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Comparative Effects of Dexamethasone and Testosterone on Erythropoiesis in a Strain of Mice Partially Unresponsive to Hypoxia *

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Androgens stimulate red cell production by enhancing the endogenous erythropoietin titer, while adrenal cortical steroids have been reported to exert stimulatory or suppressive effects on erythropoiesis. The action of testosterone and dexamethasone was compared in short and longterm experiences that combined administration of the hormones with hypoxia in a strain of mice that show little erythropoiein production when subjected to hypobaric hypoxia.

Both hormones, if used alone, show little erythropoietic activation. Testosterone combined with hypoxia increases radioiron uptake into red cells, resulting in a significative increment of the red cell mass. The combination of dexamethasone with hypoxia reveal a similar erythropoietic response, suggesting that, at least with this experimental model, androgens and this synthetic steroid have a similar pharmacologic action.

The effect of steroid hormones on red cell production has been repeteadly studied under diverse clinical and experimental conditions (12, 13, 19, 22). Both androgenic and anabolic compounds have shown to stimulate erythropoiesis (4), if not exclusively, at least in part through an increased production of erythropoietin (17, 18).

Conversely, the role of adrenal cortical steroids is confuse. Although from the clinical point of view they may potentiate the ameliorative effects of androgens on hypoplastic anemias (2), being also capable of inducing remissions when used alone (20), experimental data suggest that their influence upon erythropoiesis may be stimulatory (7, 10) or suppressive (6, 15). It is so possible that their effects depend on the previous status of the animal, the dosage and time of administration of the hormones (14).

In previous experiences, we have ob-

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served (1) that testosterone increases erythropoietin production in a strain of mice partially unresponsive to hypobaric hypoxia. To investigate the action of corticoids over this experimental model, the action of testosterone and dexamethasone (a synthetic steroid not found in adrenal extracts) were compared in short and long-term experiences that combined administration of the hormones with hypoxia in BALB/ep mice. Radioiron incorporation into red cells and red cell mass were employed as the erythropoietic criterion.

Materials and Methods

In all experiments, female adult mice of the BALB/ep strain were used. Each group of experimental individuals contained 8-10 animals.

SHORT-TERM EXPERIENCES. On day 1 animals were injected subcutaneously with a single dose of 2 mg testosterone cyclopentylpropionate (TS) (Testergon, Millet), dexamethasone sodic hemisulphate (DM) (DexaScherosona, Schering Corp. U.S.A.), diluted in the same volume of peanut oil, or the diluent. Immediately they were subjected to 16 hours of hypoxia at 0.30 atmospheres in a low pressure chamber similar to that described by WRIGHT (23). On days 3, 4, 5 and 6 groups of animals were separated and injected intravenously with 0.2 microcuries of ^{59}Fe diluted in 0.2 ml saline. Twenty four hours after the radioiron injection mice were bled out via cardiac puncture and ^{59}Fe uptake in red cells determined with a well-type scintillation counter and expressed as a percentage of the injected dose using an appropriate ^{59}Fe standard.

LONG-TERM EXPERIENCES. Animals were subjected to chronic hypoxia at the altitude and time conditions above mentioned, for a period of 14 days. They were injected every other day with 2 mg of TS or DM, or the diluent, reaching a total dose of 14 mg of hormone for each animal. Three days after removal from the chamber total blood volume was measured by the ^{59}Fe labeled red cells dilution technique (9).

Red cell volume (RCV) was obtained by means of blood volume and hematocrit data, and the results expressed as per cent of body weight.

Controls for both short and long-term experiences were normoxic animals injected with TS, DM or the diluent.

Hematocrits were measured by a micromethod.

Statistical evaluation of the data was carried out utilizing the techniques described by BANCROFT (3).

Animals were weighed before and after the period of hypoxia.

Results

EFFECT OF TS AND DM ON ^{59}Fe UPTAKE INTO RED CELLS

Figure 1 show radioiron uptake into red cells in mice treated with hypoxia and TS, compared with oil-injected controls and normoxic animals. The erythropoietic response is significative at 96 hours in the TS group, while controls show little activation.

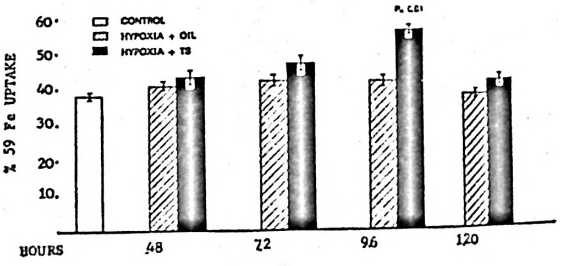

Fig. 1. *Radioiron uptake into red cells at different intervals after administration of hypoxia and testosterone (TS).*
Vertical bars delineate standard deviation. p value reported only when significative if compared with control.

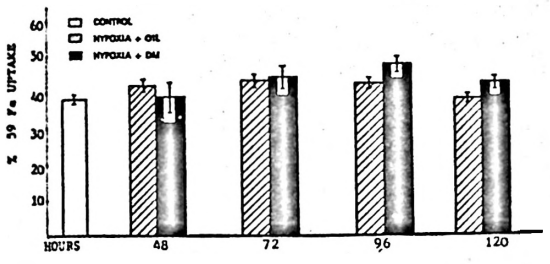

Fig. 2. *Radioiron uptake into red cells at different intervals after administration of hypoxia and dexamethasone (DM).*
Vertical bars delineate standard deviation.

A similar experience combining hypoxia and DM is detailed in figure 2. By the second day there is a slight, not significative decrease in radioiron uptake, while the effect at 72,96 and 110 hours, although also slight, is stimulating.

Effect of TS and DM on RCV

Figure 3 indicates that hypoxia, TS or DM, if given alone, fail to increase significantly red cell production, while the combination of both steroid with hypoxia will produce an important increase in RCV.

Hematocrit values paralleled the increase in RCV in all groups (Table I).

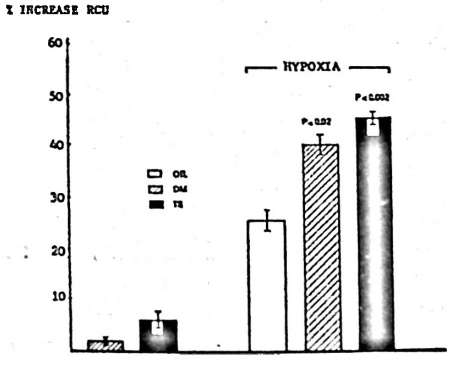

Fig. 3. *Effect of hypoxia alone or combined with testosterone (TS) and dexamethasone (DM) on red cell volume (RCV).*
Results are expressed in percent increase of controls. Vertical bars delineate standard deviation. p values reported only when significative if compared with controls.

Table I. *Effect of testosterone (TS) or dexamethasone (DM) and hypoxia on hematrocrit.*
Mean values ± standard deviation.

Treatment	Hematocrit
Normoxic controls	50.0±0.6
TS	55.0±1.1
DM	52.7±0.9
Hypoxia	59.5±1.4
Hypoxia+TS	63.2±1.8
Hypoxia+DM	61.5±1.7

Total body weight decreased in the hypoxic animals and increased slightly in the normoxic ones. There were no striking differences between the oil-injected, TS and DM groups.

Discussion

Androgens may enhance erythropoietin production by a direct action on the producer organ or by increasing the sensitivity of the hypoxia receptor charged to induce production of the hormone (16). The present experiments confirm and extend previous findings (1) that TS exerts a stimulatory effect on erythropoietin production in a strain of mice partially unresponsive to hypobaric hypoxia. Radioiron uptake into red cells rises significantly 96 hours after injection, showing a time-course effect closely similar to that reported in other experiences that studied the androgen action on rodent erythropoiesis (6, 8).

In our experiments, the effect of DM on ^{59}Fe uptake into red cells is similar to that observed by administration of TS. Although not very important, if repeated the stimulus is also able to increase RCV in the animals. The data also indicate that the combination of both TS and DM with hypoxia causes a potentiation of effects, resulting in a significative increase in RCV while either stimulus adminstered sepa-

rately do not show appreciable erythropoietic activity. The close similarity between both erythropoietic responses suggest that, at least with this experimental model, their pharmacological effects depend on a similar mechanism of action. Our results with DM, however, do not rule out the possibility of a potentiation of the erythropoietic effect of endogenous erythropoietin or a direct action not requiring the presence of the hormone. It is noteworthy that the stimulating effects of steroids on erythrocyte production may not neccessarily depend on androgen activity: the anabolic group is also active (4). Furthermore, recently has been reported (5) that steroids may act to trigger hemopoietic stem cells into cell cycle or to shorten their cell cycles and that steroids with potent androgenic action are not required for this kind of action.

Forty-eight hours after injection of DM, radioiron uptake fell slighthy below control values. It has been reported (21) that another synthetic steroid, betamethasone, exerts its lymphocytolytic effect on spleen, resulting in a depression on the splenic erythropoietic compartment. Since an important fraction of mice erythropoiesis is situated in the spleen (11), a transitory blockade of these erythropoietic compartment could explain our results. DM may then have different and opposed effects on spleen than in the rest of the erythropoietic tissue, but the increase in RCV observed in the long-term experiences show that the stimulatory effect is more important and overcomes the suppressive one.

Resumen

Los andrógenos estimulan la producción de hematíes por aumento en la producción de eritropoyetina, mientras que los resultados obtenidos con los esteroides corticosuprarrenales son contradictorios. Se compararon los efectos de la testosterona y de la dexametasona en experiencias agudas y crónicas en las que se combinaron ambas hormonas con hipoxia, en una cepa de ratones que se caracteriza por escasa producción de eritropoyetina cuando se la somete a baja concentración de oxígeno ambiental.

Ambas hormonas, administradas solas, no muestran activación eritropoyética significativa. La combinación de testosterona con hipoxia aumenta la captación de hierro radiactivo en los hematíes, dando como resultado un considerable incremento de la volemia globular en los animales. La combinación de dexametasona con hipoxia muestra una respuesta eritropoyética similar, lo que sugiere que, por lo menos con este modelo experimental, los andrógenos y este corticoide sintético tienen una acción farmacológica parecida.

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