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ORIGINAL ARTICLE

Induction of erythropoietin-hypersecretory state by the androgenic steroid 5α-dihydrotestosterone but not by its non-androgenic isomer 5β-dihydrotestosterone

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Abstract Erythropoietin-hypersecretory state (EPO-HS) has been defined as a condition elicited by inducers, which is easily observed in hypertransfused polycythemic rodents in which hypoxia-stimulated EPO secretion is higher than in non-treated controls at equal levels of polycythemia. Testosterone (T) is a potent inducer of EPO-HS. T has the potential of acting itself or of being metabolized to either 5α-dihydrotestosterone (5α-DHT) or 5β-dihydrotestosterone (5β-DHT). The former binds to the androgen receptor while the latter does not. However, both isomers can stimulate erythropoiesis, although through different mechanisms and possibly through different receptors. The objective of this investigation was to characterize the role of both receptors in mediating the EPO-HS induced by T. Male CF#1 mice were orchidectomized when aged 30 days. One month later, groups of 10 animals each received graded doses (0–3,200 μg) of T, 5α-DHT or 5β-DHT, subcutaneously, 3 times a week for 4 weeks. Mice were made polycythemic 4 days after the injection period and exposed to hypobaric air (506.5 mbar) for 6 h, 1 day later. Plasma EPO concentration (pEPO) was estimated by immunoassay at the end of the exposure period and taken as the expression of EPO production rates. Androgenic activity of the steroids was estimated by seminal vesicle weight, whereas the nephrotropic activity of the steroids was derived from the kidney weight. Orchidectomy significantly reduced the weights of both seminal vesicle and kidney. Dose-related increases of organ's weights were elicited by both T and 5α-DHT; 5β-DHT being ineffective. The pEPO response to hypobaric hypoxia increased as a function of the dose of the androgenic steroids administered up to the 800 μg dose with no further increments beyond this dose. Administration of 5β-DHT had no effect on pEPO. The induced EPO-HS was associated with the androgenic and renotrophic actions of both testosterone and 5α-DHT; 5β-DHT being ineffective as EPO-HS inducer. Data indicate that the induction of an EPO-HS by testosterone requires the activation of the androgenic receptor. The possible activation by the steroid of the non-androgenic receptor, which appears to exert a direct erythropoiesis-stimulating effect on the bone marrow, does not induce an EPO-HS.

Keywords Androgens · Erythropoiesis · Erythropoietin · Hypoxia

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Introduction

Numerous studies conducted on humans and laboratory animals have shown that androgenic hormones stimulate red cell production probably in response to an enhanced erythropoietin (EPO) formation (Besa 1994). However, its mechanism has not been entirely clarified because other studies have suggested that androgens stimulate erythropoiesis by direct, EPO-independent mechanisms (Shahidi 1973).

EPO is a glycoprotein that participates in feedback control of erythropoiesis (Jelkmann 1992; Koury 2005). EPO synthesis and secretion mainly depend on oxygen supply to tissues relative to their oxygen needs (Fried et al. 1957). Recent findings have suggested that hypoxic induction of EPO synthesis is expected to reflect the