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Inhibition of Estrogen-Induced Sexual Receptivity of Female Hamsters: Comparative Effects of Progesterone, Dihydrotestosterone and an Estrogen Antagonist[1]

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DE BOLD, J. F., P. H. RUPPERT AND L. G. CLEMENS. *Inhibition of estrogen-induced sexual receptivity in female hamsters: Comparative effects of progesterone, dihydrotestosterone and an estrogen antagonist.* PHARMAC. BIOCHEM. BEHAV. 9(1) 81–86, 1978.—In the first experiment ovariectomized female hamsters were administered varying dosages of progesterone (P), dihydrotestosterone (DHT) or CI–628 at the same time (concurrently) as estrogen (EB) or 48 hr after EB (sequentially). All groups also received 500 μg P 4 hr before being tested for sexual receptivity. P was more effective in reducing receptivity when given sequentially with estrogen than when given concurrently. Thus, the inhibitory effect of P increased with an increased interval between EB and P treatment. More CI–628 than P was required to inhibit lordosis and unlike P, CI–628 was equally as effective when given concurrently with EB as when given sequentially. DHT did not inhibit receptivity when given in either paradigm. In the second experiment ovariectomized hamsters were treated with varying dosages of DHT 12 hr before EB. An amount of DHT which had no effect in Experiment 1 significantly inhibited receptivity when given 12 hr before EB. The relative inhibitory effects of these three compounds were discussed in terms of the possible similarities and differences in their mechanisms of action for inhibiting lordosis.

Sexual behavior Estrogen Progesterone Dihydrotestosterone CI–628 Inhibition of lordosis

AS IN OTHER laboratory rodents, sexual receptivity is most effectively induced in ovariectomized hamsters by treatment with estrogen and, 24 to 72 hr later, progesterone [12]. In addition to its facilitation of estrus, progesterone may also inhibit sexual receptivity under certain conditions. This can occur when the sequence or timing of estrogen and progesterone administration does not adhere to the pattern of their normal secretion during the estrous cycle or during continued exposure to progesterone as in the luteal phase of the estrous cycle of some rodents (for reviews see [10,23]). Progesterone can inhibit estrogen-induced estrus if it is present during the initial priming action of estrogen. However, progesterone can also inhibit receptivity after the completion of estrogen priming. This later effect of progesterone has usually been observed as a reduced response to a second injection of progesterone. These two forms of progesterone inhibition have been termed, respectively concurrent and sequential inhibition [30].

In a recent report [8] we demonstrated that progesterone was capable of inhibiting sexual receptivity in the female hamster either when given at the same time as an injection of estrogen (concurrent inhibition) or at 48 hr after estrogen administration (sequential inhibition). In that experiment, we found the hamster to be very sensitive to sequential inhibition by progesterone but we did not attempt to determine the threshold sensitivity for concurrent inhibition. More recently, two groups of investigators have shown that in the rat less progesterone is required for inhibition of sexual receptivity using the sequential paradigm than with concurrent administration of estrogen and progesterone [5, 6, 22]. The fact that less progesterone is required for inhibition when administered in sequence with estrogen is important because of its implications for the possible mechanisms of progesterone action. These studies have raised the question of whether concurrent and sequential inhibition reflect the same neural process. Therefore, one purpose of the present study is to expand the current base of comparative studies on the relative effectiveness of concurrent and sequential inhibition to the hamster.

Progesterone is not unique in its ability to inhibit estrogen-induced sexual receptivity. For example, CI–628, a synthetic anti-estrogen, will block receptivity when given concurrently with the priming dose of estrogen in female rats and hamsters [1, 14, 15, 18, 27, 29, 38] but not at similar dosages in guinea pigs [35]. This effect of CI–628 may reflect a species specific disruption of the initial actions of estrogen.

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For example, in rat hypothalamus, CI–628 has been shown to compete for estradiol uptake and inhibit nuclear binding of estradiol [7, 15, 16, 32] and reduce estradiol receptor repletion [39]. However, in addition to inhibiting these initial actions of estradiol, CI–628 also appears to inhibit receptivity when given long after the priming action of estradiol is complete [6]. This delayed inhibition by CI–628 may be analogous to sequential inhibition with progesterone.

When given chronically, 5α-dihydrotestosterone (DHT) has also been reported to inhibit sexual receptivity in estrogen treated rats, mice and hamsters [2, 3, 4, 17, 19, 28]. As with progesterone and CI–628, the mechanism of inhibition of receptivity due to DHT is not clear. Baum and his coworkers [2, 3, 4] have suggested that DHT may inhibit estrogen action although not at the level of estrogen uptake and binding [34]. Another group has proposed that it may interfere in some complex fashion with both estrogen and progestin action [17,19] or with the release of LH–RH [20]. Again, it is possible that DHT may act via the same inhibitory mechanism as progesterone.

The female hamster has been found to be much more sensitive to the inhibitory actions of progesterone than the rat [8]. Perhaps by comparing the pattern of the effectiveness of these three behavioral anti-estrogens in the hamster, we may be able to find a consistent explanation of their inhibitory actions on estrogen and progesterone induced sexual receptivity.

GENERAL METHOD

Female golden hamsters were obtained from Engle's Laboratory Animals (Farmersburg, Indiana) at 50 days of age. Sexually experienced male hamsters were from a population maintained in our laboratory derived from Charles River Laboratory (Lak:LVG; Wilmington, Mass.). All animals were kept in a 14:10 reversed light-dark cycle, with lights off at 1100 hr. Ambient temperature was maintained at approximately 22°C. Food and water were available ad lib throughout the experiment. Females were housed in pairs in cages measuring 28×22×15 cm and males were housed in groups of five or six in cages measuring 38×33×17 cm. All females were ovariectomized under ether anesthesia at 60 days of age. Experimental treatments began 7 days later.

Dihydrotestosterone (5α-androstan-17β-ol-3-one) (DHT) was purchased from Sigma Chemical Co. (St. Louis, Mo). Progesterone (4-pregnen-3,20-dione) (P) and estradiol benzoate (1, 3, 5(10)-estratrien-3, 17β-diol 3-benzoate) (EB) were generously provided by Schering Corporation (Bloomfield, NJ) and CI–628 (1-[2-(p-[α-(p-methoxy-phenyl)-β-nitrostryrl] phenoxy) ethyl] pyrrolidine monocitrate) by Parke-Davis (Ann Arbor, MI). The steroids were dissolved in a benzyl benzoate-sesame oil solution (20:80, v:v) and CI–628 in distilled water. The two highest DHT concentrations (2.5 and 5.0 mg/0.05 ml) did not completely dissolve in the oil-benzyl benzoate vehicle even after sonication in an ultra-sonic water bath. Therefore, they were injected as a suspension. All treatments were administered subcutaneously in 0.05 cm^3 of the appropriate vehicle.

All tests for female sexual behavior were conducted in an air-conditioned room connected to the laboratory colony. Observations were done in dim illumination between 1700 and 1900 hr. Ten gallon aquaria with San-i-cel bedding covering their floors were used as test arenas. Each experimental female was placed into the arena with a sexually vigorous male for 10 min. If the male failed to repeatedly mount the experimental female within the first few minutes of the test he was replaced with a fresh stimulus male. An Esterline-Angus event recorder was used to record the occurrence and duration of the lordosis response by the female. Total lordosis duration (TLD), the number of seconds the female remained in a rigid lordosis posture during the 10 min test, was then used as a measure of receptivity. At least one week separated the initial test of a female and retesting under a new hormone regime.

The effects of the various treatments on TLD were analyzed using appropriate analysis of variance programs, followed by the Newman-Keuls procedure for individual comparisons [40].

EXPERIMENT 1

Although progesterone, CI–628 and DHT have all been found to inhibit estrogen-induced receptivity in the female hamster, the time course and dosages which have been used to demonstrate this effect have not been comparable for all three compounds. In this initial study CI–628 and DHT were given in the concurrent and sequential paradigms previously demonstrated to be effective with progesterone in hamsters [8]. If similar neural mechanisms underlie the inhibitory actions of these three compounds then they should have similar patterns of effectiveness.

The dosages of CI–628 were chosen from within the range used in earlier experiments on rats and hamsters [1, 6, 14, 15, 27, 29, 32]. There were no previous experiments on the effect of a single injection of DHT on sexual receptivity to draw from, therefore DHT was given in a wide range of dosages equal to that of both progesterone and CI–628.

Procedure

Ovariectomized female hamsters were randomly assigned to treatment groups, eight females per group. For each treatment, females were tested in two paradigms, concurrent and sequential administration of the experimental compound, in counterbalanced order. In the concurrent paradigm, females received 5 μg EB at Hour 0 (1700 hr) with either P, DHT or CI–628 also administered at Hour 0. At Hour 44, these females received 500 μg P, and then were tested for lordosis responding at Hour 48. In the sequential paradigm, all females received 5 μg EB at Hour 0, and at Hour 48 either P, DHT or CI–628. Then the females received 500 μg P at Hour 68, and were tested for lordosis behavior at Hour 72. Doses of P for both the concurrent and sequential paradigm were 0, 25, 100 and 500 μg; DHT doses were 0, 25, 100 and 500 μg; and for CI–628, 0, 0.25 mg, 1.0 mg and 5.0 mg were given. A second set of 24 females received larger dosages of DHT. These females were also tested in both the concurrent and sequential paradigms and given 0, 1.0, 2.5 or 5.0 mg DHT.

Results

The effects of concurrent and sequential administration of progesterone are shown in Fig. 1. Receptivity scores were significantly reduced after progesterone treatment in the sequential paradigm. When as little as 25 μg of progesterone was given 48 hr after estrogen subsequent sexual receptivity was reduced ($p<0.05$). Larger doses of progesterone also inhibited receptivity ($p<0.01$); animals receiving 500 μg of progesterone were completely unreceptive. In contrast, progesterone given concurrently with estrogen was less ef-

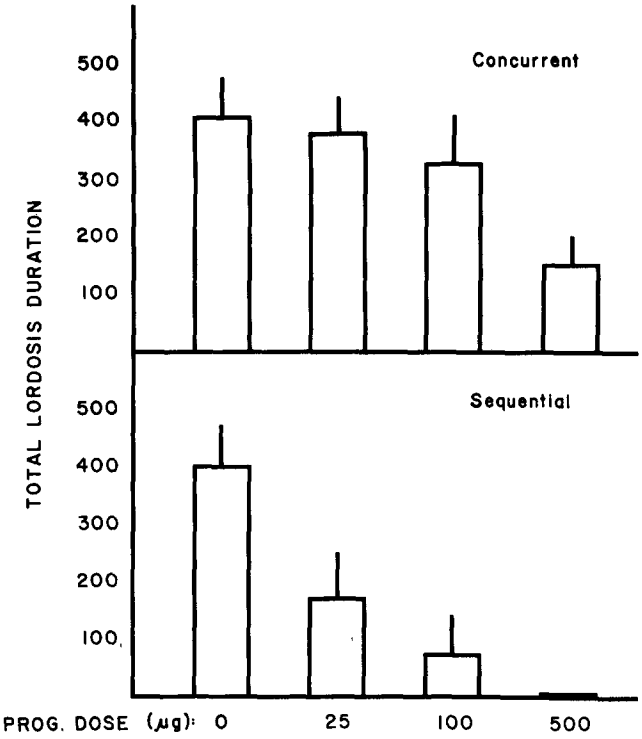

FIG. 1. The total lordosis duration ($\bar{X} \pm$ SEM) of female hamsters receiving varying amounts of progesterone concurrently with estrogen or 48 hr after estrogen (sequential). All animals also received 500 μg of progesterone 4 hr before behavioral testing.

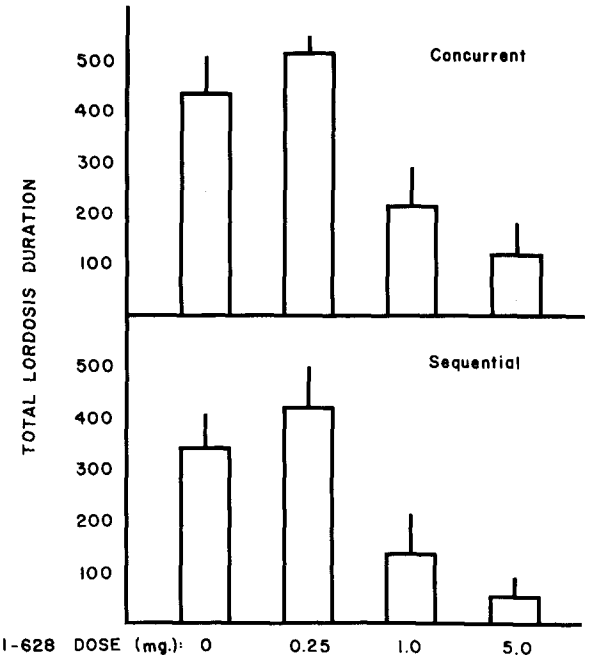

FIG. 2. The total lordosis duration ($\bar{X} \pm$ SEM) of female hamsters receiving varying amounts of CI-628 concurrently with estrogen or 48 hr after estrogen (sequential). All animals also received 500 μg of progesterone 4 hr before behavioral testing.

fective in reducing sexual receptivity (Fig. 1). In the concurrent paradigm 500 μg of progesterone was required to achieve a statistically significant inhibition of receptivity ($p<0.05$).

Figure 2 illustrates the effect of the sequence of CI-628 administration on receptivity. On a dosage basis it took far more CI-628 than progesterone to have any effect. In addition, CI-628 was effective in suppressing lordosis either when given concurrently with estrogen or when given sequentially (i.e., at 48 hr after estrogen). However, unlike with progesterone, the dosage-response pattern of CI-628 effectiveness was similar in both paradigms. Receptivity scores were suppressed by both 1 mg and 5 mg of CI-628 and not by 0.25 mg CI-628 in both paradigms ($p<0.05$).

The receptivity scores of animals receiving DHT treatment are shown in Table 1. In this experiment there were no effects of DHT, at any dosage, on sexual receptivity in either paradigm.

EXPERIMENT 2

Experiment 1 failed to find any inhibitory effect of DHT on estrogen-induced sexual receptivity. This is in contrast to an earlier demonstration of reduced receptivity in female hamsters after chronic treatment with DHT [28]. It is possible that chronic treatment with DHT is effective because repeated injections allow a buildup of DHT levels. Although even very large dosages of DHT were ineffective in Experiment 1, the total amount of DHT available may not be the important factor in this effect. DHT could be similar in some respects to MER-25. This anti-estrogen (MER-25) is much more effective in disrupting estrogen-induced receptivity if it is given a few hours before estrogen than when given concurrently [27,32]. Chronic administration of DHT may effectively provide the same pretreatment effect. In an attempt to demonstrate this with acute administration of DHT, Experiment 2 examined the effect of DHT given 12 hr before estrogen treatment.

Method

The same 24 ovariectomized female hamsters used for the higher dosages of DHT in Experiment 1 were used in this experiment. One week after their last hormone treatment these animals were randomly assigned to three groups of eight. Twelve hr prior to 5 μg EB they were injected with 0, 1.0 or 2.5 mg DHT. All animals then received 500 μg P 44 hr after estrogen and were tested for sexual receptivity 4 hr later.

Results

The effect of prior treatment with DHT on estrogen-induced receptivity is shown in Fig. 3. Prior treatment with 2.5 mg DHT significantly reduced lordosis duration ($p<0.05$). The mean lordosis duration of the females receiving 1 mg DHT 12 hr before estrogen treatment was also somewhat lower than vehicle controls but this effect was not significant.

GENERAL DISCUSSION

The results of Experiment 1 demonstrate that in the hamster, as in the rat [5, 6, 22], less progesterone is required for sequential inhibition than for concurrent inhibition. How-

TABLE 1

TOTAL LORDOSIS DURATION (TLD) OF FEMALE HAMSTERS GIVEN DHT CONCURRENTLY WITH ESTROGEN OR SEQUENTIALLY

Treatment DHT Dose	n	Paradigm* Concurrent ($\bar{X}$ TLD+SE)	Sequential ($\bar{X}$ TLD+SE)
0	8	365 ± 74	320 ± 75
25 μg	8	469 ± 72	450 ± 63
100 μg	8	410 ± 72	294 ± 90
500 μg	8	483 ± 71	321 ± 86
0	6	491 ± 56	423 ± 88
1.0 mg	6	460 ± 50	349 ± 64
2.5 mg	6	433 ± 88	373 ± 92
5.0 mg	6	453 ± 96	485 ± 77

* Concurrent paradigm: Hr 0, estrogen+DHT; Hr 44, 500 μg progesterone; Hr 48, behavioral test. Sequential paradigm: Hr 0, estrogen; Hr 48, DHT; Hr 68, 500 μg progesterone; Hr 72, behavioral test.

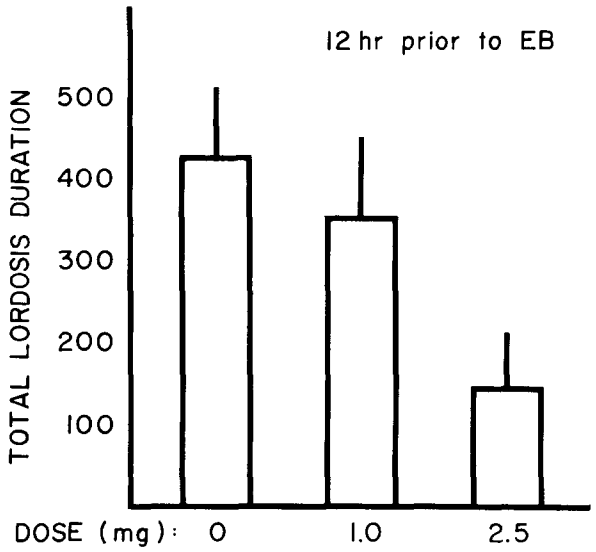

FIG. 3. The total lordisis duration ($\bar{X}$ ± SEM) of female hamsters receiving varying amounts of DHT 12 hr prior to estrogen. All animals also received 500 μg progesterone 4 hr before behavioral testing.

ever, in terms of absolute sensitivity, the rat is much less sensitive to the inhibitory effects of progesterone than the hamster, requiring approximately ten times more progesterone for inhibition in either paradigm than the hamster [5, 6, 22]. The progesterone sensitivity of the hamster is comparable to that seen in the guinea pig [10, 26, 37].

Our findings appear to support the suggestion [6,22] that there may be a single mechanism underlying inhibition of receptivity by progesterone. In the present experiment 25 μg of progesterone given 48 hr after estrogen was equivalent in effect to 500 μg of progesterone given concurrently with estrogen. This difference in effectiveness is of the same order of magnitude as the rate of clearance of progesterone from plasma over a similar period of time in the guinea pig [37]. If we can extrapolate from the guinea pig to the hamster, the larger amounts of progesterone given concurrently with estrogen could still be available after the priming action of estrogen was complete. Thus concurrent inhibition could be a special case of sequential inhibition. This would be consistent with our earlier failure to find any disruption of the initial molecular actions of estrogen by concurrent progesterone treatment [8]. In addition, some recent neuropharmacological findings in the rat also suggest that progesterone inhibition is independent of estrogen priming [31].

Alternatively, the increased effectiveness of progesterone 48 hr after estrogen treatment might reflect a time-dependent decreased influence of estrogen. In other words, if progesterone is thought of as inhibiting estrogen action at some level, then its inhibitory effect might increase with the clearance of estrogen. However, this view is not supported by the response to CI–628, a potent anti-estrogen. If the influence of estrogen had diminished enough to account for a 20-fold difference in progesterone effectiveness, a similar dose-response relationship would have held for CI–628. Although less progesterone was required 48 hr after EB to inhibit receptivity, CI–628 appeared equipotent in either paradigm. In addition, the influence of estrogen as measured by receptivity was not seen to decrease appreciably between 48 and 72 hr after EB (Figs. 1 and 2).

The demonstration of the strong inhibitory effects of CI–628 in the sequential paradigm was somewhat surprising. In a recent report [27] a relatively weak sequential effect of CI–628 was found in hamsters. In that earlier experiment, CI–628 given concurrently with estrogen was much more effective than when given 24 hr after estrogen. However, a comparison of the timing of injections employed in the present study and in other reports may reveal an important aspect of CI–628 action. In general, anti-estrogens have been found to have strong inhibitory effects on sexual receptivity when given close to the time of estrogen administration [1, 14, 15, 27, 38] or close to the time of behavioral testing [6, 9, 10]. However, the effect of CI–628 decreased if given more than a few hours after estrogen administration [1, 14, 38]. Time points between this early drop in effectiveness and the longer latencies used in sequential paradigms have not been well explored. The weak effect of CI–628 at 24 hr after estrogen [1,27] could be the result of the treatment falling between these two periods of inhibition. It is possible that concurrent and sequential inhibition of receptivity by CI–628 are subserved by different mechanisms of action. Concurrent effects of CI–628 probably reflect the disruption of estrogen uptake and retention processes [15,32]. The late or sequential effect of CI–628 could be due to an inhibition of other estrogen actions independent of estrogen uptake or to neural events separate from those of estrogen. Although complete dose-response data are not available, the results of some recent experiments with female guinea pigs are consistent with the possibility of two separate actions of CI–628. When given to guinea pigs concurrently with estrogen CI–628 fails to reduce estrus or 3H-estradiol uptake [35,36], however, CI–628 will inhibit receptivity when given sequentially in that species [9]. A comprehensive time course study of CI–628 effects could test the separate nature of these two periods of inhibition by CI–628 in the hamster.

An additional possibility to consider is whether the inhibitory action of progesterone could be mechanistically similar to that of CI–628 in the sequential paradigm. One group of investigators [6] has attempted to separate the behavioral effects of CI–628 and progesterone in the sequential paradigm in the rat. They found that CI–628 given in combi-

nation with progesterone 24 hr after estrogen reduced receptivity 13–14 hr later. However, no inhibition of receptivity was seen in estrogen-primed animals which received only a large amount of progesterone. Unfortunately in the rat the dosage of progesterone sufficient for inhibition also facilities sexual receptivity [6,22]. Therefore, in the rat the measurement of the latency of inhibition by progesterone is confounded by its initial excitatory effect, whereas CI–628 has no facilitative action. Consequently, it is unclear whether the sequential actions of progesterone and CI–628 are separable in that species. In female hamsters and guinea pigs very small amounts of progesterone can have inhibitory effects without facilitating receptivity [8,26]. A comparison of the latency of the inhibitory effect of both progesterone and CI–628 on sexual receptivity in hamsters or guinea pigs would be a more appropriate evaluation.

The present experiments also demonstrated that inhibition of estrogen-induced sexual receptivity by DHT requires treatment with DHT before estrogen administration. This pattern is clearly different from that of progesterone. However, this dependence of DHT effectiveness on pretreatment is similar to that seen under some conditions with MER–25 [21, 27, 32] which is thought to block behavior by competing for estrogen receptors [32,34]. Although hypothalamic estrogen receptors have little or no affinity for DHT [34] it is still possible that DHT could affect the availability of estrogen receptors. It has been demonstrated in rat uterus that DHT can cause nuclear accumulation of estradiol receptors and thereby deplete available cytoplasmic estradiol receptors [33]. It has not been demonstrated whether this might occur in brain. It has also been suggested that some effects of DHT on estrogen receptor might be mediated by its metabolism to 3α-androstanediol [4]. This androgen metabolite, like MER–25, is a weak competitor for hypothalamic estrogen binding [34] and thus might reduce receptivity, again by reducing the availability of the estrogen receptor. Either of these possibilities suggest that the action of DHT may be similar to the early component of CI–628 action; a disruption of estrogen priming. The difference in effectiveness of CI–628 and DHT in the concurrent paradigm may be related to the solvents for these two compounds [32]. CI–628 was administered as an aqueous solution, while DHT was in an oil vehicle. Certainly solvents can differentially effect the availability and behavioral effectiveness of steroids [13] and the oil vehicle may have significantly retarded access of DHT to the relevant neural sites.

In summary, the inhibitory effects of progesterone on estrogen-induced sexual receptivity in the hamster appear to be mediated in a different fashion from the inhibitory effects of DHT. In addition, the temporal effectiveness of CI–628 raises the interesting possibility that this synthetic antiestrogen may have two separate modes of action—one similar to that of DHT and the other perhaps similar to that of progesterone.

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