The sum total of iron metabolism is shown in the diagram (Fig. 5.11). About 27 mg of iron is turned over every day. Of this, about 20 mg is obtained from breakdown of red blood cells, 1–2 mg from newly absorbed iron and remainder from the iron stores. Iron is utilized for hemoglobin synthesis by bone marrow, additional amount is stored in tissue and very little is excreted out of body.

There is very little excretion of iron except in cases of losses of blood due to physiological or pathological causes. As iron is bound to protein in plasma (transferrin), it is not lost in urine (less than 0.4 mg/day). Dermal losses are negligible. Unabsorbed iron is passed in the stool.

Iron is mainly lost from the body when there is blood loss in any form. This may be physiological as in case of menstruation or pregnancy or pathological as in hemorrhages or intestinal worms. Theoretically, on an average, females lose about 0.5–1.0 mg Fe/day on account of menstruation. Similarly, it is concluded that each pregnancy entails a net loss of 500 mg iron. Although milk is poor in iron, lactation for 6 months accounts for loss of approximately 180 mg of iron from the lactating mother.

Functions

1. The major function of iron is formation of hemoglobin. In respiration process, when oxygen enters the lungs, it combines with the iron containing protein, hemoglobin, present in RBCs forming the complex oxyhemoglobin. On reaching the tissues, the complex dissociates releasing oxygen. Simultaneously, CO_2 formed as a waste product in catabolic reaction in the tissues, enters RBC and combine with hemoglobin to form hemoglobin carbamate. On reaching lungs, hemoglobin carbamate dissociates, releasing CO_2, which is exhaled.
2. In muscles, oxygen is combined with iron containing muscles protein, myoglobin. When strenuous exercise markedly lowers the oxygen content of muscle cells, myoglobin releases oxygen for mitochondrial synthesis of ATP, permitting continued muscular activity.
3. Iron is a part of heme, a constituent of enzyme peroxidase and catalase which catalyzes oxidation and reduction reaction. Physiologically, these two enzymes are very important since they bring about degradation of toxic peroxide molecules as

$$H_2O_2 + AH_2 \longrightarrow 2H_2O + A$$
$$2H_2O_2 \longrightarrow 2H_2O + O_2$$

Accumulation of peroxide can lead to generation of free radicals (ROO^*, RO^*, OH^*), which in turn can disrupt membrane and could cause cancer and atherosclerosis.

4. Iron, as a part of heme, is present in various cytochromes. Cytochrome is component of the mitochondrial electron transport chain. Here they function as carrier of electron from flavoprotein on the one hand to cytochrome oxidase on the other. In liver microsome, cytochrome P_{450} and b_5 play an important role in detoxification (converting toxic compounds to non-toxic intermediates).

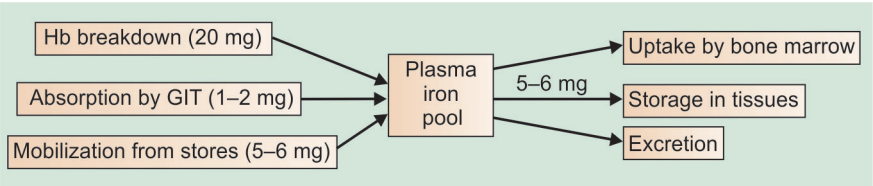

Fig. 5.11: Overview of iron metabolism

Fig. 5.13: Food sources of copper

incorporated into a specific copper-binding protein ceruloplasmin. This protein exports copper to other tissues.

Copper is the constituent of several enzymes (oxidases) and proteins, e.g. ferroxidase I (ceruloplasmin), erythrocuprin found in RBCs, cerebrocuprin (found in brain), cytochrome oxidase, monoamine oxidase, lysyl oxidase, superoxide dismutase, etc. Plasma ceruloplasmin has ferroxidase activity, so it oxidizes ferrous ion into ferric ion for incorporation into iron–transport protein transferrin. The enzyme xylyl oxidase is responsible for forming cross links between collagen/elastin fibers.

Copper deficiency is uncommon but whenever occur naturally or experimentally develop hypochromic microcytic anemia due to its role in iron storage, transport and mobilization from stores.

An inherited disease of copper metabolism is Wilson's disease. It is characterized by excessive absorption of copper leading to its deposition in liver, kidney and brain causing liver cirrhosis, kidney damage and neurologic disturbances, respectively.

Zinc

Zinc is an essential element although human body contains only 2 g. Dietary absorption is only 5–10% due to interfering ions—phosphate, phytate and calcium.

Sources

The richest sources are oysters, crabs and shell fish. Zinc content of food varies with the soil and fertilizers in which the foods are grown (Fig. 5.14). In general, the zinc is proportionate to protein intake, since muscles meat and sea birds have the highest content. The vegetable sources contain zinc but due to anions, they are not absorbed.

The amount of zinc in daily diet is around 6–12 mg/dl which is adequate to meet the requirement.

Zinc is a constituent of many metalloenzymes whose activity is reduced in zinc deficiency. Important ones are alcohol

Fig. 5.14: Food sources of zinc

MECHANISM OF ENZYME ACTION

The exact mechanism of action of individual enzymes differs. However, certain general features of mechanism of enzyme action are considered here.

1. Enzymes have molecular weight in the range of 10^4 to 10^6 while substrates in the range of 10^2 to 10^3. Thus, enzymes are 100 to 1000 times larger than the substrates.
2. The enzymes lower the energy of activation (Fig. 6.6).
3. The active site is that part of the enzyme with which the substrate is actually bound. The part of the enzyme molecule not in physical contact with the substrate but function in the catalytic process is known as catalytic site.
4. The active site takes up a relatively small part of the total volume of an enzyme.
5. The substrate is bound to enzyme by relatively weak forces.

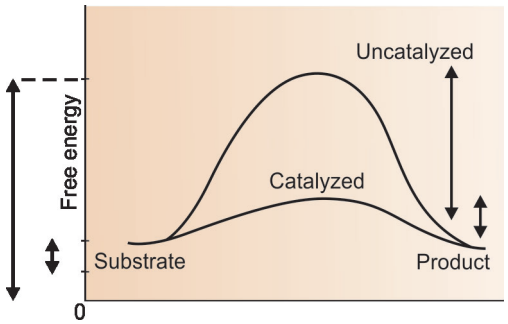

Fig. 6.6: Decrease in activation energy by enzyme

Based on these generalizations, two theories have been proposed to explain their mechanism of action. These are similar to those for catalysts in inorganic chemistry.

a. Physical adsorption theory
b. Chemical combination theory.

Physical Adsorption Theory

This theory suggests that substrate molecules are adsorbed on the surface of enzyme molecule. This view is supported by large size of enzyme molecule as compared to substrate where physical adsorption is expected to play a role. Physical proximity of reactants may increase collisions between molecules. The fact that the enzyme lowers the energy of activation of a reaction also supports this theory.

$$A + B \xrightarrow{E} C + D$$

Chemical Combination Theory

This theory suggests that enzymes actually take part in the reactions.

$$E + S \longrightarrow \underset{\text{Activated complex}}{ES} \longrightarrow P + E$$

The chemical combination between substrate and enzyme is supported by following evidences.

1. X-ray crystallographic, electron microscopic and spectroscopic examination of enzyme and substrate during catalysis show changes in the enzyme structure with progress of reaction.
2. The curve of the rate of reaction *versus* substrate concentration with a fixed concentration of enzyme (Fig. 6.2) also supports enzyme substrate complex (ES) formation because if the substrate and enzyme did not combine, the curve would have been a straight line.

Thus, regarding enzyme catalysis, the two theories seem to be complementary rather than contradictory.

ENZYME ACTIVITY VERSUS ITS SPECIFICITY

Two views have been proposed to relate enzyme activity and the specificity.

1. **Lock and key hypothesis of Fisher:** The active site is considered as a rigid template and compounds with complementary structure to active site would combine, just as 'key fits a lock' (Fig. 6.7a). This also explains competitive inhibition.
2. **Induced fit hypothesis of Koshland:** The binding of substrate to enzyme can bring

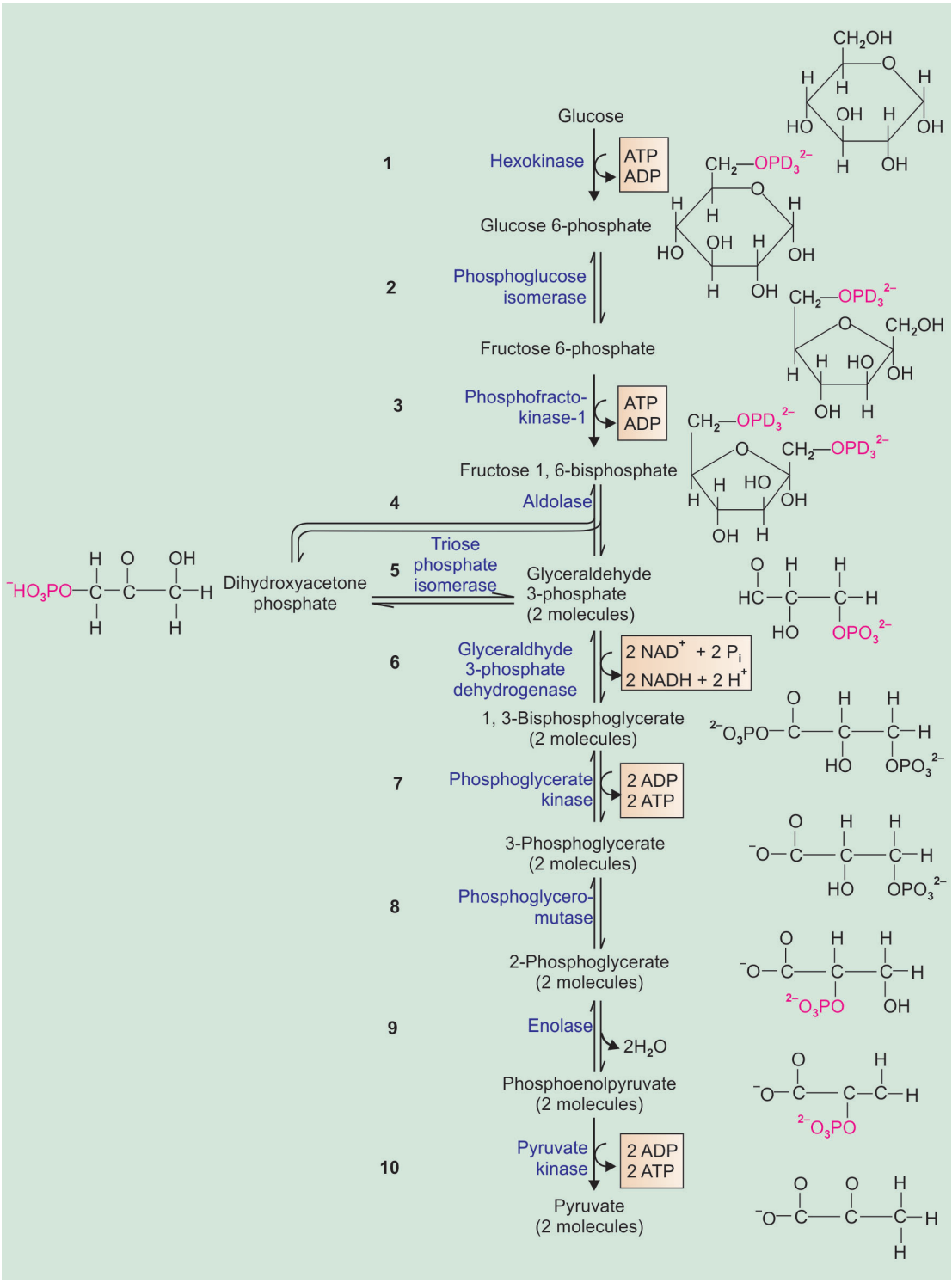

Fig. 7.7: Flow chart of glycolysis