BIOCHEMISTRY AND BIOPHYSICS

INTERMEDIATE IRON METABOLISM DURING POSTHEMORRHAGIC ANEMIAS

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The treatment of anemias sometimes produces different results under seemingly similar pathological conditions. Iron preparations are the basic means of treating anemias. Much work has been devoted to the study of the iron metabolism under various pathological conditions and during anemic states, as well as to the clarification of the therapeutic action of various iron preparations [1-5, 7].

The complexity of the investigative methods, the presence of iron in food products, as well as in all tissues and organs, have limited the possibility of studying the metabolism of iron. A number of questions connected with its absorption into the organism, its participation in the synthesis of hemoglobin, and the role of various organs in iron metabolism have not yet been fully clarified.

Application of the method of tagged atoms permits the tracing of the paths by which iron is assimilated in to and distributed through the system, and can help clarify the roles of individuals organs in this distribution and the participation of iron introduced into the system in the synthesis of hemoglobin. In addition to determining the qualitative characteristics of the metabolism, the amount of iron participating in this or that phase of the metabolism can be determined more or less accurately. Work devoted to the study of iron metabolism using tagged atoms has been conducted primarily on dogs. There are only single investigations of healthy people and of patients with various kinds of anemia.

Kahn, Balfour and Ross [6] studied the absorption of iron by various sections of the gastro-intestinal tract (the stomach, duodenum, and ileum).

They established the fact that assimilation occurs in all three sections, and that 100% of the iron is never assimilated. When small doses are employed, 50-60% of the iron introduced is assimilated, with larger doses down to 5%. More iron is assimilated by anemic animals than by healthy ones. Four hours after administration of radioactive iron, it was found in the erythrocytes already.

The time required for the iron to appear in the erythrocytes did not depend on the method of introduction – oral or intravenous.

In the present work we set ourselves the following problems: 1) what is the reaction of an anemic and of a healthy system to iron which is administered, 2) how great a role do the liver, spleen and bone marrow play in the distribution of iron through the system, and 3) what is the difference in the rate of assimilation of iron by anemic and healthy systems.

In order to fulfill the assignment, experiments were carried out on anemic and healthy rabbits. The ascorbate of the radioactive isotope of iron (Fe^{59}), four mg per 1 kg of weight, in a physiological solution was administered to the animals in both groups. The rabbits were killed in groups by means of repeated blood-lettings from the carotid artery 4 hours, 1, 4, 8, and 14 days after the administration of the iron. The total and the tagged iron was determined in the blood, liver, spleen, bone marrow, urine, and feces.

The experiments were carried out on 37 rabbits, of which 21 had artifically induced posthemorrhagic anemia and 16 were controls.

The indications of some authors, that only 4 hours after administration radioactive iron appeared in the erythrocytes, provoked doubt. We carried out experiments in vitro in order to discover whether this might not be the result of some kind of unstable union of the administered radioactive iron with the erythrocytes.

Two series of experiments were set up. In one series, human blood mixed with tagged iron was kept at a temperature of 37° in a thermostat, while in the other series, it was kept at room temperature. Analyses for tagged iron in the erythrocytes were carried out at various times in the course of the 6 days after mixing. In no case was radioactive iron found in the protein portion of the erythrocytes. This testifies to the fact that iron does not penetrate mature erythrocytes. This process, active in nature, can only occur in the bone marrow while the erythrocytes are maturing.

The Distribution of Tagged Iron and Its Application to the Synthesis of Hemoglobin in Rabbits During Intravenous Administration

Iron in blood plasma. In both groups of rabbits, iron was found in the blood plasma for 4 days after administration, and there was more in the control group of animals during the first hours. This may indicate that the administered iron was used more quickly in the system of anemic rabbits, since analysis of the amount of iron retained in the liver, spleen and bone marrow showed that it was greater in anemic rabbits. After the fourth day, tagged iron was not found in the blood plasma of either group of rabbits although, undoubtedly, it was present in insignificant amounts (at the expense of the liver and other organs).

Excretion of iron. Not only is the administered iron not harmless to the system, but it is a poison in large doses. Therefore, the system uses only part of the administered iron, while the remainder is excreted.

The kidneys and mucosa of the large intestine play an active part in the excretion of iron which has been administered intravenously.

Analysis of the feces, urine, mucosa of the large intestine for tagged iron showed that it was excreted more intensively and over a longer period of time in the control group of rabbits; thus, it was found in the anemic rabbits for four days, but in the control group, for eitht days.

Iron in the erythrocytes. The difference in the reaction of the anemic and the healthy system to administered iron was more clearly apparent in the utilization of iron for the synthesis of hemoglobin in maturing erythrocytes.

In the control rabbits, traces up to 0.4% of the administered iron were found after 4 hours; after a day — 1.5-2.5%; after 4 days — 4-5%; after 8 days — 5-8%; after 14 days — from 3 to 9%. A slow increase in the use of tagged iron was observed in the control rabbits, while the degree to which it was used differed little on the 14th day from that on the 8th day.

The picture was different in anemic rabbits. After a day, 4-6% of the administered iron was found in the erythrocytes; after 4 days, 6-13%; after 8 days, 12-17%; after 14 days, 16-25%. Consequently, the tagged iron was constantly and more rapidly used by anemic rabbits.

The more intensive utilization of tagged iron by anemic rabbits is explained by the depletion of the reserves of iron in the tissues, by more intensive erythropoiesis, and, consequently, by a greater iron requirement.

It was indicated above that administered iron can be found in the erythrocytes after only 4 hours. The results of experiments carried out in vitro exclude the possibility of penetration of the erythrocytes by the iron. Consequently, the iron thus found was an integral part of the hemoglobin. Such rapid appearance of administered iron in the erythrocytes allows the supposition that iron may be involved in the synthesis of hemoglobin during the last phases of erythrocyte maturation.

Iron in the liver. Comparing the data we obtained regarding the iron content of the liver after various periods of time after its administration, it can be noted that after 4 hours, the liver of the control rabbits contains less iron (14-25%) than that of anemic rabbits (25-37%). This was explained by longer retention of iron in their

plasma, especially in the first hours after administration. After a day, almost all the iron was found in the liver of the control rabbits and there was already somewhat more of it than in the liver anemic rabbits, although the total amount of iron found was not greater in the control rabbits than in the anemic ones. At the same time, the controls had more iron in the bone marrow, spleen, and erythrocytes. Throughout the experiment, the liver of the control rabbits had more iron than that of the anemic ones. This was connected, apparently, with a more intensive utilization of it in the system of anemic rabbits for the synthesis of hemoglobin. A gradual decrease is observed also in the iron deposited in the liver, and this decrease is more noticeable in the control rabbits: if 38-63% of the iron was found in the liver of the control animals on the first day, 3-9% was found on the 14th day; in anemic ones the amount on the first day was 34-42%, on the 14th day, 9-13%.

Apparently, iron was used not only for the synthesis of hemoglobin, but it was also excreted from the system. The system retained only the amount it required in the form of reserve iron and used it for the synthesis of hemoglobin. The excess was ecreted from the system.

Iron in the spleen. An insignificant amount of the administered tagged iron was retained by the spleen (it composed tenths and hundredths of one percent). From the total amount of iron deposited in the spleen and from the change in its amount during the 14 days after its administration, it can be assumed that the spleen did not play a significant role in the iron metabolism of rabbits.

Iron in the bone marrow. The total iron retained by the bone marrow cannot be calculated since it is impossible to remove all of the bone marrow. From 0.5 to 1 g of bone marrow was used for the analyses.

After four hours and after one day, the tagged iron content of the bone marrow was found to be higher in anemic rabbits than in the controls. This indicated that the tagged iron played a larger role in the synthesis of hemoglobin in anemic rabbits, a fact confirmed by its discovery in the erythrocytes. By the fourth day, both groups of rabbits showed a decreased percentage of tagged iron content. On the 14th day, the amount of tagged iron was also somewhat higher in the bone marrow of anemic rabbits than in the controls. This points to a greater release of it from the depot as a consequence of the more intensive erythropoiesis of anemic rabbits and, naturally, of the greater iron requirement.

On examination of all of the organs which have a close relation to erythropoiesis and to the excretion of iron, it can be observed that the greatest amount of tagged iron (96-98%) was found in the liver and erythrocytes.

If the amount of iron found in the liver and erythrocytes is taken as 100%, its content varied in the following manner during the course of the experiment: in anemic rabbits, 85-90% of the total amount of iron was found in the liver after a day and 5-10% in the erythrocytes; after 14 days, 55-65% was found in the erythrocytes and, correspondingly, 45-35% in the liver. In the control rabbits, as a result of slower utilization of the administered tagged iron, 96-98% of the iron was found in the liver after one day, 4-2% in the erythrocytes; after two weeks, 50-60% in the liver, and 50-40% in the erythrocytes.

Consequently, more of the stored iron was used for the synthesis of hemoglobin by the anemic rabbits than by the controls. Naturally, more iron was stored as a reserve by the latter.

The above experimental results show the different reaction of the anemic and the healthy system to administered iron. This difference is revealed not only in the fact that the anemic system retains a greater amount of administered iron, but also by the fact that it utilizes it differently. In anemic rabbits, it is used primarily for the synthesis of hemoglobin, while in the controls it is retained as a reserve, chiefly in the liver.

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