

Case 8

Hemoglobin, the Oxygen Carrier

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Focus concept

A mutation in the gene for hemoglobin results in an altered protein responsible for the disease sickle cell anemia. An understanding of the biochemistry of the disease may suggest possible treatments.

Prerequisite

Hemoglobin structure and function concepts.

Background

Normal adult hemoglobin is called Hemoglobin A (Hb A). Ninety-eight percent of adult hemoglobin is Hb A and 2% is Hb A₂. There are other forms of hemoglobin. For example, the developing fetus has a different kind of hemoglobin than most normal adults. Fetal hemoglobin (or Hemoglobin F) consists of two α chains and two γ chains, whereas adult hemoglobin (Hemoglobin A) consists of two α chains and two β chains. Fetal hemoglobin is synthesized beginning at the third month of gestation and continues up through birth. After the neonate is born, hemoglobin F synthesis declines (because synthesis of the γ chain declines) and hemoglobin A is synthesized (because synthesis of β chains begins). By the time the baby is six months old, 98% of its hemoglobin is Hemoglobin A.

There is also a mutant form of hemoglobin called Hemoglobin S which is found in persons with the disease sickle cell anemia. The disease sickle cell anemia is one of the major health problems facing the African-American community. The World Health Organization estimates that 250,000 babies world wide are born with sickle cell anemia. Currently there is no cure. A person afflicted with sickle cell anemia has inherited a defective gene from each parent. (Parents who are carriers of the sickle cell gene are heterozygous AS, whereas the person afflicted with sickle cell anemia is SS; non-carriers are designated AA.) The defective gene is the one coding for the β -chain. The amino acid at position 6 on each β chain has been mutated from a glutamate to a valine. Normal α chains have a decreased affinity for the mutated β chains; thus assembly of the HbS tetramer is more difficult. Red blood cells containing HbS form a sickle shape because the Hb S molecules polymerize. Hb S molecules are more likely to polymerize when in the deoxygenated T form than in the oxygenated R form. The polymerized Hb deforms the normal discoid shape of the red blood cells, producing a sickle-shaped cell. The sickle shaped red blood cells become trapped in capillaries and organs, depriving the victim of adequate oxygen supply and causing chronic pain and organ damage.

In this case we will consider our patient, a 10-year-old black male child named Michael B., who was admitted to the hospital because he was experiencing severe chest pain. He had been hospitalized on several previous occasions for vaso-occlusive episodes that caused him to experience severe pain that could not be managed with non-prescription drugs such as ibuprofen. He was slightly jaundiced, short of breath and easily tired, and feverish. A chest x-ray was taken and was abnormal. An arterial blood sample showed a p_{O_2} value of 6 kPa (normal is 10-13 kPa).

Questions

1. You suspect that Michael has sickle cell anemia and you have ordered an isoelectric focusing analysis of the child's lysed red blood cells. (Lysing the red blood cells releases the hemoglobin.) Draw a diagram of the predicted results. Why will this test allow you to diagnose this child's disease?
2. Why do you think that Hb S molecules would be likely to clump together whereas Hb A molecules do not?
3. In the emergency room, oxygen (100%) was administered to the patient. (Inspired air normally is about 20% oxygen.) Why was this an effective treatment?
4. You recall reading in the medical literature about a dramatic new drug treatment for sickle cell anemia, and you'd like to try it on this patient. The drug is hydroxyurea, and is thought to function by stimulating the afflicted person's synthesis of fetal hemoglobin. Exactly how hydroxyurea stimulated fetal hemoglobin synthesis is unclear, but it is believed that hydroxyurea is metabolized to NO, which binds to a soluble guanylate cyclase enzyme which then catalyzes the synthesis of a second messenger, cyclic GMP (cGMP). The cGMP interacts with transcription factors in a manner that is not completely understood to induce the transcription (and then translation) of the fetal hemoglobin gene.
 - a. In a clinical study, patients who took hydroxyurea showed a 50% reduction in frequency of hospital admissions for severe pain, and there was also a decrease in the frequency of fever and abnormal chest x-rays. Why would increasing the synthesis of fetal hemoglobin result in alleviating the symptoms of sickle cell anemia?
 - b. Medical practitioners who used hydroxyurea as a treatment for sickle cell anemia noted that their patients seemed to benefit from the administration of the drug long before the synthesis of fetal hemoglobin had time to take effect. It has recently been determined that hydroxyurea can react directly with the iron ion of oxy- and deoxyHb to form iron nitrosyl hemoglobin (HbNO). Why would this be of benefit to the sickle-cell anemic patient?
 - c. And finally, hydroxyurea has been shown to produce NO directly, in less than an hour after hydroxyurea administration. It's also possible that HbNO could produce NO, either directly or indirectly. NO is an important second messenger which, even in nanomolar amounts, stimulates vasodilation. How could NO production help the sickle-cell anemic patient?
5. A year ago, at a conference, one of your colleagues told you that she had "cured" a patient of sickle cell anemia by performing a bone marrow transplant. Why would this procedure "cure" sickle cell anemia?
6. The patient's parents tell you that they are planning on having another child and that they are confident that subsequent children will not have sickle cell anemia, since they already have a child with the disease. What will you tell them?

References

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