Alteration of Maternal Behavior in Mice following Administration of Cyproterone Acetate

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Abstract □ Administration of a long-acting progestational, antiandrogenic compound, cyproterone acetate, to mice at randomly selected stages of gestation altered the maternal behavior at the time of parturition. This reversal of behavior resulted in cannibalization of all offspring of treated mothers immediately or shortly after birth. Gross examination of the newborn pups revealed no anatomical malformations, thus eliminating this factor in the mutilation of the offspring by the mothers. Caesarian section of other groups of treated mothers confirmed that the fetuses were normal in size, weight, and appearance. The possibility exists that cyproterone acetate, by altering the hormonal balance of the mother, may cause atypical maternal behavior.

Keyphrases □ Cyproterone acetate—effects on maternal behavior in mice, cannibalism □ Antiandrogenic agents, cyproterone acetate—effect on maternal behavior in mice, cannibalism □ Behavior, maternal—effects of cyproterone acetate in mice □ Cannibalism, drug induced—following administration of cyproterone acetate to pregnant mice

Administration of a long-acting progestational, antiandrogenic compound such as cyproterone acetate to pregnant mice revealed that the male offspring of these treated mothers follow a female pattern of development (1). A number of experiments involving cyproterone acetate treatment of pregnant rabbits demonstrated dose-dependent destruction of the Wolffian ducts and inhibition of the prostate glands and external genitalia in males which were indistinguishable from those in normal females (2).

The mechanism of action of antiandrogenic agents has been explained as a competition for the receptors of androgens at the target organs (3–5). In this manner, the antiandrogen prevents the testicular hormone from exerting its normal effects on the organism without interfering with the secretion of the hormone.

All experiments and documented observations were restricted to the developmental response of the offspring as a result of drug exposure during gestation. The present investigation was undertaken, therefore, to determine the effects of cyproterone acetate on the behavioral response of the mother to her offspring.

EXPERIMENTAL

The test animals were Swiss-Webster mice[1], approximately 65 days of age and weighing between 25 and 30 g. Upon arrival, the female mice were housed individually and the males were housed in groups, allowing them to adjust to their surroundings.

All animals were handled in a similar manner in terms of environmental control, housing, feeding[2], cleaning, and other necessary manipulations. At the end of 1 week, the females were randomly assigned to one of the following groups:

Group 1—Control (50 female mice, no treatment).

Group 2—Placebo (50 female mice divided into five subgroups according to day of treatment).

Group 3—Experimental (50 female mice divided into five subgroups according to day of treatment).

At 75 days of age, the animals were mated by introducing the males into the cages of the females in a 1:2 ratio. Copulation was determined by observing the animals for mating behavior and was confirmed by the presence of a vaginal plug or spermatozoa in the vaginal washings. This time was designated Day 1 of pregnancy.

The days randomly chosen for injections were Days 7, 10, 12, 15, and 17 of gestation. All injections were administered subcutaneously into the right hindleg; each animal within a subgroup received only one injection, and it received that on the day assigned to its group.

Female mice in the experimental subgroups were treated on the designated day with a dose of 0.5 mg cyproterone acetate[3] suspended in 0.25 ml benzyl benzoate[4] plus 50% peanut oil[5]. Female mice in the placebo subgroups were treated on the designated day with 0.25 ml of the vehicle.

Following treatment, the course of pregnancy was permitted to continue undisturbed until the animals came to term. This precaution was necessary since handling of pregnant mice has been shown to affect the behavior of the offspring (6, 7). The mothers delivered their offspring unassisted. As soon as delivery was complete, the offspring were examined for manifestations of gross anatomical malformations and the mother was observed for characteristic signs of maternal behavior (cleaning the pups, carrying them to the nesting area, hovering over them, and nursing them).

RESULTS

The results obtained in two separate experiments using cyproterone acetate are shown in Table I. The second experiment was a replication of the first in terms of methodology and was run to confirm the findings of the initial experiment.

In Experiment 1, all mothers in each of the five treatment groups mutilated and killed their offspring immediately or within 24 hr following delivery. When the mothers were observed during delivery, they appeared to be experiencing no unusual difficulty. However, in all instances when cannibalism did not occur immediately, the mother would push the newborn pup to a corner of the cage and ignore it, making no attempt to clean it. Neither did any of the treated mothers carry the surviving offspring to a nesting corner nor attempt to nurse them. Within 24 hr, all surviving offspring in the first experiment and most offspring in the second experiment were cannibalized by the mothers.

In those cases where the animals were not immediately cannibalized, they were able to be examined for gross anatomical malformations. None was observed in any offspring, although they were subsequently destroyed by the mothers.

The results obtained in the experimental animals were in contrast to those obtained in both the placebo and control groups where the percentage of cannibalism was less than 10.

By using smaller groups of pregnant mice and injecting them randomly with a single dose of cyproterone acetate (Days 7, 10, 12, 15, and 17 of gestation), an attempt was made to confirm that the fetuses, just prior to delivery, were alive and fully developed. Caesarian section was performed on Day 19 of gestation. The results are summarized in Table II.

[1] Camm Research Institute, Wayne, N.J.
[2] Standard laboratory animal diet, Rockland Mouse/Rat Diet (Complete), Tekland, Inc., Monmouth, Ill.
[3] Berlin Laboratories, Division of Schering, Bloomfield, N.J.
[4] Eastman Organic Chemicals, Rochester, N.Y.
[5] Magnus, Mabee and Reynard, Inc., New York, N.Y.

Table I—Effect of a Single Dose of Cyproterone Acetate on Maternal Behavior

Group	Litter Size, Mean ± *SD*	Percent Offspring Killed at Birth, Mean ± *SD*	Length of Gestation, days
Control, 50 mothers	8.2 ± 1.5	8.0 ± 1.4	20–21
Placebo (Days 7, 10, 12, 15, and 17), 50 mothers	8.3 ± 1.8	6.4 ± 1.5	20–21
Cyproterone acetate, 0.5 mg/animal			
Experiment 1 (Days 7, 10, 12, 15, and 17), 50 mothers	7.7 ± 2.1	100.0 ± 0	21–22
Experiment 2 (treatment as in Experiment 1), 50 mothers	8.1 ± 1.8	94.4 ± 1.2	21–22

Table II—Comparison of Fetal Viability, Fetal Mortality, and Litter Size in Treated *versus* Untreated Mice[a]

Group	Number of Pregnant Mice	Percent Fetal Mortality, Mean ± *SD*	Litter Size, Mean ± *SD*
Control	15	3.2 ± 1.1	12.2 ± 3.2
Placebo (Days 7, 10, 12, 15, and 17), total	15	2.4 ± 1.0	12.5 ± 2.1
Cyproterone acetate (Days 7, 10, 12, 15, and 17), total	15	2.9 ± 1.8	12.3 ± 3.6

[a] Caesarian section performed on Day 19 of gestation.

No gross malformations were noted in any of the fetuses, whether alive or dead, except that in most cases the dead fetus was smaller in size. In each major group, there was also at least one incompletely formed fetus, possibly due to death during the earlier stages of development. In all instances, the findings were consistent and not unusual.

DISCUSSION

The fact that cyproterone acetate reversed the maternal behavior of female mice to such an extent that all offspring were destroyed by the mothers at birth is indeed significant. Cyproterone acetate is a progestational, antiandrogenic compound which has been investigated in rats at a much higher dosage than that employed in this study. The action of cyproterone acetate is one of competitive inhibition with testosterone in peripheral tissues, and it has little effect on testosterone uptake by neural tissues (8).

If one were to postulate that increased amounts of testosterone are secreted during pregnancy, then cyproterone acetate could raise the blood titer of testosterone by inhibiting its uptake in peripheral tissues. Since cyproterone acetate has a prolonged duration of action and since neural uptake of testosterone is not inhibited, the possibility presents itself that increased amounts of testosterone entering the brain tissue might account for the alteration in maternal behavior.

Estrogen and prolactin interaction have also been implicated in the maternal behavior of mice toward their newborn pups (9). Administration of progesterone several days before delivery was believed to be responsible for altering the balance of these hormones, thereby resulting in destruction of 50% of the litters by the mothers. Since cyproterone acetate is a progestational compound, it is conceivable that the cannibalistic behavior observed in the mothers following treatment with cyproterone acetate was a result of some drug-induced hormonal imbalance.

There are, of course, other possible hypotheses to account for this type of behavior; however, further investigations are necessary to clarify the underlying mechanism of this particular aspect of abnormal behavior.

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