The Inhibitory Effects of Anti-Androgen (SH-714) on Erythropoietic Activity

Erythropoietin (ESF) release in man, dogs, and rodents[1–5] is augmented by treatment with exogenous androgens[1–5]. The stimulatory effects of androgens on erythropoiesis have thus been well documented. The majority of investigators favor the viewpoint that androgen erythropoietin action is in part related to increased ESF production. This fact was established by MIRAND et al.[2] and confirmed by FRIED et al.[3] by injecting androgen into plethorized mice. A new synthetic compound, a strong anti-androgen (cyproterone acetate, SH-714[6]) has recently been available for study. The compound is devoid of estrogenic or pituitary inhibitory properties[7]. This compound thus provides an experimental opportunity to investigate the postulated mechanism of action of androgens on erythropoiesis.

Materials and methods. Plethoric Ha/ICR Swiss mice over 8 weeks old and over 30 g body weight were used. A minimum of 5 animals were used in each experimental subgroup. All treatments were given i.m. Depo-testosterone cyclopentylpropionate in sesame oil was given to plethoric mice at a dose rate of 10 mg as a single dose or coincident with the first of a 3-day injection course of 1 unit per animal of purified sheep ESF (Connaught Medical Research Laboratories, Willowdale, Ontario, Canada). Cyproterone acetate (SH-714) in solution was given at a dose of 10 mg per animal alone and with or without depo-testosterone or purified ESF. Experimental subgroups included (1) saline injected controls, (2) SH-714 only, (3) depo-testosterone only, (4) ESF only, (5) ESF plus sesame oil, (6) SH-714 plus depo-testosterone, (7) ESF plus depo-testosterone, (8) SH-714 plus ESF, and (9) SH-714 plus ESF plus depo-testosterone. On the fourth day 1 μc Fe^{59} was injected i.v. and on the fifth day 24-hour % blood radio-iron uptake was carried out to determine the level of erythropoiesis in plethoric mice. To prevent any false-positives, only plethoric mice with hematocrit above 59-volume % were used in the calculation of the data.

The effect of anti-androgen cyproterone acetate (SH-714) on the erythropoietic effects of depo-testosterone and erythropoietin (ESF) in plethoric mice

Groups	Average 24 h Fe^{59} uptake in plethoric mice	± S.E.
1. Saline control	0.43	0.08
2. SH-714	0.38	0.03
3. Depo-Testosterone	4.19	0.45
4. ESF	25.84	1.25
5. ESF + Sesame Oil	24.01	0.87
6. SH-714 + Depo-Testosterone	0.87	0.07
7. ESF + Depo-Testosterone	27.42	1.02
8. SH-714 + ESF	14.52	1.06
9. SH-714 + ESF + Depo-Testosterone	14.37	1.15

Results and discussion. The Table summarizes the erythropoietic activity noted in treated animals. Note that SH-714 alone has no erythropoietic activity (compare subgroups 1 and 2). As shown, depo-testosterone alone is capable of stimulating erythropoietic activity in plethoric mice (subgroup 3). This effect is significantly diminished by concurrent SH-714 treatment (subgroup 6). ESF given exogenously with or without sesame oil (subgroups 4 and 5) and with depo-testosterone (subgroup 7) markedly increases erythropoietic activity as measured by radio-iron incorporation. In the presence of SH-714, the increased erythropoietic activity noted with ESF (subgroup 8) or ESF plus depo-testosterone (subgroup 9) is decreased significantly. These experiments thus affirm the fact that SH-714 at a dose level of 10 mg is an effective anti-androgen as determined by the ability to inhibit testosterone stimulated ESF release. Attempts to inhibit testosterone stimulated ESF release with 2 and 6 mg of SH-714 were ineffective. The inhibitory effect of SH-714 was also detectable to some degree in the presence of purified sheep ESF. One might theorize from this response that SH-714 might neutralize ESF in the plasma directly or that SH-714 has an effect on the ESF-sensitive cells in the bone marrow or spleen which results in less measurable erythropoietic activity in the blood. It is more reasonable to assume that the latter might be the case. It is not known how SH-714 neutralizes androgen, but the mechanism of action of SH-714 is thought to be through competition with androgens for reception sites[8, 9].

Zusammenfassung. Der erythropoietische stimulierende Effekt von Depo-Testosteron-Zyklopentylpropionat in plethorischen Mäusen kann durch ein neues Antiandrogenpräparat (Cyproteronazetat – SH-714) verhindert werden. Dasselbe Präparat verhindert in plethorischen Mäusen ebenfalls die nach einer Standarddosis von Erythropoietin erwartete Blutneubildung.

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8 This investigation was supported in part by a grant from the New York State Kidney Institute, New York State Department of Health, and grants No. CA-08847 and CA-07745 from the U.S. Public Health Service, National Institutes of Health, and the John A. Hartford Foundation, Inc.
9 Acknowledgments: The authors are grateful to A. BULBA, E. DYWINSKI, J. JIVIDEN, A. MIRAND, Dr. P. TRUDEL and W. TRUDEL for their technical assistance.