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HEMOGLOBIN: STRUCTURE, FUNCTION AND GENETIC DISORDERS

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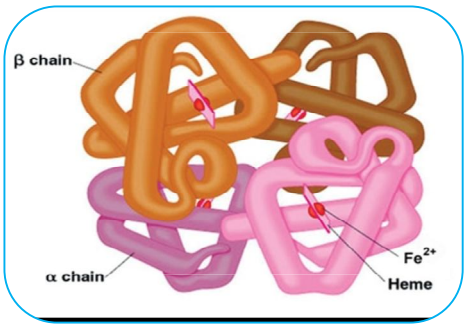

The oxygen-carrying pigment in the red cells of mammals is known as "hemoglobin". Hemoglobin is a protein with a molecular weight of 64,450. Hemoglobin is a globular molecule and consists of four subunits. Each subunit consists of a heme moiety conjugated to a polypeptide. While heme is an iron-containing porphyrin moeity, two pairs of polypeptides form the globin portion of the hemoglobin molecule. The two polypeptide are termed as alpha chains and beta chains particularly in normal adult human hemoglobin (that is hemoglobin A). Hemoglobin A is designated as alpha 2 and beta 2. All the hemoglobin in the blood of normal adult is not hemoglobin A. Approximately 2.5% of the hemoglobin is hemoglobin A2 in which beta chains are replaced by delta chains. (alpha 2 and delta 2). The delta chain consists of ten individual amino acid residues that are not similar to those in beta chains. There are less amounts of hemoglobin A derivatives closely confirmed with hemoglobin A that indicate glycosylated hemoglobin's, particularly hemoglobin A1C (Hb A1C) consists of glucose bound to the terminal valine in each beta chain and is of special interest because it enhances in blood of patients with uncontrolled diabetes mellitus. Hb A1C is measured as a clinical point of view as a marker of the progression of that disease or the effectiveness of treatment.

REACTIONS OF HEMOGLOBIN

Oxygen attaches with the ferrous in the heme moiety of hemoglobin and leads to the formation of oxyhemoglobin. The affinity of hemoglobin for oxygen is influenced by temperature, pH and concentration in the red cells of 2,3 – biphosphate glycerate (2, 3 – BPG). 2,3 – BPG and H+ compete with oxygen for attaching with deoxygenated hemoglobin and reducing the affinity of hemoglobin for oxygen by shifting the positions of the four polypeptide chains (quaternary structure). If blood is exposed to various drugs and oxidizing agents in vitro or in vivo, the ferrous iron (ferric 0) that is generally observed In hemoglobin is changed in the formation of methemoglobin. Methemoglobin is a dark – colored pigment, and if it is observed in more quantities in the circulation, it leads to the discoloration of the skin that is similar to cyanosis. Some oxidation of hemoglobin to methemoglobin takes place generally, but an enzyme system in the red cells, the dihydronicotinamide adenine dinucleotide (NADH) – methemoglobin reductase system, changes

methemoglobin back to hemoglobin. Congenital absence of this system leads to the occurrence of hereditary methemoglobinemia.

Carbonmonoxide combines with hemoglobin and results in the formation of carboxyhemoglobin. The affinity of hemoglobin for oxygen is much lower than its affinity for carbon monoxide, which automatically displaces oxygen on hemoglobin and reducing the oxygen - carrying capacity of blood.

FETAL HEMOGLOBIN

The blood of the human fetus generally consists of fetal hemoglobin. Its structure looks alike that of hemoglobin A. Its oxygen content at a given PO2 is greater than that of adult hemoglobin because it attaches with 2, 3 - BPG less avidly. Hemoglobin F is more essential to enhance movement of O2 from the maternal to the fetal circulation especially at later stages of gestation where oxygen demand enhances. In young embryos there are eta and delta chains and result in the formation of Gower 1 hemoglobin e2 E2) and Gower 2 hemoglobin (alpha 2 E2).

FORMATION OF HEMOGLOBIN

The synthesis of hemoglobin starts primarily in the proerythroblasts and maintains its continuation upto the rericulocyte stage of the red blood cells. Even after the entry of reticulocytes into the blood stream, after leaving the bone marrow, the reticulocytes are capable of forming meager quantities of hemoglobin for another day or so until their conversion into mature erythrocyte. Hemoglobin formation takes place from Succinyl CoA and glycine. Succinyl CoA combines with glycine and results in the formation of a pyrrole molecule, and four such pyrrole rings unite to form a molecule of protoporophyrin IX. Protoporphyrin IX unites with iron and leads to the formation of heme molecule. Lastly, each heme molecule unites with a long polypeptide chain, a globin synthesized by tissues , forming a subunit of the hemoglobin known as hemoglobin chain. Each chain consists of a molecular weight of about 16,000 and four of the chains unites together in a loose fashion for the formation of whole hemoglobin molecule.

SYNTHESIS OF HEMOGLOBIN

The average normal hemoglobin content of red blood cell is 16 g/dL in men and 14 g/dL in women. In the body of a 70 Kg, 900 g of hemoglobin is present. Normally the destruction of 0.3 g of hemoglobin and 0.3 g of synthesis of hemoglobin also takes place. The synthesis of the heme portion of the hemoglobin molecule occurs from glycine and succinyl CoA.

CATABOLISM OF HEMOGLOBIN

The globin part of the hemoglobin molecule is split off and the heme is changed into biliverdin because of the destruction of old red blood cells by tissue macrophages. The enzyme involved is an heme oxygenase type and the formation of carbon monoxide occur in this process. Carbon monoxide acts as an intercellular messenger like nitric oxide. In human beings, most of the biliverdin is changed into bilirubin and its excretion takes place in the bile. The iron from the heme is reutilized for the synthesis of hemoglobin. Bilirubin is changed into lumirubin due to exposure of the skin to white light. Lumirubin have less half life than bilirubin. Phototherapy (exposure to light) is of value in treating infants with jaundice because of hemolysis. Iron is responsible for the synthesis of hemoglobin. Iron deficiency anemia occurs because of loss of blood from the body and inefficiency of correction of iron deficiency.6

HEMOGLOBINOPATHIES

Hemoglobinopathy is a genetic disorder due to the formation of abnormal polypeptide chains of hemoglobin's. Some of the hemoglobinopathies are

a) HEMOGLOBIN C

The beta chains show abnormality. It is observed in people with hemoglobin C disease which is characterized by mild hemolytic anemia and splenomegaly.

b) HEMOGLOBIN E

The beta chains exhibit abnormality. It is seen in people with hemoglobin E disease which is also characterized by mild hemolytic anemia as well as splenomegaly.

c) HEMOGLOBIN M

It is the abnormal hemoglobin seen in the form of methemoglobin. It happens because of the mutations of genes of both alpha and beta chains resulting in abnormal replacement of amino acids. It is observed in babies affected by hemoglobin M disease or blue baby syndrome. It is an inherited disease and it is characterized by methemoglobinemia.

THALASSEMIA

Different types of abnormal hemoglobins are observed. The polypeptide chains are reduced, absent or show abnormality. In alpha thalassemia, the alpha chains are reduced, absent or exhibit abnormalities. In beta thalassemia, the beta chains are lowered, absent or show abnormalities. Some of the abnormal hemoglobin's observed in thalassemia are hemoglobin G, H, I, Borts, Kenya, Lepore and constant spring.

CLINICAL ASPECT

In solutions with a lower osmotic pressure, red cells swell and become spherical rather than disk – shaped and gradually lose their hemoglobin (hemolysis). The hemoglobin of hemolyzed erythrocytes generally dissolves in the plasma with a red color. A 0.9% NaCl solution is isotonic with plasma. If osmotic fragility is normal, erythrocytes start to hemolyze after suspension in 0.5% saline whereas 50% lysis takes place in 0.40 - 0.42% saline and complete hemolysis occurs in 0.35% saline. In hereditary spherocytosis (congenital hemolytic icterus), the erythrocytes are spherocytic in normal plasma and hemolysis takes place readily than normal cells in hypotonic NaCl solutions. Destruction and trapping of abnormal spherocytes occur in the spleen that is hereditary spherocytosis is one of the most common causes of hereditary hemolytic anemia. The spherocytosis occurs by mutations in proteins that make up the membrane skeleton of the red blood cell, which generally regulate the shape and flexibility of the erythrocyte along with spectrin, the transmembrane protein band 3 and the linker protein ankyrin. Hemolysis of erythrocytes occurs by drugs particularly sulfa drugs, penicillin and infections also. The susceptibility of erythrocytes to hemolysis by these agents is enhanced by deficiency of the enzyme glucose – 6 – PO4 dehydrogenase (G6PD), which catalyzes the beginning step in the oxidation of glucose with the help of hexose mono – phosphate pathway (HMP). This pathway generates dihydronicotinamide adenine dinucleotide phosphate (NADPH), which is essential for the regulation of normal red cell fragility. Severe G6PD deficiency also reduces the killing of bacteria by granulocytes and predisposes to heavy infections.

TREATMENT

More severe cases of hereditary spherocytosis can be treated by removing spleen. Mild cases can be treated by administering dietary folate supplementation and blood transfusion. Treatment of other forms of hemolytic anemia is based on the underlying cause. Some forms are autoimmune in nature and exhibit the benefit from treatment with corticosteroids.

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