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F. de Las Heras & A. Negro-vilar

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Effect of Aromatizable Androgens and Estradiol on Prolactin Secretion in Prepuberal Male Rats

F. DE LAS HERAS and A. NEGRO-VILAR

Intact and castrated male rats were injected daily for 10 days, beginning at 35 days of age, with either oil or one of the following steroids: testosterone propionate, dihydrotestosterone benzoate, androsterone acetate, androstenedione, androstandiol, or estradiol benzoate. Doses were 200 μg/rat/day for all androgens and 0.5 μg or 2 μg/rat/day for estradiol. Significant increments in prolactin levels (fourfold over control values) in intact and castrated males were obtained after testosterone propionate and androstenedione treatment. Dihydrotestosterone, androsterone, and androstandiol did not induce any changes in either intact or castrated rats. Estradiol-treated males showed a four- and sevenfold increment in serum prolactin with the 0.5- and 2-μg doses, respectively. These results suggest that androgens have a role in the control of prolactin secretion, particularly those that can be aromatized to estrogens by different tissues, including the hypothalamus.

Key Words: Androgens; Estrogens; Aromatization; Prolactin; Males.

INTRODUCTION

Prolactin secretion is regulated by hypothalamic inhibiting and releasing factors [8]. Unlike other pituitary hormones, prolactin apparently lacks direct feedback from the target tissues it stimulates. Since there is a predominant tonic inhibitory control of the hypothalamus, most factors that influence its secretion are stimulatory in nature. Gonadal steroid hormones, in general, induce an increase in blood prolactin levels, estradiol being the most potent stimulator [2, 6, 14]. Very little is known about the feedback control of prolactin secretion in the male rat and the role played by gonadal steroids. Serum prolactin levels during sexual development in the male rat [10] are very low before weaning, with values increasing after weaning and during the prepuberal and puberal periods.

This experiment was designed to study the effects of androgens that can be aromatized to an estrogenic form by different tissues (including the brain) and those of several nonaromatizable androgens, as well as estradiol, on serum prolactin levels in intact and castrated prepuberal male rats. Part of this work has previously been reported in abstract form [3].

MATERIALS AND METHODS

Male Wistar rats were housed in colony cages (four to a cage) in a light- and temperature-controlled room. At 35 days of age animals of similar body weight were randomly distributed

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From the Instituto de Neurobiologia, Buenos Aires, Argentina.

Address reprint requests to: A. Negro-Vilar, Department of Physiology, Southwestern Medical School, Dallas, Texas 75235.

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into experimental and control groups. Intact and castrated rats received one of the following steroids obtained from Sigma: testosterone propionate, dihydrotestosterone benzoate, androsterone acetate, androstenedione, androstandiol, and estradiol benzoate. Control groups received the oil vehicle. Castrated animals received the first injection within 2 hr after the operation. All steroids were given at a daily dose of 200 μg/rat for 10 days. No significant differences in body weights were observed between any of the groups.

At the age of 45 days, all animals were brought to the laboratory 2–3 hr before the time of sacrifice. Around noon, the animals were rapidly decapitated. Each group had 8–10 rats, and for each treatment a control group was sacrificed simultaneously. Serum prolactin was measured by radioimmunoassay. All samples were expressed in terms of the NIAMDD rat prolactin RP-1 standard. Statistical differences between each set of control and experimental groups were calculated by Student's t test. A two-way analysis of variance was used to compare intact and castrated control groups.

RESULTS

Intact rats treated with testosterone propionate or androstenedione had significantly ($p < 0.001$) higher prolactin values, about four times above control animals (Fig. 1a). Dihydrotestosterone, androsterone, or androstandiol did not affect prolactin levels.

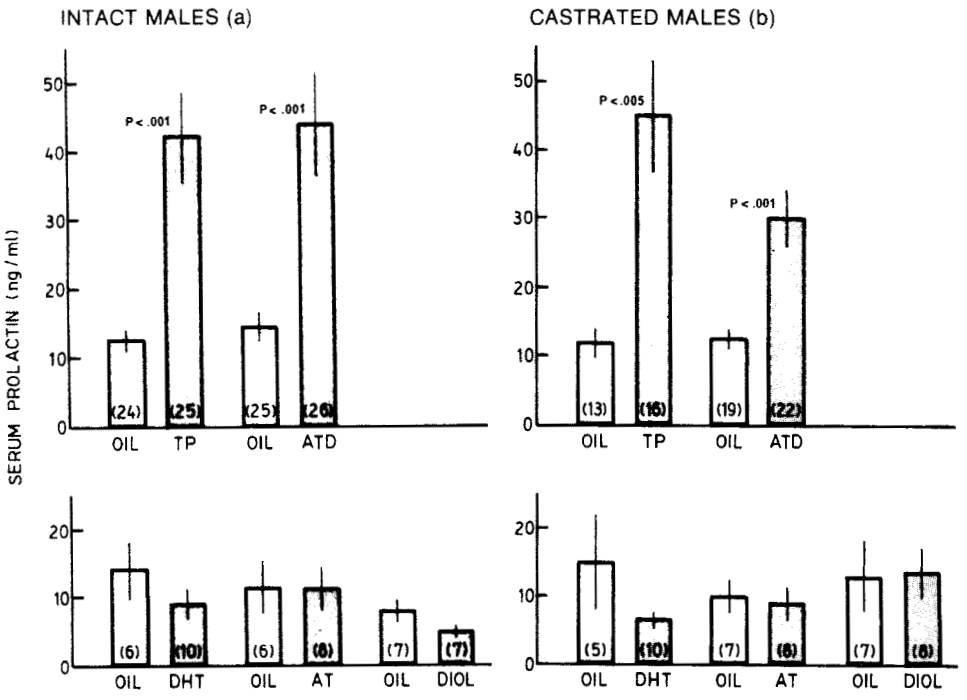

FIGURE 1. Serum prolactin levels in prepuberal male rats after treatment with different androgens. a. Intact rats. b. Castrated rats. Values are means ±SEM. The number of animals per group is indicated in parentheses at the bottom of the bar. *TP*, testosterone propionate; *ATD*, androstenedione; *DHT*, dihydrotestosterone; *AT*, androsterone; *DIOL*, androstandiol.

In castrated males, prolactin was elevated three- to fourfold above control levels in animals treated with testosterone ($p < 0.005$) or with androstenedione ($p < 0.001$) (Fig. 1b). Castrated rats treated with dihydrotestosterone, androsterone, or androstandiol did not show any change in prolactin levels. Comparison of intact (Fig. 1a) versus castrated (Fig. 1b) control rats showed that serum prolactin levels in castrated, oil-treated controls ranged from 9.9 to 14.8 ng/ml and were not significantly different from intact control groups (range 8.1–14.6 ng/ml).

In another experiment, littermates were either orchidectomized or sham orchidectomized at 20 days of age and killed when they reached 90 days of age. A significant ($p < 0.005$) decline in serum prolactin was seen in orchidectomized rats (4.2 ± 0.9 versus 14.9 ± 2.6 ng/ml in sham-operated controls).

Administration of a daily dose of 0.5 or 2 μg estradiol benzoate increased serum prolactin in intact males by four- and sevenfold, respectively (Fig. 2a). Castrated males showed a similar response, with prolactin levels increasing four- and sevenfold with the 0.5- and 2-μg doses, respectively (Fig. 2b). As in the previous groups, the increments observed with each dose were quite similar in both intact and castrated males.

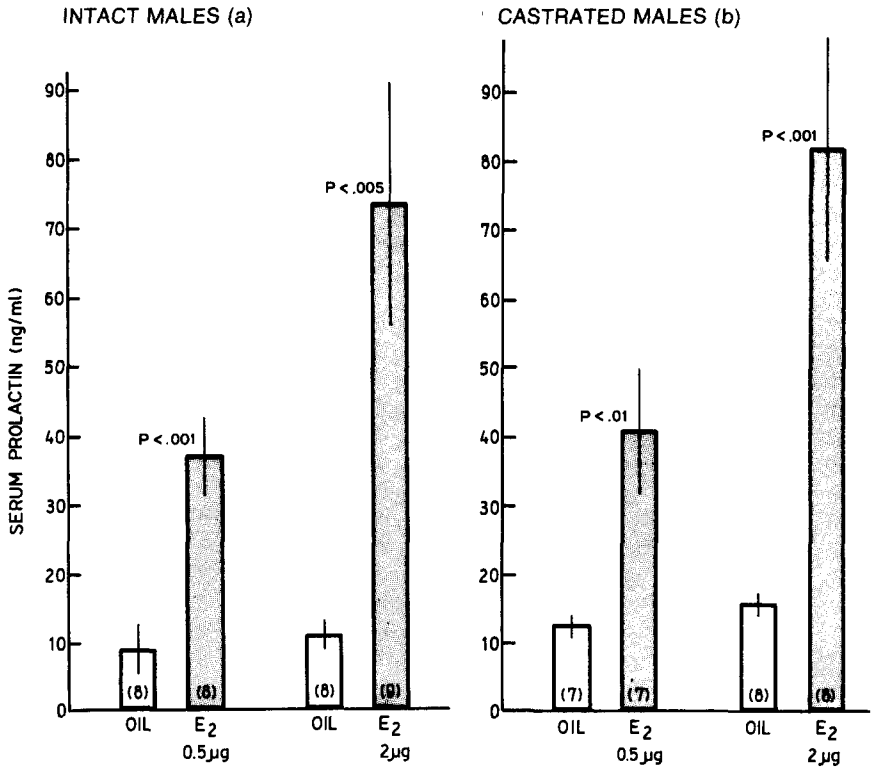

FIGURE 2. Serum prolactin levels in prepuberal male rats after treatment with estradiol benzoate (E_2). a. Intact rats. b. Castrated rats. Values are means ±SEM.

DISCUSSION

Increasing evidence has accumulated over the past several years indicating that testosterone can stimulate prolactin secretion in intact or castrated rats [6, 7, 13, 14] and in juvenile rhesus monkeys [5]. Indirect evidence to this effect has also been obtained in man [4, 12]. This report confirms and extends those findings, indicating that in prepuberal male rats, testosterone and androstenedione can effectively stimulate prolactin secretion in intact or castrated animals. Similarly, very low doses of estradiol benzoate readily stimulated prolactin secretion in both types of animals. On the other hand, three different nonaromatizable androgens had no effect on serum prolactin levels in the two models studied. In agreement with these results, dihydrotestosterone did not change prolactin levels in prepuberal or adult male rats [11].

Our observation that only aromatizable androgens can stimulate prolactin secretion clearly indicates that prior conversion to estrogens in vivo may be required for androgens to enhance prolactin release. Several tissues of the rat, including the brain, can aromatize testosterone and androstenedione to estrogens [9, 16]. However, only a small fraction of testosterone (<0.1%) can be converted into estrogen [9]. In our study, 0.5 μg estradiol benzoate induced prolactin increments similar to those elicited by 200 μg testosterone propionate in both intact and castrated animals, suggesting that even small amounts of estrogen derived from androgens can influence prolactin release.

Castration slightly decreases [13, 15] or has no effect on serum prolactin levels in male rats [7, 11]. Castration of prepuberal rats for 10 days did not alter serum prolactin levels in this study. When the animals were castrated before weaning, at a time that prolactin levels are still very low [10], and sacrificed 3 mo later, prolactin values were significantly lower than in controls. In adult males, long-term castration has little, if any, effect on serum prolactin levels (Negro-Vilar, unpublished). Since prolactin secretion in the male rat has been reported to be pulsatile [17], analysis of differences between basal prolactin levels based on a single determination may be misleading. An alternative possibility is that some androgens may actually be inhibitory to prolactin secretion. In our studies, the lowest values among all groups were obtained in animals treated with dihydrotestosterone or androstandiol, although the differences never achieved significance. Nolin et al. [11] reported that dihydrotestosterone significantly suppressed prolactin levels in intact female rats.

In view of the increasing number of reports suggesting an involvement of prolactin in the regulation of Leydig cell function in rats and man [1], it is conceivable that androgens may be physiologically implicated in the regulation of prolactin secretion.

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