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Variation in Infanticide and Parental Behavior in Male Mice Due to Prior Intrauterine Proximity to Female Fetuses: Elimination by Prenatal Stress

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VOM SAAL, F. S. *Variation in infanticide and parental behavior in male mice due to prior intrauterine proximity to female fetuses: Elimination by prenatal stress.* PHYSIOL BEHAV **30**(5) 675–681, 1983.—When sexually-naive male mice are placed together with newborn young, some males will commit infanticide (kill the young) while others will behave parentally (retrieve the young to a nest and keep them warm). The intrauterine position of male mouse fetuses, which is recorded at Cesarean delivery, has previously been found to influence the titers of estradiol that male fetuses are exposed to in utero. In adulthood, most male mice that developed in utero between male fetuses (2 M males) behaved parentally toward young, while most males that developed in utero between female fetuses (0 M males) committed infanticide. When 0 M and 2 M males were castrated at birth and tested with young in adulthood, few males committed infanticide. But, when these same males were tested with young after 25 days of treatment with testosterone, more 0 M than 2 M males committed infanticide and more 2 M than 0 M males behaved parentally. In contrast to the above findings, more 2 M than 0 M males that were castrated when 28 days old behaved parentally without treatment with testosterone; few of the non-parental males committed infanticide, but, instead, ignored the young. Finally, stressing pregnant mice by placing them under bright lights during the last third of pregnancy eliminated the effect of developing next to female fetuses in the male offspring, and all prenatally-stressed males resembled 2 M males in their behavior toward young: most prenatally-stressed males were parental rather than infanticidal when tested with young. The significance of these findings to models of hormonal effects on sexual differentiation is discussed.

Sexual differentiation Fetal development Infanticide Pup killing Parental behavior Estrogen Testosterone Prenatal stress Maternal stress

WHEN male house mice (*Mus musculus*) encounter young, they either commit infanticide (kill the young), behave parentally, or ignore the young. The significance of the finding that some male mice spontaneously commit infanticide when they encounter young (about 45 percent of CF-1 males typically commit infanticide) has been the subject of some controversy. On the one hand, infanticide has been viewed as a pathological behavior that is observed during times of social stress in rodents [6,9]. In contrast, it has been proposed that in some situations, infanticide can be an adaptive trait [13, 20, 24, 29]. This hypothesis does not imply that in some situations infanticide might be maladaptive; for example, in high density mouse populations the incidence of both infanticide and aggression between adults increase dramatically, and this appears to be a response to a general breakdown in social structure [7,15].

During prenatal life in all mammals, the testes of males differentiate and begin secreting high concentrations of testosterone, which results in the induction of the male phenotype (masculinization) and the suppression of female traits (defeminization; [2]). Infanticide is just one of a host of sexually-dimorphic behaviors that are influenced by testosterone during perinatal (prenatal and neonatal) life in mice, and which also require the presence of testosterone to be exhibited in adult animals [25].

A naturally occurring phenomenon, that I have termed the intrauterine-position phenomenon, has provided a unique method of investigating the relationship between variation in prenatal hormone titers and adult behavior in mice. The intrauterine-position phenomenon refers to the fact that during prenatal life in house mice, a polytocous (multiple-birth) species, fetuses can develop randomly next to, and thus potentially be influenced by the hormonal secretions of, fetuses of the same or opposite sex. This phenomenon also occurs in rats [8,23].

Previous research has revealed that male mouse fetuses

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secrete higher titers of testosterone than do female fetuses, and female fetuses secrete higher titers of estradiol than do male fetuses [27,28]. Male mice that develop between two other male fetuses in utero (2 M males) do not differ from males that develop between two female fetuses (0 M males) in their blood or amniotic fluid titers of testosterone during fetal life. But, 0 M male mouse fetuses have significantly higher titers of estradiol in their amniotic fluid than do 2 M male fetuses [28].

The titers of gonadal hormones that mice are exposed to during perinatal life influence the tendency to commit infanticide in adulthood [11,17]. Since intrauterine position influences the titers of sex steroids that male mouse fetuses are exposed to, the influence of prior intrauterine position on the behavior of male mice toward young was examined.

METHOD

Procedures utilized in all of the experiments will be described in this section, and methodological details for the specific experiments will be presented with the results. To obtain offspring from known intrauterine positions, adult nulliparous female Crl:CF1BR (CF-1) albino mice, maintained as an outbred strain in a closed colony, were timemated. The animals were maintained on a 14L:10D cycle with lights on at 0600 hr. Food and water were available ad lib. The offspring were delivered by Cesarean section shortly before normal parturition as described previously [23]. There are three potential intrauterine positions that males can occupy: 2 M males=between two male fetuses, 1 M males=between a male and a female fetus, and 0 M males=not next to a male fetus (between 2 female fetuses). The classification scheme utilizes contiguous males as the reference, but is not intended to imply that proximity to male rather than female fetuses mediates differences in phenotype due to intrauterine position in male mice.

The intrauterine position of each animal (0 M, 1 M or 2 M) was recorded at Cesarean delivery, and the young were raised by foster mothers. Foster litters consisted of 10 males, five 2 M males and five 1 M males, or five 0 M and five 1 M males. Some of the males were gonadectomized either within 1 hr of Cesarean delivery or when 28 days old (about one week prior to puberty). Surgery was conducted with ether anesthesia. All animals were weaned when 23 days old and housed individually when 35 days old, just prior to the age at which the males would enter puberty and begin to fight.

Behavior testing consisted of placing two 1-day-old young into a corner of the cage of a 75-day-old male and examining the young 30-min later. Three beahviors were recorded at the end of the 30-min test session: (1) infanticide—one or both young were dead; (2) parental behavior—one or both of the young had been retrieved into a nest that resembled the nest of a postpartum female mouse, the male was crouched over the young, and the young were warm (newborn mice cannot thermoregulate); (3) ignore—neither of the young were harmed or in a nest, and both young were cold. Previous studies have demonstrated that: (1) neither the sex nor the age (1–10 days old) of the young or (2) the length of the test (15 min–4 hr) influence the behavior of male mice toward young [18, 24, 29].

RESULTS

The Behavior of Gonadally-Intact, 75-Day-Old Males Toward Young

To determine whether intrauterine position influenced the behavior of males toward young, two 1-day-old mice were placed into the cage of individually housed, 75-day-old 0 M, 1 M and 2 M male mice (30/Group). The results presented in Table 1 reveal that the behavior of gonadally-intact male mice toward young varies as a function of prior intrauterine position, with most 0 M males committing infanticide and most 2 M males exhibiting parental behavior. The 1 M males were equally likely to commit infanticide or behave parentally.

TABLE 1

THE NUMBER (AND PERCENT) OF GONADALLY-INTACT, 75-DAY-OLD 0 M, 1 M, AND 2 M MALE MICE THAT COMMITTED INFANTICIDE, WERE PARENTAL TOWARD, OR IGNORED TWO NEWBORN MOUSE PUPS THAT WERE PLACED INTO A MALE'S CAGE FOR 30 MINUTES

	Intrauterine Position of Male			
	2 M	1 M	0 M	Total
Infanticide	7 (23)	12 (40)	19 (63)	38 (42)
Parental	20 (67)	11 (37)	8 (27)	39 (43)
Ignore	3 (10)	7 (23)	3 (10)	13 (15)

$\chi^2(4)=14.2$, $p<0.01$.

This Table previously appeared in an unrefereed review article (see [23]).

The Behavior of Gonadally-Intact, 8-Month-Old Males Toward Young

The effect of intrauterine position on the behavior of male mice toward young was also examined in 8-month-old males to determine whether the previously observed difference in 75-day-old males would still be observed in older 0 M and 2 M males (30/Group). In this study, 1 M males were not examined. The basis for examining the effect of age on the behavior of CF-1 males toward young was the report of Svare and Mann [19] that there is an increase in the frequency of infanticide in DBA/2J male mice between 2 and 4.5 months of age: 20–30 percent of 2-month-old DBA males commited infanticide, but when DBA males that were older than 4.5 months were tested, 60–70 percent committed infanticide.

The proportion of 8-month-old 0 M and 2 M males that committed infanticide was almost exactly the same as had been observed in the 75-day-old animals (see Table 2). Overall, fewer males behaved parentally, although again, more 2 M than 0 M males exhibited parental behavior. It is concluded that the difference between 0 M and 2 M males in the tendency to commit infanticide does not change between 2 and 8 months of age in CF-1 male mice. The finding that the incidence of parental behavior appears to decrease as a function of age will be discussed below with the results of Experiment 5.

The Behavior of Castrated Males Toward Young

The 0 M and 2 M males that had been castrated within 1 hour of Cesarean delivery or when 28-days-old (1 week prior to puberty) were examined for their behavior toward two 1-day-old mice without being treated with testosterone. The males were 75-days-old when tested with young. The results presented in Table 3 reveal that for the males that were castrated at birth, there was no difference in the behavior of the

TABLE 2

THE NUMBER (AND PERCENT) OF GONADALLY-INTACT 8-MONTH-OLD 0 M AND 2 M MALES THAT COMMITTED INFANTICIDE, WERE PARENTAL TOWARD, OR IGNORED 2 NEWBORN MOUSE PUPS THAT WERE PLACED INTO A MALE'S CAGE FOR 30 MIN

	Intrauterine Position of Male	
	2 M	0 M
Infanticide	8 (27)	19 (63)
Parental	9 (30)	4 (13)
Ignore	13 (43)	7 (24)

$\chi^2(2)=8.2$, $p<0.02$.

0 M and 2 M males toward young, and most males behaved parentally. However, for the males that were castrated when 28-days-old, the 0 M and 2 M males differed in their behavior toward young, and significantly more 2 M than 0 M males exhibited parental behavior. The above findings reveal that the difference between 0 M and 2 M males in the tendency to behave parentally is observed whether or not males are gonadally-intact. But, it appears that for a difference in parental behavior to be observed in castrated 0 M and 2 M males, castration must occur after the neonatal period.

The Behavior of Castrated, Testosterone-Treated Males Toward Young

This experiment was designed to test whether 0 M and 2 M males that had been castrated at Cesarean delivery would differ in their behavior toward young after being treated with testosterone. The objective was to determine whether the difference between 0 M and 2 M male mice in terms of the tendency to commit infanticide was due to a differential sensitivity to the activational effects of testosterone. Holding blood testosterone titers in the gonadectomized 0 M and 2 M males equivalent by administering a known amount of testosterone serves to eliminate any difference that might exist between 0 M and 2 M males in the rate of secretion of endogenous testosterone.

Twenty-eight 0 M and 28 2 M males that had been castrated within one hour of Cesarean delivery were tested with two 1-day-old mice when 75-days old and then implanted with a 10-mm long silastic capsule (Dow 602-285) containing 5 mg testosterone in 0.02 cc sesame oil. This dose of testosterone maintains seminal vesicles in castrated male mice [1]. The males were retested with two 1-day-old mice 25 days later. The results presented in Table 4 confirm the previous finding that 0 M and 2 M males that are castrated at birth and not treated with testosterone do not differ in their behavior toward young. After 25 days of testosterone treatment, more 0 M than 2 M males commited infanticide while more 2 M than 0 M males behaved parentally, although the results were not statistically significant. The results of Experiments 3 and 4 thus reveal that for adult male mice to commit infanticide, and for differences in the tendency of male mice to commit infanticide due to intrauterine position to be observed, either the testes must be functional (see Tables 1 and 2) or testosterone must be present in the circulation concomitant with behavior testing.

TABLE 3

THE NUMBER (AND PERCENT) OF ADULT 0 M AND 2 M MALE MICE THAT HAD BEEN CASTRATED AT CESAREAN DELIVERY OR WHEN 28 DAYS OLD THAT COMMITTED INFANTICIDE, WERE PARENTAL TOWARD, OR IGNORED 2 NEWBORN MOUSE PUPS THAT WERE PLACED INTO THE MALE'S CAGE FOR 30 MIN

	A Castrated at Birth		B Castrated When 28 Days Old	
	2 M	0 M	2 M	0 M
Infanticide	3 (15)	2 (10)	0 (0)	2 (14)
Parental	12 (60)	10 (50)	11 (61)	2 (14)
Ignore	5 (35)	8 (40)	7 (39)	10 (72)
	*		†	

*Not significant.

†Parental vs. not-parental: $\chi^2(1)=5.4$, $p<0.05$.

The males were tested without being treated with testosterone when they were 75 days old.

TABLE 4

THE NUMBER (AND PERCENT) OF 75-DAY-OLD 0 M AND 2 M MALE MICE THAT HAD BEEN CASTRATED AT BIRTH THAT COMMITTED INFANTICIDE, WERE PARENTAL TOWARD, OR IGNORED 2 NEWBORN MOUSE PUPS THAT WERE PLACED INTO THE MALE'S HOME CAGE FOR 30 MIN

	A Pre T		B Post T	
	2 M	0 M	2 M	0 M
Infanticide	2 (7)	3 (11)	14 (50)	21 (78)
Parental	20 (72)	22 (82)	11 (39)	4 (15)
Ignore	6 (21)	2 (7)	3 (11)	2 (7)
	*		†	

*Not significant.

†$\chi^2(2)=3.44$, $p=0.18$.

Testing occurred both before and 25 days after the males were implanted subcutaneously with a 10 mm long silastic capsule containing 5 mg testosterone (T) in 0.02 cc oil.

The Behavior of Prenatally-Stressed Males Toward Young

Stressing pregnant female rats has been found to alter the pattern of secretion of testosterone in male fetuses [31]. Prenatally-stressed male rats have also been found to exhibit decreased levels of male copulatory behavior relative to non-stressed males [30]. The effect of prenatal stress on the behavior of 0 M, 1 M and 2 M male mice toward young was examined to determine whether prenatal stress would influence the previously observed difference in the behavior of 0 M, 1 M and 2 M males toward young. The procedure of Ward [30] was used.

Female mice were housed in a room on a reversed 14L:10D cycle with lights on at 1800 hr. One-hundred females were time-mated, and beginning 13 days later, one-half of the females were placed in Plexiglas mouse restraining chambers under 150 W flood lights (350 ft-c). The ambient temperature inside of the restraining chambers during

the stress sessions was 38°C. There were three 30-min stress sessions per day at 0830, 1230 and 1630 hr from day 13 to 18 of pregnancy (18 sessions in all). Control females remained undisturbed throughout pregnancy. Parturition in CF-1 mice occurs reliably 19 days after insemination. The offspring of the stressed and control females were delivered by Cesarean section on Day 19 after mating, and the intrauterine positions of the offspring were recorded. The offspring were raised as described above in like-treatment groups.

There were no significant differences between the stressed and control animals in terms of fetal mortality. But, regardless of intrauterine position, the prenatally-stressed males weighed significantly less at birth (n=123; mean±SEM=1.26±0.01 g) than did the control males, n=124; mean±SEM=1.37±0.01 g; $F(1,245)=54$, $p<0.001$. There were no significant differences based on prenatal treatment or intrauterine position in postnatal survival. On the day after weaning (at 24 days old), there were also no significant differences based on prenatal treatment or intrauterine position in body weight (mean±SEM: control males=12.2±0.19 g; prenatally-stressed males=12.0±0.19 g). Similar findings were obtained for comparisons of the female offspring of stressed and control mothers.

Gonadally-intact, prenatally-stressed and control 0 M, 1 M and 2 M males were tested for their behavior toward two 1-day-old mice when they were 75-days-old. The results presented in Fig. 1 reveal that prenatal stress eliminated the effect of developing next to one or between two female fetuses on the tendency of male mice to commit infanticide (i.e., all prenatally-stressed males resembled 2 M males, which tend to behave parentally toward young). The proportion of control 0 M, 1 M and 2 M males that committed infanticide was almost identical to the results presented in Table 1, again demonstrating the reliability of this finding. In contrast, the big effect on the tendency of males from different intrauterine positions to behave parentally toward young that was observed in Experiment 1 was not observed in the control males, although again, more 2 M than 0 M control males behaved parentally.

In numerous studies that have been conducted concerning the behavior of male mice toward young, in which the prior intrauterine position of the males has not been known, the proportion of males that have been found to commit infanticide has been remarkably consistent (about 45% with group sizes of 30). But, the proportion of males that have behaved parentally has been found to vary from as low as 25% up to 55% [24,29]. Prior to conducting these studies, this variation was hypothesized to be due to differences in the proportions of 0 M, 1 M and 2 M males in the groups of males that were tested, but this apparently is not the case. For example, more 75-day-old males behaved parentally in Experiment 1 (see Table 1) than did the 8-month-old males in Experiment 2 (see Table 2). However, this does not appear to be due to an effect of age on the tendency of males to behave parentally toward young, since fewer 75-day-old control males in Experiment 5 (see Fig. 1) behaved parentally than did the 75-day-old males tested in Experiment 1 (see Table 1). The reason why there is considerable variability among noninfanticidal males in the tendency to either ignore or parent young is not known at this time. Obviously some variable(s), in addition to intrauterine position, that has not as yet been identified, influences the behavior of noninfanticidal males toward young.

The above issue has been raised because of the finding that a higher proportion of the prenatally-stressed males

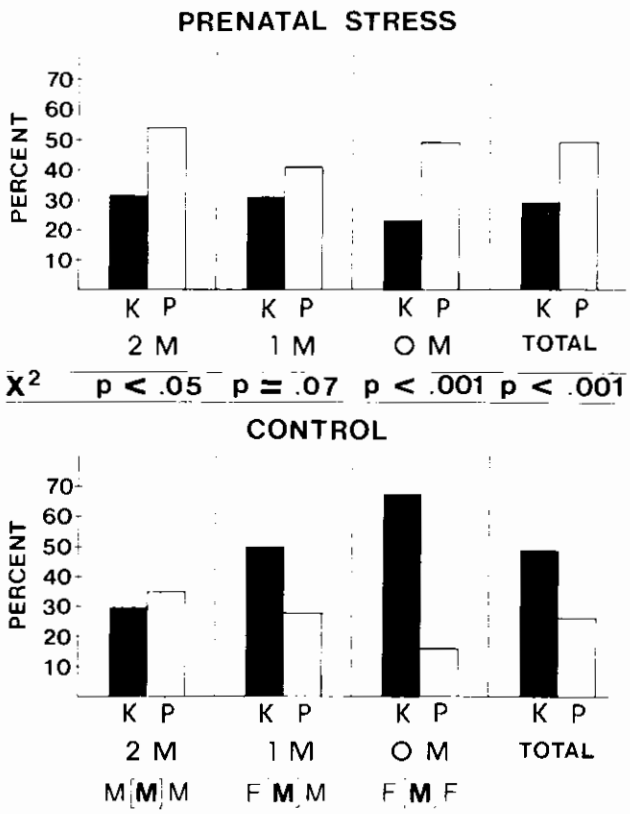

FIG. 1. The percent of adult 0 M, 1 M and 2 M control and prenatally-stressed male mice (45–50/Group) that killed (K) or behaved parentally toward (P) two newborn young that were placed into a male's cage for 30 min. In all groups some males also ignored the young. TOTAL represents the combined mean for all 0 M, 1 M and 2 M males tested. Significance levels are for Chi Square comparisons of prenatally-stressed vs. control males from each intrauterine position.

tended to exhibit parental behavior than did the control males, regardless of prior intrauterine position. It is unclear whether prenatal stress actually results in an increase in the proportion of males from all intrauterine positions that behave parentally toward young, or whether the prenatally-stressed males really just resemble control 2 M males in both the tendency to commit infanticide and behave parentally toward young, which a comparison of the data from the prenatally-stressed males with the data from the control males presented in Table 1 would suggest.

Previously, Ward [30] reported that in rats, male offspring from stressed mothers exhibited lower levels of sexual behavior than males from non-stressed mothers. In both rats and mice, 2 M males (which all prenatally-stressed males appear to resemble in phenotype) have been found to exhibit lower levels of sex behavior (mounts, intromissions and ejaculations) than 0 M males when tested with a sexually-receptive female [28]. These findings, as well as the present results, suggest that the finding of Ward [30] might also be due to the elimination of males with both a 0 M and a 1 M phenotype in litters produced by stressed rats.

DISCUSSION

The influence of perinatal gonadal hormone titers on adult

behavior is an area of intense interest. However, relatively little attention has been paid to the hormonal regulation of infanticide. What is known, and what the present experiments confirm, is that for infanticide to be exhibited by adult male mice, either the testes must be present or testosterone must be administered concomitant with behavioral testing. In the present experiments, infanticide was observed in about 10% of gonadectomized males, regardless of prior intrauterine position or age at gonadectomy. Infanticide is thus similar to many other behaviors, such as intermale aggression, urine marking, and male copulatory behavior, in that activation by testosterone is necessary to observe differences in adult behavior due to differences in gonadal hormone exposure during early life [4,25]. The findings presented in Table 4 suggest that the difference between gonadally-intact 0 M and 2 M males in the tendency to commit infanticide reflects the fact that 0 M males are more sensitive to the activational effects of testosterone on the neural areas mediating infanticide than are 2 M males.

Infanticide is unlike other behaviors that are modulated by testosterone during early life and then activated by testosterone in adulthood: a mouse that is exposed to elevated titers of testosterone around the time of birth is less sensitive to the activational effects of testosterone in adulthood, i.e., is less likely to commit infanticide, than is a mouse that is exposed to low titers of testosterone during early life [11,17]. In contrast, exposure of mice to elevated titers of testosterone during early life results in an increase in sensitivity to the activational effects of testosterone on intermale aggression in adulthood [22]. Thus, during perinatal life testosterone appears to have a desensitizing effect on the neural areas mediating infanticide and a sensitizing effect on the neural areas mediating intermale aggression (with regard to the capacity of these neural areas to respond to testosterone during adult life).

The above findings, together with the results of the present experiments that 0 M male mice are more likely to commit infanticide than are 2 M males, led to the hypothesis that 0 M males might be less aggressive than 2 M males. When 0 M and 2 M males that had been castrated at Cesarean delivery were implanted with a capsule containing testosterone (as described above) and tested for aggression against a male opponent every other day, more 2 M males exhibited aggression and they also had larger seminal vesicles than did the 0 M males [28]. Thus, a correlate of developing between two male fetuses is enhanced aggressiveness toward other males, a decreased tendency to commit infanticide, and an increased tendency to behave parentally.

For the males that had been gonadectomized when 28-days-old, significantly more 2 M than 0 M males behaved parentally toward young without treatment with testosterone. In fact, the difference between 0 M and 2 M males that were gonadally-intact (see Table 1) or gonadectomized when 28-days-old (see Tabe 3-B) in the tendency to behave parentally toward young is remarkably similar. This finding suggests that the difference between 0 M and 2 M males in the tendency to behave parentally does not require the presence of the gonads or gonadal hormones to be exhibited, but only if castration occurs after the neonatal period. One potential explanation for the finding that activation by testosterone in adulthood does not appear to be necessary for differences in parental behavior to be observed in 0 M and 2 M male mice is that the neural areas mediating parental behavior are organized by gonadal hormones during early (prenatal and neonatal) life, similar to the organizational effects of gonadal hormones on play behavior in rhesus monkeys and on the urination pattern in beagels (activation by gonadal hormones is not necessary for the expression of behaviors which are organized by gonadal hormones during early life in monkeys [10,16] and dogs [3]; for reviews see: [4,25]). An alternative explanation is that at birth, all males have the potential to behave parentally, and the tendency to behave parentally is suppressed in gonadally-intact 0 M but not 2 M male mice between birth and 28 days of age. The evidence for this hypothesis is that: (1) no difference in the tendency to behave parentally toward young was observed in the 0 M and 2 M males that were castrated at birth and not treated with testosterone prior to being tested for their behavior toward young (most males behaved parentally; see Tables 3-A and 4-A), and (2) most 2 M males that were castrated when 28 days old (see Table 3-B) or that were gonadally-intact (see Table 1) behaved parentally toward young, but few 0 M males that were castrated when 28 days old (see Table 3-B) or that were gonadally-intact (see Table 1) behaved parentally toward young.

Intrauterine position also influences morphology, physiology and behavior in female mice. Of particular relevance to the present report is the finding that female mice that develop in utero between two male fetuses (2 M females) are more aggressive and less likely to commit infanticide than are females that do not develop next to a male fetus [23,24]. Differences in phenotype due to intrauterine position in the female offspring of the stressed mothers described above were also found to be eliminated: all prenatally stressed female mice resembled 2 M females in their anogenital distance at birth, timing of puberty, and length of adult estrous cycles ([23] unpublished). Prenatal stress thus seems to result in the elimination of the effect of developing in utero next to female fetuses in both male and female mice. This is opposite to what had been predicted would occur (cf, [23]).

The finding that 0 M and 2 M male mouse fetuses differ in the concentrations of estradiol that they are exposed to based on their proximity to female fetuses, but do not differ in their testosterone titers, makes interpreting the relationship between fetal hormone titers and adult behavior quite complicated. The 0 M male mize have been found to have high levels of estradiol during fetal life. In adulthood, 0 M males have smaller seminal vesicles and are less likely to exhibit intermale aggression than 2 M males [28]. The 0 M males thus appear as if they had been exposed to an antiandrogen during fetal life. It has been proposed, therefore, that estrogens serve to inhibit the action of testosterone in the neural areas mediating intermale aggression and in the seminal vesicles [26,28], perhaps by estradiol passing from the circulation into selected brain cells and binding to (and inhibiting) androgen receptors (which are present during fetal life in rats and mice in some neural areas as well as in the seminal vesicles; [21]).

The present results suggest that in the neural areas mediating infanticide, circulating estradiol may also interfere with the action of testosterone, such that 0 M males, with the highest fetal titers of estradiol, appear to have been exposed to the lowest titers of testosterone during fetal life. Again, in contrast to the enhancing effects of testosterone exposure during fetal life on most behaviors (i.e., intermale aggression), testosterone has an inhibiting effect on the development of the neural substrate mediating infanticide. This hypothesis does not imply that in the neural areas mediating male sexual behavior (mounting, intromitting and ejaculating) estradiol has a similar inhibitory effect on testosterone.

In fact, the evidence is that in the neural areas mediating male sexual behavior, testosterone acts intracellularly after being aromatized to estradiol, and circulating estradiol can facilitate the effects of testosterone on the development of male sexual behavior [26,28]. The interaction of circulating estrogens and androgens in different neural areas is thus quite complex and may be determined by the type of steroid receptors present in particular neural areas during sensitive periods in development. These hypotheses are based entirely on correlational studies, and experimental studies to test these ideas are being conducted.

In humans, female fetuses also have higher titers of estrogens than do male fetuses, and this difference is due to sex differences in the secretion of adrenal androgens, which are converted to estrogens in the placenta [5]. The source of estradiol in both the fetal and maternal circulation during pregnancy in mice is unknown, but the available evidence suggests that it is also of fetal/placental origin [12]. This hypothesis is supported by the finding that female mouse fetuses have over twice the circulating concentrations of estradiol as do their mothers two days prior to parturition [27]. The present finding that the effect of developing next to a female fetus is eliminated in the male offspring of pregnant females that are severely stressed suggests that the stress procedure has eliminated the sex difference in estradiol secretion such that female fetuses carried by stressed mothers do not secrete higher titers of estradiol than males, and 0 M male fetuses do not have higher titers of estradiol than do 2 M male fetuses. This hypothesis is currently being examined. This could occur if the fetal adrenal is involved in the sex difference in estradiol titers, since the corticosterone that is secreted by the adrenals of stressed mothers would pass into the circulation of fetuses and suppress adrenocorticotropin (ACTH) secretion by the fetal pituitary (ACTH secreted by the fetal pituitary regulates secretions from the fetal adrenals). Maternal ACTH, on the other hand, cannot cross the placenta [14]. Implicit in this hypothesis is the assumption that circulating estrogens are not completely inhibited from passing into cells by plasma proteins, such as alpha-fetoprotein [26].

In mice, both sex differences in behavior and variation among males and among females due to intrauterine position may thus be due to an interaction of circulating estrogens (possibly derived from adrenal secretions) and androgens. It is suggested, therefore, that in mice, and possibly all mammals, adrenal secretions may interact with gonadal secretions in regulating sexual differentiation (sex differences in adrenal morphology and physiology are known to exist after birth in mice as well as most species that have been studied; [7,14]).

The fact that hormones regulate the ontogeny and expression of a host of behaviors that directly influence reproductive success is quite interesting in terms of the evolution of behavior. It is certainly not unreasonable to propose that behaviors are subjected to selection similar to other aspects of phenotype. For example, morphological characteristics are presumed to exist because they are adaptive and have been selected for from a wide variety of options available within a species during the course of evolution. The finding that during early life, testosterone has opposte effects on infanticide and intermale aggression is thus intriquing, since intuitively, these two behaviors would appear likely to be positively rather than negatively correlated. Presumably, selection has operated to have intermale aggression enhanced and infanticide inhibited as a consequence of exposure to elevated titers of testosterone during perinatal life in mice. The significance of this relationship is unclear, however.

In some ecological situations committing infanticide may increase the reproductive success (fitness) of male mice. The evidence for this hypothesis is the observation that male mice that commit infanticide when they come in contact with a female and her nursing litter produce their own offspring at a faster rate than do male mice that do not commit infanticide. In addition, the act of mating with a female serves to inhibit a male mouse from committing infanticide exactly during the time that its own offspring would be nursing (between 3 and 7 weeks after mating) [24,29]. These findings, together with the observation that the incidence of infanticide varies among different genetic strains of mice [18,19], provide support for the hypothesis that infanticide is an evolved behavior in mice [13, 20, 24].

There is little argument that during fetal life, hormones act to bias the potential to exhibit behaviors rather than "lock in" the animal to a particular behavior pattern. It is not surprising, therefore, that the tendency of male mice to commit infanticide or behave parentally has been found to be markedly influenced by postnatal experiences, such as the duration of time since mating as described above. Dominance status (i.e., experience fighting) also influences the tendency of male mice to commit infanticide: defeat results in an inhibition of infanticide in male mice, while achieving dominance induces males to commit infanticide, unless they have recently mated [24,29].

In summary, a random developmental event, intrauterine positioning next to male or female fetuses, results in the production of male mice that differ in the tendency to commit infanticide or behave parentally toward young. Whether circulating estrogens will be found to mediate differences in phenotype due to intrauterine position in male mice as the present results suggest, and whether such differences will prove to be of significance to the reproductive ecology of wild mice remains to be determined.

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