oxygen in the lungs is around 100 mm Hg (air pressure at sea level 760 mm Hg; the pO_2 in ambient air at sea level is ~160 mm Hg, but in the lungs, the partial pressure of CO_2 and the humidity lower the PO_2 to about 100 mm Hg). Hemoglobin binds oxygen when pO_2 is high, and releases the oxygen when the PO_2 is low.

Due to the structure of hemoglobin, the upper limit of binding is four oxygen molecules per molecule of hemoglobin. Once this saturation is reached, no more oxygen can be bound as there are no more binding sites, even if the pO2 increases. At lung (atmospheric) pO_2, the hemoglobin molecules are saturated. As the blood moves from the lungs through the systemic vasculature the pO_2 drops to about 40 mm Hg; the affinity decreases and oxygen is dropped at the tissues. In muscles (skeletal and heart), the dropped oxygen is bound by myoglobin (similar to hemoglobin, but it only has one binding site for oxygen). Note the shape of the graph to the right; the line is not linear but sigmoidal in shape. This pattern has to do with the cooperative binding properties of the molecule. In addition to the conformational changes noted with additional oxygen binding, other molecules can alter the affinity of hemoglobin for oxygen. These types of molecules are termed allosteric regulators (they bind to a site other than the main [here, oxygen] binding site to alter the function of the molecule).



Questions

4. Using the graph above, at what partial pressure of oxygen would you expect hemoglobin to be fully saturated with oxygen? Would the molecule be in the R state or the T state at this point?

5. Describe what happens to oxygen-hemoglobin binding affinity in a right- vs. left-shifted binding curve.

6. Describe how increases and decreases in each of the following shift the binding affinity of hemoglobin for oxygen: pH, temperature, and CO_2 partial pressure (include right vs. left shift in your response).

Part III –Carbon Monoxide

Carbon monoxide (CO) is an odorless, colorless, and tasteless gas. It can be found in the body (in very small quantities), in the products of combustion (vehicle exhaust), from burning of natural gas, from the metabolism of certain chemicals (e.g., methylene chloride), and from cigarette smoke. CO binds to hemoglobin readily; the heme iron in hemoglobin has a higher affinity, roughly 200–250 times greater, for CO as compared to oxygen. Given its high affinity, CO out-competes oxygen for hemoglobin binding and can displace oxygen from hemoglobin. Additionally, binding of CO to hemoglobin changes the structure of that molecule toward the relaxed state, making it more difficult to drop oxygen at tissues. When CO binds to hemoglobin, the product is carboxyhemoglobin or COHb. The COHb releases the CO more slowly than OHb (oxygenated hemoglobin) releases oxygen. The elimination half-life of COHb is around 4–6 h when an individual is breathing normal sea-level atmospheric air. Signs and symptoms of carbon monoxide exposure can appear when COHb levels are 10–20% and death generally occurs when COHb concentrations are 60% or greater. COHb percentage can be as high as 15% in smokers! (For comparison, levels are ~1–3% in non-smokers.)

Questions

7. Draw the structural formula (e.g., Lewis Dot, ball and stick, or simple structural bonding diagram) of oxygen gas, carbon monoxide gas, and carbon dioxide gas.

8. What route does carbon monoxide take to enter the body?

9. In respect to hemoglobin, how would you suspect that carbon monoxide leads to hypoxic tissue injuries and eventually death?

10. Based on what you now know, how do you think CO will shift the oxygen binding curve? Why?

11. Now, look at the following article:
    Blumenthal, I. 2001. Carbon monoxide poisoning. *Journal of the Royal Society of Medicine* 94(6): 270–272. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1281520/>.
    Was your prediction in Question 10 consistent with the data? (It is okay if the answer is “no.”) Explain.

12. Based on what you have learned so far, why do you think carbon monoxide poisoning causes the body to turn cherry red?

13. Discuss within your group whether you think carbon monoxide can be absorbed after death. Why or why not? (If you are unsure, list what information you would need to know to answer this question.)

Part IV – The Trial

In December of 1926, Ms. Beauregard invited herself over to Mr. Taft's house and after a few hours they began to argue. Mr. Taft asked Ms. Beauregard to leave his residence and she refused. Mr. Taft had been standing by the open door, attempting to tell Ms. Beauregard to exit his home when she knocked a pot of boiling water over on the gas stove. (The water extinguished the pilot light.) They continued to argue, but after this memory Mr. Taft failed to recall any other events thereafter because he lost consciousness. The defense attorney for Mr. John Taft entered a plea of not guilty on his behalf and presented an argument with the help of Dr. Norwood, the New York medical examiner. The argument stated Ms. Frannie Beauregard died of carbon monoxide poisoning due to the extinguished stove. This argument was supported by the cherry red color of the victim's skin. The prosecutor countered this argument, claiming her body absorbed the carbon monoxide after Mr. Taft had murdered her.

Questions

14. The prosecution proposed a hypothesis about Ms. Beauregard's cause of death. State that hypothesis and then determine (and state) the corresponding null hypothesis.

15. Based on the above answer, design an ethical experiment to test the prosecution's hypothesis. Be sure to include the independent and dependent variables as well as the predicted results.

Part V – Medical Experiment Reveals the Truth

Dr. Norwood asked Dr. Grant, a medical researcher, to design an experiment to determine the process by which the human body absorbs carbon monoxide. Doing so would allow the team to determine if a dead body could absorb the toxic gas. Grant obtained a large tank and three unclaimed cadavers from the morgue and sealed them into the controlled area. He then pumped carbon monoxide into the sealed tank and let it sit for several days. Afterward, the bodies showed no sign of color change.

Question

16. Does it appear the cadavers used in the experiment absorbed any carbon monoxide? Explain your rationale.

Part VI – Case Closed

John Taft was able to explain his side of the story during the trial in the spring of 1927. He claimed that his neighbor, Ms. Beauregard traveled to his house and asked for a drink. Together, they finished off a bottle of alcohol and he then requested that she go home. He claimed she refused and the next thing Taft remembered was waking up on the floor with Ms. Beauregard's dead body next to him. Because Taft was near an open door, it is hypothesized that he did not inhale as much of the carbon monoxide as Ms. Beauregard. Thus, he did not die of carbon monoxide poisoning; he just felt some of the side effects of exposure. Upon discovering her dead body on his return to consciousness, he became obsessed with disposing of her body, as he thought he may have murdered her. Because she was a large woman, the first idea in his panicked state was to cut her up so that he could carry her more easily and dispose of the dead body.

Dr. Grant then was able to testify that Ms. Beauregard's body could not have absorbed the carbon monoxide after death, as was shown in his cadaver experiment. Therefore, it was determined that the carbon monoxide itself was what caused her death. The source of the gas was revealed as the extinguished stove (it was releasing gas unbeknownst to the apartment occupants). Taft simply survived due to either lower exposure or higher tolerance and had awoken the next morning. Beauregard, on the other hand, had not.

Dr. Grant and Dr. Norwood, through their experiments, saved Taft from being sentenced to death. The jury found him not guilty of murder, but he served time for illegally disposing of a body.

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