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Divergent roles for estrogens and androgens in the expression of female goat sexual behavior

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Abstract

We tested the hypothesis that the activation of the androgen receptor (AR) is required for full expression of female goat sexual behavior. Once a week for 6 weeks, ovariectomized (OVX) females were given priming doses of progesterone 72 and 48 h before behavioral observation. Estradiol (E_2; 100 μg), testosterone (T; 100 mg), or sesame oil was supplied 14 h before behavioral testing. Six goats received the AR antagonist flutamide (9 mg/kg sc) 8 h before and 4 h after steroid injection. Six goats received the carrier only. After 3 weeks, flutamide and carrier treatments were switched so that all females received all treatments. Treatments with E_2 and T were equally effective in eliciting estrus-typical behaviors (sniffing, courting, leg kicks, mount attempts by males, bouts of thrusting by males, ejaculations, and flehman responses) compared to treatment with oil. Flutamide treatment enhanced proceptive behaviors in E_2-treated females compared to other treatment groups; this was most likely via enhanced tail wagging. Moreover, compared to goats given T + carrier, T + flutamide significantly reduced receptivity in females. The results of this experiment implicate the AR as an important facilitator of some aspects of the female goat sexual behavior. However, the results of this experiment do not show whether androgens influence estrous behaviors alone or in some combination with estrogen.

Keywords: Flutamide; Proceptivity; Tail wagging; Receptivity; Libido

In most ovariectomized (OVX) female mammals that are spontaneous ovulators, induction of estrus is accomplished by sequential administration of estradiol (E_2) or progesterone (P_4) in some combination. For example, although E_2 alone elicits some components of estrus in OVX female rodents, only E_2 plus P_4 (24–48 h after E_2) allows for the full complement of female sexual behavior (Auger, 2001). However, estrus in OVX goats may be induced by E_2 alone or, outside the breeding season, by P_4 treatment before E_2 administration (Billings and Katz, 1997).

In addition to estrogens, androgens may be important modulators of female sexual behavior (see review by Dörner, 1976) either directly or following aromatization to estrogen. Work done using sheep and goats supports the notion that the androgen receptor (AR) may play a facilitative role in female sexual behavior. In the ovary-intact goat, both estrogens and androgens are produced concomitant with the regression of the corpus luteum (Homeida and Cooke, 1984). Plasma testosterone (T) and E_2 concentrations continue to increase in the female, and when a threshold level is reached, estrus is observed. In sheep, the antiandrogen cyproterone acetate in conjunction with T administration blocked receptivity; however, this work is controversial as cyproterone acetate also functions as a progestin (Fabre-Nys and Signoret, 1980).

Preliminary data in our laboratory suggested that the aromatizable androgens T and androstenedione (A_4) induce the expression of female goat sexual behavior (Lindia and Katz, 2000). These researchers attempted to induce estrus in OVX goats using E_2, T, A_4, or DHT. They found that E_2, A_4, and T all increased expression of estrous behavior. However, T and A_4 tended to elicit higher attractivity and receptivity scores than E_2 treatment. Dihydrotestosterone alone had no effect on sexual behavior. Increased doses of E_2 did not enhance behavioral responses. Taken together, these obser-

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vations suggest that female goat and sheep sexual behavior is not solely due to estrogens derived from aromatization, but may require, in addition, androgen action.

The biological effects of androgens are transduced via the AR (Roy et al., 2001). If androgens, in conjunction with estrogens, are necessary for full expression of female goat sexual behaviors, we hypothesize that blockade of the AR should reduce attractivity or receptivity scores. In the present report, we examined the effects of a highly specific, nonsteroidal AR antagonist flutamide on the sexual behavior of OVX female goats given E_2, T, or sesame oil.

Materials and methods

General methods

This experiment was conducted between 31 January and 1 April, 2003 at the Cook College Small Animal Research Facility in New Brunswick, NJ (40°30′N). Ambient day length ranged from 10.1 to 12.7 h of light. Twelve adult, French-Alpine and Alpine-Boer crossbred nulliparous females and four sexually experienced French-Alpine and Alpine-Boer crossbred adult males, born between 1995 and 2001, were used in this experiment. Females were bilaterally OVX via midventral laporatomy under general anesthesia and were given 2 months to recover. Four females had prior sexual experience. Body weights of females averaged 55 ± 3 kg (range: 40–84 kg). Females were group-housed in a closed barn with natural lighting and had free access to an outdoor field. Males were group-housed with other males in a separate open-sided barn, also with outdoor access. All goats were fed a complete diet that met National Research Council standards for goats (NRC, 1981) and consisted of a pelleted ration and grass hay, along with ad libitum access to water and a mineral block. All animal maintenance and research procedures were in accordance with regulations established by the Rutgers University Animal Care and Facilities Committee.

Drug treatments

Estradiol (1,3,5 (10)-estratrien-3, 17β-diol), T (4-androsten-17β-ol-3-one), and P_4 (4-pregnen-3,20-dione) were purchased from Steraloids Inc. (Newport, RI). Flutamide (2-Methyl-*N*-[4-nitro-3(trifluoromethyl)-phenyl] propanamide) was purchased from Sigma-Aldrich (St. Louis, MO). All drugs were supplied in a subcutaneous injection. T (50 mg/ml) and E_2 (100 μg/ml) were first dissolved in ethanol and then placed in a sesame oil vehicle 1:1. Progesterone was dissolved in a 90% sesame oil/10% benzyl benzoate solution at a concentration of 10 mg/ml. Flutamide was dissolved in a 98% propylene glycol/2% ethanol carrier at a concentration of 50 mg/ml.

To our knowledge, a dose of flutamide has not been established for goats. However, bull calves of comparable body weight given a dose of 9 mg/kg flutamide experienced significant increases in luteinizing hormone secretion compared to control bulls (Rawlings and Evans, 1995). Two separate doses of flutamide (9 mg/kg, sc) were administered to ensure that the AR, if present, would be blocked during any hormone administration. Also, because we opted to supply an aromatizable androgen to the goats, flutamide was administered to E_2-treated goats to balance the experimental design.

Induction of estrus and behavior test

Females were given sc injections of P_4 72 h (10 mg P_4/goat) and 48 h (5 mg P_4/goat) before T, E_2, or oil injections, and behavior tests were conducted 14 h later. Eight hours before and 4 h after assigned hormone treatment, goats were given either flutamide or carrier.

The experiment lasted 6 weeks. During the first 3 weeks, half of the females were assigned to the flutamide treatment ($n = 6$) and the remainder received the carrier ($n = 6$). Each week during this period, two females from the flutamide group and two females from the carrier group were randomly selected to receive T, E_2, or oil, respectively, so that by the third week, each flutamide- or carrier-treated female had received each steroid treatment. During the second 3-week period, flutamide and carrier treatments were switched so that all goats eventually received all treatments.

Females were tested in their home pen. Before each 15-min test period began, males were retrieved from their barn and brought to the female's barn. Males were kept in a holding pen but were allowed to view sexual interactions (Price et al., 1984). To avoid confounding treatment and stud, males were randomly assorted each week. During each behavior test, a male was placed into a test pen to acclimate for 15 min. A female was then led into the pen and two students observed sexual behavior; one student softly called out behaviors for the other student to record. All observers were blind to treatment.

The frequency of the following behaviors was recorded separately for males and females: body sniffing—sniffing of any part of the body except the anogenital region; anogenital sniffing; tail wagging; leg kicks—striking with the foreleg with the knee held straight; flehmen response; courting—goat with tongue extended taking several prancing steps toward a conspecific and vocalizing; head-butting; mount intentions—goat stands up on rear legs as if to mount but does not; mount attempts—goat mounts from any orientation where both forelegs come in contact with the other goat; mounts; bouts of thrusting while mounting female; ejaculations; stands—the female remains immobile while the male mounts or attempts to mount. Each interaction was counted as one event.

Sexual behaviors of the goat were classified as attractivity, proceptivity, or receptivity (Beach, 1976). Attractivity was defined as the sum of all behaviors the male directed at the female. Receptivity was defined as the number of times