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Postnatal ACTH and Corticosterone: Effects on Reproduction in Mice

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POLITCH, J. A. AND L. R. HERRENKOHL. *Postnatal ACTH and corticosterone: Effects on reproduction in mice.* PHYSIOL BEHAV 32(3) 447–452, 1984.—At birth, male and female mice were selected at random and injected subcutaneously with either 1 IU ACTH/0.05 ml saline, 0.5 IU ACTH/0.05 ml saline, 300 μg corticosterone acetate/0.05 steroid suspending vehicle or 0.05 ml saline vehicle alone on Postpartum Days 1 through 3. ACTH (0.5 IU) significantly lengthened the estrus cycle of female progeny and reduced the weights of litters born to them. Corticosterone significantly reduced the proportion of females inseminated as well as the proportion giving birth. Corticosterone also reduced one parameter of sexual receptivity. Both ACTH (1 IU) and corticosterone significantly increased some masculine copulatory behaviors in male offspring in adulthood. Thus neonatal administration of glucocorticoids and ACTH may disrupt normal development of reproductive functioning in male and female mice.

Postnatal ACTH Postnatal corticosterone Reproduction Mice

IT is generally recognized that the expression of adult patterns of gonadotrophin secretion and sexual behavior depend upon the presence of gonadal hormones during critical stages of sexual differentiation [11]. Chemical or surgical castration of genetic males during perinatal life feminizes and demasculinizes reproductive function [9, 12, 16, 21, 32]. Conversely, exposure of genetic females to androgen during a critical developmental stage masculinizes and defeminizes reproductive physiology, morphology and behavior [2, 4, 8, 15, 25, 31]. Severity of the masculinizing and defeminizing action of perinatal androgen depends upon the amount of hormone administered and timing of hormone exposure within the perinatal stage [10, 11, 13, 14].

Effects that are analogous to androgen on brain-pituitary-gonadal interaction have been reported on endocrine and behavioral characteristics for glucocorticoids and ACTH. Corticosterone, the primary glucocorticoid in the rat, differentially alters pituitary-adrenal functions depending upon the perinatal stage. When corticosterone is implanted into neonatal rats at 3, 6, 12 or 18 days of age, sexual receptivity uniformally is impaired [30]. All neonatally-treated females have lordosis quotients in adulthood that are lower than those in untreated controls [30]. However vaginal cyclicity is affected differentially. The most frequent impairment in adulthood in those females treated with corticosterone implants on Days 3 or 6 is persistent vaginal estrus whereas prolonged vaginal diestrus is the most frequent impairment in females treated on Days 12 or 18 [30]. Also, it has been demonstrated that reproductive development can be impaired in immature mice by systemic treatment with ACTH [6, 7, 20] and by hypothalamic implants of cortisol in immature rats [28]. Because treatment in those experiments did not commence before 22 days of age, and in more recent investigations until Day 3 [30], it was of interest to determine the effects of earlier hormonal exposure on later reproductive activity. The present experiment was conducted therefore to investigate the effects on gonadal function and sexual receptivity of systemic injections of corticosterone or ACTH administered on Days postpartum 1–3, a period corresponding to the peak of the critical period for androgen [11]. In addition, the effects of postnatal glucocorticoids and ACTH were examined in littermates of both sexes instead of in members of only one sex, as has been reported in a number of previous experiments [6, 7, 29, 30].

METHOD

Twenty-seven female albino CD-1 mice (Charles River Laboratories, Wilmington, MA) were time mated at 75 days of age. Following insemination, animals were housed individually in 32×29×14.5 cm fiberglass maternity cages with the room temperature kept at 24°C, food and water provided ad lib, and 12:12 hour light/dark cycle (lights were on from 0800 to 2000 hours). At birth, offspring of both sexes were selected at random and injected subcutaneously with either 1 IU ACTH/0.05 ml saline, 0.5 IU ACTH/0.05 ml saline, 300 μg corticosterone acetate/0.05 steroid suspending vehicle or 0.05 ml saline vehicle alone on Postpartum Days 1 through 3 (Day 0=birth). Leakage of hormone was prevented by sealing the site of injection with petroleum jelly.

Reproduction in Female Mice

Fertility indices in the experiments included information on vaginal opening, length of estrus cycle, proportion of females becoming pregnant and giving birth, and survival of progeny. To determine whether insemination difficulties

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TABLE 1

EFFECTS OF POSTNATAL ACTH AND CORTICOSTERONE ON REPRODUCTION IN FEMALE MICE

Treatments	Vaginal Opening		Estrus Cycle		Sexual Receptivity			
	N	Age in Days[1]	N	Median Length in Days[1]	N	Median Quality[1,2]	Maximum Response[1,2]	Median Quotient[1,2]
1 IU ACTH[4]	15	32.33±0.36	15	6.63±0.60	14	1.25±0.15	2.43±0.20	23.92± 6.55
0.5 IU ACTH[4]	11	33.64±0.62	10	8.75±1.48*	11	1.45±0.20	2.73±0.20	35.20±10.63
300 μg Corticosterone[5]	12	32.50±0.42	12	6.21±0.45	12	1.21±0.10	2.17±0.24*	17.06± 7.15
0.05 ml Saline	22	33.91±0.67	22	5.91±0.30	22	1.45±0.11	2.82±0.08	38.12± 6.50

[1]Means ± standard errors.
[2]Based on up to 5 tests or until inseminated, whichever came first.
[3]Number of litters.
[4]Vehicle was 0.05 ml saline.
[5]Vehicle was 0.05 steroid suspending vehicle.
*Compared with saline controls, $p<0.05$, Duncan's Multiple Range Test.
*[1]Compared with saline controls, $p<0.01$, χ^2-test.
*[2]Compared with saline controls, $p<0.005$, χ^2-test.

with experimental females could be attributed to behavioral insufficiencies, sexual receptivity scores were collected at the time of exposure to stud males.

All litters were weaned on Day 21. Female offspring were housed in unisexual pairs in fiberglass cages on Day 28. Beginning on Day 30, all females were examined daily for vaginal opening. Commencing on Day 60, females were checked for stage of the estrus cycle by vaginal lavage for 20 consecutive days. On Day 80, subjects were placed under reversed lighting conditions so that light onset occurred at 0800. On Day 120, the taking of daily estrus smears was resumed, 2 hr after the onset of the dark phase of the light/dark cycle. If females were found to be in estrus (indicated by smear consisting primarily of cornified cells), they were tested for feminine copulatory behavior. Tests for female behavior were conducted in a 30×13.5×30 cm plywood box with a Plexiglas front panel. The interior of the chamber was coated with polyurethane to minimize the absorption of urine and feces. Testing commenced approximately 2 hr after vaginal lavage by placing a proven stud male CD-1 conspecific in a clean test chamber for a minimum of 15 min for acclimation. An experimental female was then placed in the chamber and tests lasted until the subject had received 25 mounts or until the male ejaculated. Receptivity of the female to each mount was rated on a 3-point scale adapted from McGill [22]. A score of "1" represented a complete lack of receptivity (active avoidance of the stud male); "2" indicated average receptivity with some squeaking and movement during the mount, and the mount being terminated by the experimental animal; "3" represented good to high receptivity (a minimum of squeaking and movement by the experimental female, and the mount was terminated by the male). Three measures of feminine copulatory behavior were derived as described previously by Allen and Haggett [1]: the median score, the maximum score and the receptivity quotient [RQ=number of receptive responses (scores of 2 or 3)/number of mounts × 100]. Females were tested until they were inseminated or until they had received 5 behavioral tests (one test was administered on each day the female was in estrus), whichever came first. Insemination was confirmed by the presence of copulatory plugs. If females were not inseminated after receiving five tests, they were placed for approximately 15 hr with a stud male. Animals were weighed periodically throughout the course of the study. These methods were modified from those reported by Turner and Taylor [30] in female rats.

After the criterion described above was met, animals were housed singly in fiberglass cages, vaginal lavage was stopped, and females were given strips of paper for nest building. Immediately following birth, litters were culled to six pups and dams and litters were weighed daily until postpartum Day 21. If females were not parturient, they were sacrificed and examined for uterine implantation sites and gross abnormalities of the reproductive organs.

Continuous data were analyzed by one-way Analyses of Variance. Significant differences between means were assessed by Duncan's Multiple Range Test at the 0.05 level. Frequency data were analyzed by Chi-Square Tests.

Reproduction in Male Mice

All litters were weaned in fiberglass cages on Day 21 and male offspring were housed in unisexual pairs in 24.5×18×18 cm metal hanging cages (Hardco Scientific) on Day 28. Subjects were placed under reversed lighting conditions on Day 60 so that light onset occurred at 0800. On Day 80, all males were bilaterally castrated under sodium pentobarbital anesthesia (Nembutal Sodium) and testes were weighed. Following surgery, subjects were placed in single housing in hanging cages and were administered daily subcutaneous injections of testosterone propionate (150 μg/0.05 ml peanut oil). On Day 95, tests for masculine copulatory behavior

TABLE 1
(Continued)

Pregnancy		Postpartum			
Proportion of Females Inseminated	Proportion of Females Giving Birth	N[3]	Weight per Litter[1] (in g) Day 5*	Day 10*	Day 15*
12/14	10/14	10	4.56±0.12*	7.43±0.25*	14.51±0.56
10/11	10/11	9	4.43±0.11*	7.39±0.15*	13.35±0.31*
7/12*[1]	3/12*[2]	3	4.78±0.05	7.92±0.35	14.72±0.92
21/22	18/22	17	4.83±0.09	8.07±0.15	15.06±0.33

modified from methods described by Allen and Haggett [1] and McGill [22,23] commenced. Tests began approximately 4 hr after the start of the dark phase of the light/dark cycle and 3 hr following TP injection. Females had been ovariectomized previously and administered an intramuscular injection of estradiol benzoate (EB) (80 μg/0.05 ml peanut oil) on 2 successive days. Twenty-four hr after the last EB injection, females were given an IM injection of progesterone (P) (500 μg/0.05 ml peanut oil). Six hr following the P injection, females were screened for sexual receptivity by exposing each lure to a vigorous stud male; only females who received a receptivity score of "2" or higher were used for testing (see *Reproduction in Female Mice*). Tests for male copulatory behavior began immediately after screening by introducing the female into the cage of the male. A sheet of Plexiglas was placed over the top of the cage to facilitate observation. During the behavior test, the following measures of male copulatory behavior were taken (as previously described by McGill [22,23]: Mount latency, Preintromission mount duration, Intromission latency, and Time of intromission. If the experimental male did not intromit within the first 20 min, the test was terminated. If the male did intromit within the first 20 min of the encounter, the test was extended until ejaculation or until 60 min had elapsed. All animals were given three behavior tests at least 1 week apart or were tested to ejaculation, whichever came first.

After the criterion for masculine copulatory behavior was met, daily TP injections were terminated. At least 3 weeks following male behavior testing, tests for feminine copulatory behavior were begun. Tests for female behavior were conducted in a 30×13.5×30 cm plywood box with a Plexiglas front panel. The interior of the chamber was coated with polyurethane to minimize the absorption of urine and feces. On Day 140 of life, males were given the same hormone regimen previously described for female lures. Approximately 6 hr following the P injection, experimental males were placed into the test arena which contained a previously screened vigorous stud male who had been given a 15-min acclimation period in the test chamber. Subjects were tested for feminine copulatory behavior for 90 min or until they had received 15 mounts, whichever came first. Receptivity to each mount was rated on a 3-point scale adapted from McGill [22] as previously described (see *Reproduction in Female Mice*). Three measures of feminine copulatory behavior were derived from each subject's scores in two tests as described previously by Allen and Haggett [1]: the median score, the maximum score, and the receptivity quotient [RQ=number of receptive responses (scores of 2 or 3/number of mounts × 100]. Subjects were given the two tests of feminine copulatory behavior 7 days apart.

Continuous data were analyzed by one-way Analyses of Variance. Significant differences between means were assessed by Duncan's Multiple Range Test at the 0.05 level.

RESULTS

Table 1 summarizes the effects of postnatal ACTH and corticosterone on fertility and fecundity in female mice. There were no significant differences among the groups in day of vaginal opening, $F(3,56)=1.88$, $p>0.05$. One-way analysis of variance revealed a main effect for hormone treatment for the variable of median estrus cycle length, $F(3,55)=3.14$, $p<0.05$. Post hoc tests indicated that females injected postnatally with low dose ACTH had longer estrus cycles than postnatal saline-injected animals, whereas the subjects in the other experimental groups did not differ from controls. There were no significant differences in the median quality of sexual receptivity and the median receptivity quotient, F's(3,55)=0.92, 1.69 respectively, p's>0.05. There was a significant difference in the maximum sexual receptivity score however, $F(3,55)=3.14$, $p<0.05$. Compared to the saline control group, the corticosterone animals had signifi-

TABLE 2

EFFECTS OF POSTNATAL ACTH AND CORTICOSTERONE ON REPRODUCTION IN MALE MICE[1]

Treatments	N	Testis Weights (g)	Masculine Copulatory Behaviors[2] N	Mount Latency (Mdn)	N	Preintromission Mount Duration (Mdn)	N	Intromission Latency (Mdn)	N	Time of Intromission (Mdn)
1 IU ACTH[3]	19	0.29±0.01	18	758.17±84.21	10	1.25±0.67	18	1074.17±60.44*	10	18.8 ±1.97
0.5 IU ACTH[3]	10	0.31±0.01	10	875.20±99.67	6	1.25±0.85	10	1024.30±93.4	6	17.67±2.64
300 μg Corticosterone[4]	15	0.29±0.01	14	1072.14±75.86*	4	5.00±2.04*	14	1183.79±24.61*	4	23.75±5.15*
0.05 ml Saline	20	0.31±0.01	19	635.26±88.30	14	1.25±0.57	19	861.21±80.21	14	13.50±1.45

[1]Means±standard errors.
[2]Latency is reported in seconds.
[3]Vehicle was 0.05 ml saline.
[4]Vehicle was 0.05 steroid suspending vehicle.
*Compared with saline controls, $p<0.05$, Duncan's Multiple Range Test.

cantly lower maximum response scores (Ducan's t-test, $p<0.05$). An overall Chi² test showed a significant difference in the proportion of animals inseminated, $\chi^2(3)=8.78$, $p<0.05$. Individual χ^2 comparisons demonstrated that the postnatal corticoid group had a significantly smaller proportion of inseminated females in comparison to the saline group, $\chi^2(1)=7.35$, $p<0.01$. Comparisons between the remaining experimental groups and the saline group revealed no significant differences on this measure, $\chi^2(1)$'s=1.05, p's>0.01. An overall Chi² test indicated that there was a significant difference in the proportion of females who gave birth following insemination or being housed with a male, $\chi^2(3)=15.19$, $p<0.005$. Individual comparisons of the experimental groups with the saline group demonstrated that females treated postnatally with corticosteroids had a significantly smaller proportion of parturient animals in comparison to the control group, $\chi^2(1)=10.6$, $p<0.005$. Comparisons between the remaining experimental groups and saline group revealed no significant differences on this measure, $\chi^2(1)$'s=0.53, p's>0.1. In females who did not give birth, autopsies revealed no sign of implantation sites or fetal resorption. On Days 5, 10, and 21 of life, significant main effects for hormone treatment were found for the measure of offspring body weight, F(3,35)'s=3.43, 3.44 and 2.99, p's<0.05. Post hoc Duncan's Multiple Range tests indicated that offspring of both ACTH groups weighed significantly less than offspring of saline-treated females on Days 5 and 10, whereas offspring from females treated postnatally with corticosteroids did not differ from controls on this measure. On Day 21, only offspring from females treated postnatally with low dose ACTH differed significantly from controls.

Table 2 summarizes the effects of postnatal ACTH and corticosterone on reproduction in male mice. There were no significant differences among groups in testes weights in adulthood. Significant main effects for hormone treatments were found for the measures of mount latency, F(3,57)=4.78, $p<0.005$; preintromission mount duration, F(3,30)=2.89, $p<0.05$; intromission latency, F(3,57)=4.37, $p<0.01$; and time of intromission, F(3,30)=3.09, $p<0.05$. On all of these measures, according to the Ducan's test, the corticoid treatment differed significantly from the control. With respect to intromission latency, the high ACTH treatment also differed significantly from the control. Of all the measures taken on feminine copulatory behavior, only 1 difference was significant (Maximum Receptivity Response, Test 1, F(3,52=3.1, $p<0.05$): the corticoid treatment differed significantly from the control with respect to maximum receptivity response in Test 1 (Duncan's Multiple Range Test, $p<0.05$).

DISCUSSION

Postnatal ACTH and corticosterone administered in the present dosages over the first 3 days of life produced some retardation of reproductive processes in female offspring (Table 1). Compared with saline, low doses of ACTH significantly lengthened the estrus cycle and both high and low dosages of ACTH significantly reduced subsequent litter weights on most of the days the progeny born to experimentally-treated females were examined. Because postpartum behavior in these females was not observed, it is not possible to determine at the present time whether the reduction in litter weights was due to a deficiency in maternal behavior or to lactation [17,19]. Some evidence for a physiological deficit in reproduction is provided by the finding that postnatal corticosterone in the dose used significantly reduced the proportion of females inseminated, and even more so, the proportion of females giving birth. That sexual behavioral deficits also occurred is evidenced by the finding that the corticoid treated females had lower maximum sexual receptivity scores compared to the saline controls.

Overall the effects of postnatal ACTH and corticosterone reported in the present experiment in mice were not as robust as those reported for corticosterone in rats [28,30] or for ACTH in mice [6, 7, 20]. Nor were they as robust as the

TABLE 2
(Continued)

	Feminine Copulatory Behaviors					
	Median Response		Maximum Response		Receptivity Quotient	
N	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2
16	0.19±0.14	0.82±0.25	0.25±0.19	1.06±0.31	4.58± 4.58	27.08±9.82
9	0.22±0.22	0.44±0.23	0.22±0.22	0.67±0.33	11.11±11.11	12.59±7.22
14	0.14±0.14	1.04±0.28	0.14±0.14*	1.50±0.37	7.14± 7.14	31.07±9.33
17	0.71±0.21	0.88±0.19	1.00±0.31	1.24±0.29	19.22± 8.24	21.05±9.00

effects of prenatal or postnatal environmental stress cited in some reports [1,24]. Whereas Allen and Haggett [1] for example found that prenatal crowding reduced sexual receptivity in female mice, we found no effects on most parameters of sexual behavior with postnatal ACTH and corticosterone in the dosages used.

Paris and Ramaley [24] have reported widespread changes in reproductive processes in mice exposed to heat stress during late prenatal or early postnatal life, including delays in the onset of estrus cycling and irregularities in the estrus cycle. They exposed pregnant mice to heat at different weeks during gestation and found that fewer mothers exposed during the third week of gestation survived to parturition, and that litters born to these mothers showed a lower survival rate. Newborn mice were also exposed to heat stress during the first, second or third postnatal week. On the basis of vaginal opening and percentage of subsequent conceptions produced, the most significant depression in fertility outcome occurred in mice that were exposed to heat stress during the first week of life. Paris and Ramaley [24] concluded that the effects of heat exposure are ". . . reminiscent of the pattern of sexual differentiation of the hypothalamus reported in both mice and rats. It may be that the stress of heat exposure elicits adrenal secretions which result in a partial masculinization of the hypothalamus similar to that obtained with low doses of androgen, thus accounting for the irregular persistent estrous vaginal histology and the infertility after puberty (p. 544)." Such a mechanism of adrenal-induced partial masculinization of the hypothalamus might explain some of the retardation in reproduction in female offspring in the present report. It might account also for the widespread disruptions in fertility and fecundity (estrus cycle irregularities, spontaneous abortions, vaginal hemorrhaging, low birthweight young, neonatal mortality) reported in one laboratory by prenatal heat-restraint stress applied to rats [5, 17, 18].

Postnatal ACTH and corticosterone produced some significant changes in masculine copulatory behavior in male offspring but left feminine copulatory behavior virtually intact (Table 2). Compared to saline, corticosterone significantly increased mount latency, preintromission mount duration, intromission latency and time of intromission. High dosages of ACTH significantly increased time of intromission. Thus postnatal glucocorticoids and ACTH partially demasculinized sexual behavior but had virtually no feminizing effects. Prenatal injections of ACTH or corticosterone (Days 14–21) produced similar effects: compared with saline, both hormones significantly increased intromission latency in male offspring but had no significant effects on any measure of feminine copulatory behavior [26]. In contrast, Rhees and Fleming [27] report that either malnutrition, heat-restraint stress, or ACTH injections during pregnancy feminized and desmasculinized sexual behavior of male rats. Male copulatory behavior was severely impaired by all three treatments whereas all three treatments produced greater lordosis than did the control treatment.

Judging from the observation that testes weights were not reduced, a central rather than a peripheral action of postnatal ACTH or corticosterone may be invoked. More than one hormone system may be involved in the effects of perinatal hormones on sexual behavior in adulthood. The lateral septum for example is an area that concentrates dihydrotestosterone and corticosterone [29] and has been shown to be sensitive to androgen. Androgen implants into the lateral septum facilitate masculine copulatory behavior in male rats [3]. Thus it is possible that postnatal exposure to ACTH or corticoids may modify the development of brain areas involved in the androgen-activation of masculine copulatory behavior.

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