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Effects of Testosterone on Splenic and Bone Marrow Erythropoiesis of Fasted Mice *

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Fasting in normal or erythropoietin treated mice results in parallel decrease of erythropoietic activity in spleen and bone marrow. In testosterone-treated animals, starvation only decreases the splenic fraction while the bone marrow erythropoiesis shows a marked increase above normal values.

Normally a substantial fraction of the mouse erythropoiesis takes place in the spleen. If both, bone marrow and splenic fractions were identical in all respects, one would expect a similar pattern of response to either depressing or stimulating agents, which does not hold true in all the cases (2, 13, 14). The observations here reported indicate that fasting in mice pretreated with testosterone resulted in depressed erythropoiesis in the spleen in contrast with a marked elevation of bone marrow erythropoietic activity.

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Materials and Methods

Normal (C3H/FWD)F_1 female mice, 7 to 9 weeks of age were fasted for a total of 4 days with free access to water. At the end of this period, realimentation with a standard laboratory diet was reinitiated and the observations followed throughout the next 4 days. In a second experimental group the animals were injected with 5 mg of long acting testosterone (Testoviron Depot, Schering) given subcutaneously 4 days before the onset of starvation. A third group of animals were daily injected with 0.2 Units (International Reference Preparation) of erythropoietin begining 4 days before the initiation of the fasting period and maintained throughout the experiment. Daily from day 1, some animals from each experimental group were separated and the erythropoietic rate measured using the ^{59}Fe 3 h

distribution test (7). For this purpose 0.25 uC of ^{59}Fe were injected intravenously and three hours later the topographic distribution of the tracer (uptake by the spleen, both femurs, circulating erythrocytes and the non used remnant in the plasma) was calculated as per cent of the injected dose. These values were used to estimate the fraction of radioiron going to the erythroid tissues per hour and taken as parameter of the erythropoietic activity.

Results and Discussion

Fasting in otherwise unmanipulated mice markedly reduces ^{59}Fe uptake by femurs, spleen and RBC, changes which were associated to a reduced plasma disappearance rate. After food restoration, erythropoiesis recovers in the spleen and femurs, the spleen shows an overshot above normal values while the bone marrow still remains below the normal range (fig. 1, 1). Figure 1, 2, shows the time course of variations in splenic and femurs ^{59}Fe uptake in testosterone treated animals. It can be seen that during the 4 days preceding starvation, both fractions behave in a similar manner as that described in the post-fasting period in group 1, i.e., with a large increase in spleen erythropoiesis associated to a slight fall of activity in the medullar area. During the fasting period however the high ^{59}Fe uptake in the spleen at the onset of starvation, starts a sharp reduction to a negligible value. In the same time the femurs uptake raises from subnormal to a two-fold increase above normal range.

During the prefasting leg of the experiment, the erythropoietin treated group shows changes in the spleen and femurs similar to those found in the same time in the testosterone treated group. Deprivation of food however results in a decreased activity in both fractions (figure 1, 3).

A shunt in the erythropoiesis from the marrow to the spleen appears as a common pattern of response after short term stimulation with both, erythropoietin and testosterone. Fasting presumably by removing endogenous erythropoietin (8, 11,

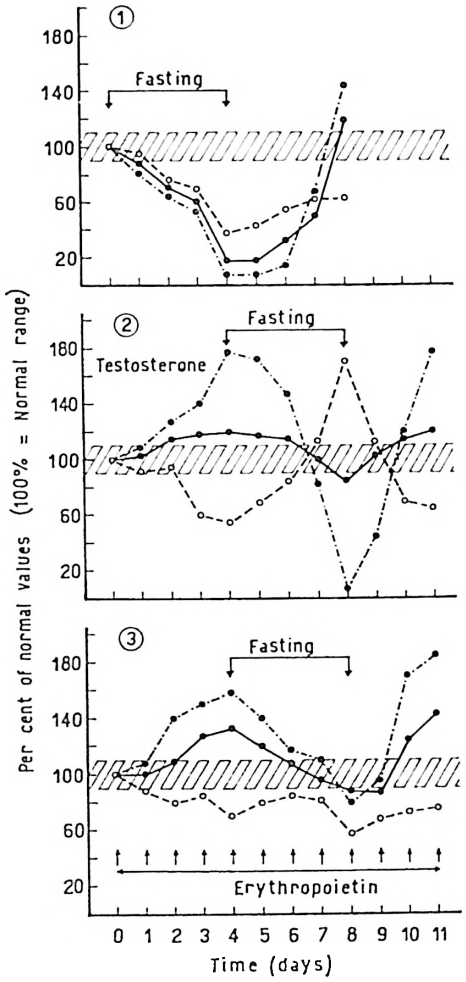

Fig. 1. *Time course of the effects of starvation on the fractional ^{59}Fe uptake by the spleen (○-----○); bone marrow (○-----○); and on total erythropoietic rate (Hodgson Index) (○——○) in normal (1); testosterone-treated (2) and erythropoietin-treated (3) mice.*

Each point represents the average of results in 10 mice. The hatched area represents the range of values found in 20 normal unmanipulated mice and is taken as the 100 % value. All results are presented as percentage of the normal value.

12) causes a sharp fall in erythropoietic activity in normal unmanipulated and erythropoietin injected mice as well. In both groups the spleen depression correlates well with that seen in the femurs, a feature that greatly contrasts with the behavior of both fractions in the testosterone-treated group. There is now evidence indicating that testosterone acts upon erythropoiesis by increasing erythropoietin production (4). The high activity found in the bone marrow at the end of starvation period, could be attributed to a higher level of endogenous erythropoietin resulting from the effects of testosterone. This interpretation however is not supported by the close parallelism in splenic and medullar changes seen during starvation in erythropoietin treated animals.

The cause of the opposite behavior of the spleen and bone marrow fractions of mouse erythropoiesis here reported is not clear. These results however clearly indicate that the two areas of erythropoiesis in this species are not functionally identical. The data also lends further support to the concept that androgens in addition of increasing erythropoietin production (4) and/or exerts a synergistic action with erythropoietin (5) may influence erythropoiesis through different mechanism (1, 3, 6, 9, 10).

Resumen

El ayuno en animales normales o tratados con eritropoyetina produce una disminución paralela de la actividad eritropoyética del bazo y de la médula ósea. En animales tratados con testosterona, el ayuno disminuye solamente la fracción eritropoyética del bazo, mientras que la de la médula ósea aumenta marcadamente por encima de los valores normales.

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