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# Examination of Some Factors that Control the Effects of Septal Lesions on Lordosis Behavior[1]

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NANCE, D. M., J. E. SHRYNE, J. H. GORDON AND R. A. GORSKI. *Examination of some factors that control the effects of septal lesions on lordosis behavior.* PHARMAC. BIOCHEM. BEHAV. 6(2) 227–234, 1977. – Various experimental parameters related to the effects of septal lesions on the lordosis behavior of rats have been examined. First, the failure of septal lesions to facilitate lordosis behavior in male rats appears to be related to the degree of exposure to androgens neonatally. The normal facilitation in lordosis behavior associated with septal destruction in adult female rats does not occur if these female rats are treated with 1.0 mg of testosterone propionate (TP) on Day 1 of life. Yet female rats given 270 μg of TP on Day 3 of life respond the same as do normal females to septal lesions. Second, these sexually dimorphic effects of septal lesions can be modified in adult rats by chronic treatment with gonadal hormones following septal destruction. Whereas previous studies indicated that chronic estrogen injections permit a facilitation in lordosis behavior to occur in septal lesioned male rats, the present results showed that chronic injections of TP following a septal lesion attenuates the facilitation in lordosis behavior typically observed in adult female rats following a septal lesion. Third, examination of the time course for the facilitation in lordosis behavior following a septal lesion revealed a four to six day delay before the appearance of heightened female sexual behavior. Fourth, in support of the possibility that modifications in lordosis behavior by septal lesions may be mediated by a depletion or imbalance in brain amines, amphetamine was found to reduce the high levels of lordosis behavior of septal lesioned female rats to control levels. Finally, further evidence of a potential role for brain amines in the effects of septal lesions was provided by the observation of significantly lower content and turnover of dopamine in the amygdala of septal lesioned female rats, relative to sham operated controls.

Septal lesions  Sex behavior  Sex steroids  Brain amines  Androgenization  Amphetamine

ALTHOUGH septal lesions markedly increase the effects of estrogen on lordosis behavior of female rats [14,15], lordosis behavior of male rats is not altered by septal destruction [16]. However, chronic exposure to estrogen or hypothyroidism after septal destruction modifies the effects of septal lesions in males, in that these male rats treated after a septal lesion subsequently show a marked and sustained increase in responsiveness to estrogen similar to that of female rats [16,19]. Additional factors which might also modify the effects of septal lesions on lordosis behavior of rats have not been tested.

In the present series of experiments, the sex difference in the effects of septal lesions on lordosis behavior is replicated and evidence is presented that this dimorphism is related to the degree of neonatal androgenization. Furthermore, it is now shown that in the female the effects of septal lesions on lordosis behavior can be modified by exposure to hormones during the post lesion period. Finally, the time course of the onset of the facilitation in lordosis behavior produced by septal lesions has been determined and the possibility that the effects of septal lesions on lordosis behavior are mediated by alterations in brain amines examined.

## GENERAL METHODS AND PROCEDURE

Simonsen Sprague-Dawley rats were used in all experiments. Animals were housed six to eight per cage, given ad lib access to Purina rat chow and tap water and maintained in a reversed light room (lights on from 10:00 p.m. to 11:00 a.m.). Brain surgery was performed under sodium methohexital (Brevital) anesthesia, whereas for castrations, if performed other than at the time of lesioning, ether was used as anesthesia. Bilateral septal lesions (de Groot [5], coordinates: 1.4 mm anterior to bregma, lateral 0.75 mm and 4.0 mm below the dura) were produced by passing anodal current (2 mA/20 sec) through a 00 stainless steel insect pin, insulated except for 0.75 mm at the tip. Sham operations were identical to the lesioning procedure except that no current was passed.

Tests for female sexual behavior were essentially the same in all experiments and started around 1:00 p.m. Test animals were placed in a Plexiglas arena that was illuminated with a 25 W red bulb with two or three sexually experienced Long-Evans male rats which had been adapted to the test arena for at least 15 min. After the test animal had been mounted the desired number of times (see specific

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experiments), a lordosis quotient (LQ) was computed for each animal by dividing the number of lordotic responses by the number of mounts and multiplying by 100.

At the end of the experiment, animals were sacrificed with ether, perfused with 10 percent Formalin, their brains removed and examined histologically. Data only from animals which had bilateral lesions which generally included the entire anterior–posterior extent of the lateral septum and occasionally the medial septum were included in the lesion groups for analysis. In all instances, lesions were comparable to those previously reported using identical lesioning parameters (refer to [14] for representative microphotographs). An analysis of variance with repeated measures and *t*-tests were used to test for statistical significance, and comparisons between means that are refered to as significant were at a probability of 0.05 or less [24].

## EXPERIMENT 1A. EFFECTS OF SEPTAL LESIONS IN MALE, FEMALE AND ANDROGENIZED FEMALE RATS ON LORDOSIS BEHAVIOR

Since the effects of septal lesions can be markedly altered by chronic exposure to estrogen in male rats [16], it appeared possible that the ability of the intact normal and androgenized female (90 μg testosterone propionate (TP) injected on Day 3 of life) to respond to septal destruction by increasing behavioral sensitivity to estrogen [14] may be related to their exposure to endogenous ovarian hormones close to the time of septal destruction [14,15]. This possibility was tested in the first experiment.

### *Method and Results*

Three groups of animals, males, females and androgenized female rats (270 μg TP injected on Day 3 of life), were all gonadectomized at 28 days of age (one week after weaning). At 75 days of age, each of these three groups was further divided into two groups and given either septal lesions or sham operations. One and two months postsurgery, all animals were tested twice for lordosis behavior following three days of 2 μg EB/day and tested on the fourth day (20 mount test).

Results, shown in Fig. 1, indicated that for female and TP female rats, septal lesioned animals had a significantly higher mean LQ than sham operated animals across both behavior tests (analysis of variance for repeated measures, [24]). In contrast, lordosis behavior of septal lesioned male rats was comparable to sham operated male rats.

### *Discussion*

These results indicate that septal lesions are capable of increasing behavioral sensitivity to estrogen in female rats independent of their exposure to endogenous ovarian estrogen around the time of septal destruction, and confirm the lack of any reliable effect of septal lesions on the lordosis behavior of male rats in the absence of chronic estrogen exposure. Effects of septal lesions in the androgenized females were comparable to those in normal female rats in that the lesioned animals showed a significantly higher LQ than sham operated animals on both tests. Thus, in spite of the well established similarity between androgenized females given this dose of TP and male rats, in terms of their similar neuroendocrine regulation and sexual behavior, the former respond to septal destruction the same as do female rats. In a second experiment, we examined whether this difference between male and androgenized female rats was related to the neonatal dose of androgen; i.e., 270 μg TP on Day 3 may be insufficient to masculinize completely the responsiveness of female rats to septal lesions.

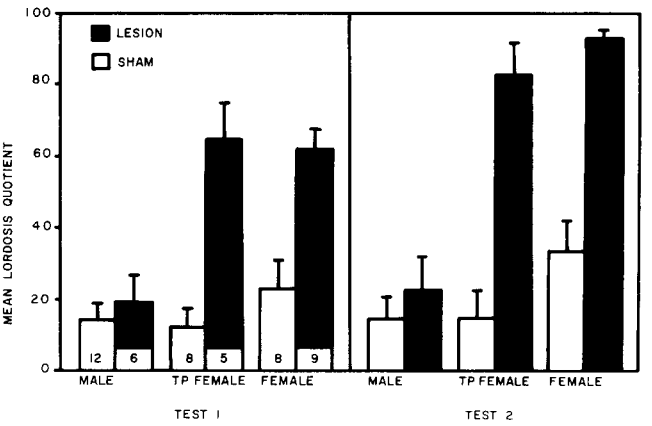


FIG. 1. Mean lordosis quotients (± SE) of septal lesioned and sham operated male, androgenized (TP) female (injected with 270 μg testosterone propionate on Day 3 of life) and female rats tested twice for lordosis behavior following 2 μg estradiol benzoate (EB)/day for three days and tested on the fourth day. The behavior tests were separated by a one-month interval. Number of animals/group is indicated at the bottom of the bar graph; SE by the vertical bars at the top of the bar graphs.

## EXPERIMENT 2B. EFFECTS OF SEPTAL LESIONS ON THE LORDOSIS BEHAVIOR OF HIGHLY ANDROGENIZED FEMALES

The ability of neonatal exposure of female rats to androgens to modify sexually dimorphic patterns of gonadotropin regulation, sexual behavior and body weight regulation [8, 9, 23] appears to be directly related to both the dose of TP and the age at the time of exposure. In general, the higher dose and the younger the animal, the more effective the masculinization. Thus, we examined the effects of septal destruction on the lordosis behavior of female rats given a high dose of TP on Day 1 of life.

### *Method and Results*

Eighteen female rats were injected with 1 mg TP on Day 1 of life. At 70–80 days of age, all animals were ovariectomized and androgen-induced sterilization confirmed by the absence of corpora lutea in the small ovaries. A majority of these androgenized females showed some sign of peripheral masculinization, clitoral hypertrophy and a lack of vaginal canalization. Beginning three weeks later, animals were divided into two groups and given either septal lesions or sham operations. One and two months postsurgery animals were tested twice for lordosis behavior on the fourth day following 0.5 μg EB/day for three days and 2.0 μg EB for three days, respectively. As shown in Fig. 2, septal lesions had no reliable effect on the lordosis behavior of these highly androgenized female rats. For both priming doses of EB, septal lesioned animals were comparable to sham operated rats.

*Discussion*

Results of Experiment 1b indicate that the sexually dimorphic effects of septal lesions on lordosis behavior of rats (Experiment 1a) are related to the degree of androgenization. Presumably the more chronic exposure to endogenous androgens during both prenatal and neonatal development in male rats accounts for the difference between males and females treated on Day 3 with 270 μg TP as shown in Experiment 1a. Thus, with respect to the effects of septal lesions, females exposed to the high (1.0 mg) dose of TP on Day 1 of life are more comparable to normal male rats than are females treated with less TP at later ages.

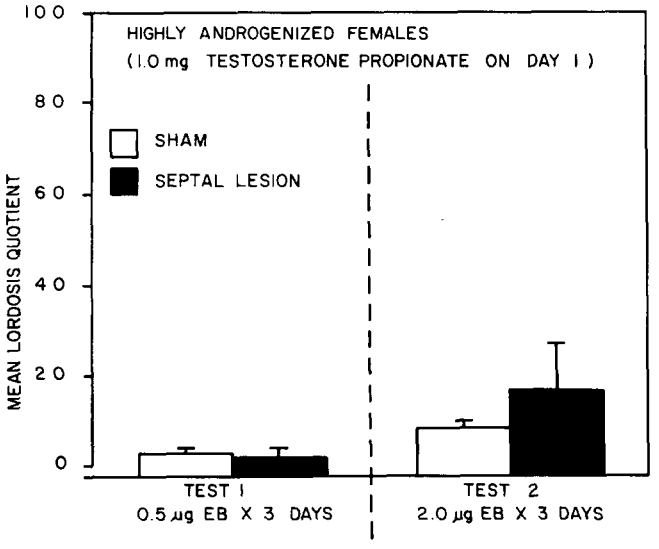


FIG. 2. Mean lordosis quotients (± SE) of septal lesioned and sham operated female rats (eight animals/group) that were highly androgenized by a 1.0 mg dose of testosterone propionate on Day 1 of life. Animals were tested twice following 0.5 and 2.0 μg estradiol benzoate (EB)/day for three days and tested on the fourth day, respectively. The two tests were separated by a one-month interval.

## EXPERIMENT 2. EFFECTS OF CHRONIC ANDROGEN EXPOSURE FOLLOWING SEPTAL LESIONS IN FEMALE RATS ON LORDOSIS BEHAVIOR

Since exposure to androgens neonatally can prevent the effects of septal lesions on lordosis behavior of female rats (Experiment 1b), it seemed possible that chronic exposure to androgens after septal destruction might likewise attenuate the effects of septal lesions on lordosis behavior of adult female rats. However, the ability of septal lesions to alter lordosis behavior in adult male rats depends upon exposing the animals to daily injections of estrogen following septal destruction; therefore, the possible effects of chronic exposure to testosterone following septal lesions in female rats was examined.

*Method and Results*

Seventy-five day old female rats were ovariectomized and, beginning one week later, were given septal lesions and sham operations. These two surgical groups were each further divided into two groups which were given either

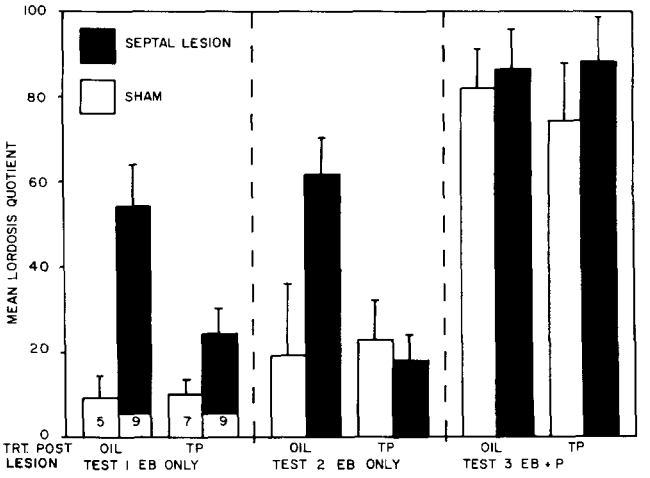


FIG. 3. Mean lordosis quotients (± SE) of septal lesioned and sham operated female rats which were given chronic daily injections of either 1.0 mg testosterone propionate (TP) or sesame oil (OIL) for 30 days following brain surgery. The first behavior test (Test 1) was conducted one month following the termination of chronic injections, and the second test occurred 30 days later. Animals were primed with 2 μg estradiol benzoate (EB) for three days and tested on the fourth day for the first and second behavior test, whereas Test 3 was conducted the day following Test 2 and 4–6 hr following 0.5 mg progesterone (P). Number of animals/group is indicated at the bottom of the bar graph.

daily injections of 1.0 mg TP or oil for 30 days following surgery. One month following the chronic injections, all animals were tested for lordosis behavior on the fourth day following daily injections of 2.0 μg EB for three days. One month later, the behavior test was replicated with the same priming dose of EB and then the animals tested a third time the next day and 4–6 hr after 0.5 mg of progesterone.

Results, shown in Fig. 3, indicate that for both Test 1 and Test 2 (estrogen only), the only significant group difference was that the septal lesioned females treated with oil for 30 days showed a significantly higher mean LQ than the other three groups (individual *t*-test). In particular, mean LQs of the septal lesioned female rats treated chronically with TP were comparable to sham operated animals. All groups responded appropriately to the synergistic effects of progesterone on lordosis behavior [9].

*Discussion*

Results of Experiment 3 show that increased behavioral responsiveness to estrogen is not an inevitable consequence of septal lesions in female rats, but rather, much like in the male rat, the behavioral consequences of septal damage can be modified by the hormone environment during the postlesion period in female rats. Whereas chronic estrogen exposure may facilitate the display of female sexual behavior by blocking or inhibiting recovery from brain damage in septal lesioned male rats [16], the present results suggest that chronic exposure to androgen may facilitate recovery in septal lesioned female rats. Although the actual mechanism underlying these lesion-hormone interactions remains to be explained, it is clear that sex steroids can have a powerful effect on the behavioral consequences of septal lesions in both sexes, presumably by interacting with dynamic neural processes during the postlesion period. In

addition, these data support an earlier contention that septal lesions may act primarily on behavioral sensitivity to estrogen [15] and not behavioral sensitivity to progesterone.

## EXPERIMENT 3. ONSET OF THE FACILITATION IN LORDOSIS BEHAVIOR PRODUCED BY SEPTAL LESIONS

Although it is possible that septal lesions could produce an immediate disinhibition of lordosis behavior, as found with emotional reactivity [2], a more gradual change in lordosis behavior following septal damage might also occur as a result of a more dynamic neural process induced by septal lesions on which gonadal hormones could act.

Since septal lesions can acutely induce the release of adrenal steroids (progesterone) [20], which in turn could synergize with estrogen resulting in high levels of receptivity [6] independent of any specific effects of septal destruction on lordosis behavior, androgenized female rats were used instead of normal females. Androgenized female rats (depending on the dose of TP and age of injection) are behaviorally unresponsive to the synergistic effects of progesterone on lordosis behavior [9], but as shown in Experiment 1, respond like normal female rats to septal lesions in terms of behavioral responsiveness to estrogen.

### *Method and Results*

Female rats were given 270 μg TP on Day 3 of life. At 65 days of age, all animals were ovariectomized and the effectiveness of the TP treatment in inducing sterility was verified by the presence of small ovaries and lack of corpora lutea. Beginning three weeks later, all animals were given daily injections of 0.5 μg EB/day, and this treatment continued throughout the entire experiment. On the seventh and tenth injection days, all animals were given preliminary tests for lordosis behavior (15 mount test). On Day 12, animals were given either septal lesions or sham operations. Beginning the next day, animals were tested daily for six days and once more on Day 9 following brain surgery.

Results, shown in Fig. 4, indicated that during the two preliminary tests, three and six days before brain surgery, the androgenized animals showed low levels of lordosis behavior. Following surgery, sham operated animals maintained their low level of lordosis responding across the remaining behavior tests. The septal lesioned group was comparable to sham operated animals for the first three days following surgery, but by Day 4, and then throughout the rest of the experiment, these animals showed significantly higher levels of lordosis behavior than sham operated animals (analysis of variance for repeated measures and individual *t*-test). It should be noted that although lordosis scores of rats in the lesioned group were significantly higher than the sham operated animals by Day 4, the lesion effect does not appear to peak until two days later, on Day 6.

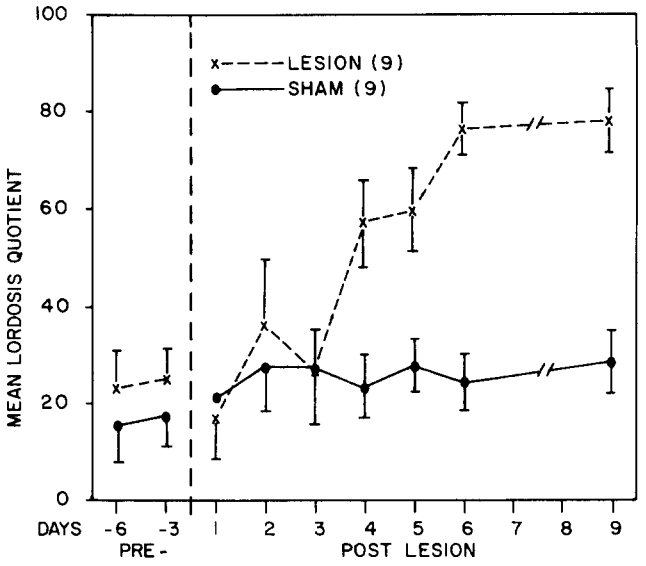


FIG. 4. Onset of the facilitation in lordosis behavior following septal lesions in androgenized female rats (injected with 270 μg testosterone propionate on Day 3 of life). Animals were injected daily with 0.5 μg estradiol benzoate throughout the experiment. Mean lordosis quotients (± SE) are plotted for 2 presurgery tests (PRE-) that were conducted on the seventh and tenth injection day and occurred six and three days prior to brain surgery, respectively. On Day 12, animals were given either septal lesions or sham operations and, beginning the next day, were tested daily for six days and once more on Day 9 following brain surgery. Mean lordosis quotients (± SE) on the postlesion tests are plotted and the number of animals/group indicated at the top of the figure.

### *Discussion*

Since the facilitation of behavioral sensitivity to estrogen is not an immediate effect of septal destruction, it appears that the effects of septal lesions on lordosis behavior represent more than a release from some type of neural inhibition. The four to six day delay in the appearance of the facilitation in lordosis behavior suggests that septal lesions initiate some neural process that requires several days for expression. This could be an adequate interval for some type of denervation hypersensitivity to develop, or else permit the occurrence of a lesion-induced depletion or change in brain amine function. That changes in brain amines (depletion of dopamine) can markedly increase lordosis behavior in estrogen primed female and male rats has been well documented [7,22]. Thus, in the next experiment, we tested the effects of amphetamine, which is generally regarded as a catecholamine releasing agent [7], on the lordosis behavior of septal lesioned female rats.

## EXPERIMENT 4. MODIFICATION IN THE LORDOSIS BEHAVIOR OF SEPTAL LESIONED FEMALE RATS BY AMPHETAMINE

If the effects of septal lesions are mediated by an imbalance in the brain amines, then it should be possible to attenuate or normalize the hyperresponsiveness to estrogen of septal lesioned animals by appropriate pharmacological intervention. Preliminary experiments involving a pharmacological elevation in brain serotonin levels by administering 100 mg/Kg of 5-hydroxytryptophan to septal lesioned rats failed to modify the increased responsiveness to estrogen in septal lesioned female rats (Nance, unpublished data). However, the ineffectiveness of these manipulations in serotonin (5-HT) levels is not entirely unexpected if we consider that 5-HT may be more related to the behavioral action of progesterone (see Everitt *et al.*

[7]) combined with the evidence that septal lesions may act primarily on responsiveness to estrogen. Since recent work of Everitt *et al.* [7] clearly suggests an inhibitory role for dopamine (DA) on the lordosis behavior of estrogen primed animals, this experiment examined the effects of alterations in the catecholamines on the lordosis behavior of septal lesioned female rats.

*Method and Results*

Seventy-five day old female rats were ovariectomized and given septal lesions and sham operations. Beginning six to eight weeks later, animals were primed for three days with 2 μg EB/day and tested on the fourth day for lordosis behavior (20 mount test). Approximately three weeks later, animals were again primed for three days with 2 μg EB/day. On the fourth day and 30–90 min prior to the behavior test (20 mounts), animals were injected with 1.0 mg/Kg d-amphetamine sulfate (Silasiand Company) (1.0 ml/100 g body weight) IP. Twenty-four hours later, all animals were given a post-amphetamine behavior test for lordosis behavior.

Illustrated in Fig. 5 are the results of the three behavior tests, indicating the preamphetamine and postamphetamine mean LQs for sham and septal lesioned animals. Dates of the behavior tests are also indicated. Septal lesioned animals showed significantly higher levels of lordosis responding than the sham operated group on the first test. However, following pretreatment with amphetamine just prior to the second test, the septal lesioned animals were not significantly different from the sham operated rats. Yet when the animals were tested the day following the amphetamine-test, septal lesioned females showed a significantly higher mean LQ than that of the sham animals. Although as shown in Fig. 5, amphetamine tended to depress the lordosis behavior of the sham operated animals, the septal lesioned rats showed a much larger absolute and relative decrease in mean LQ.

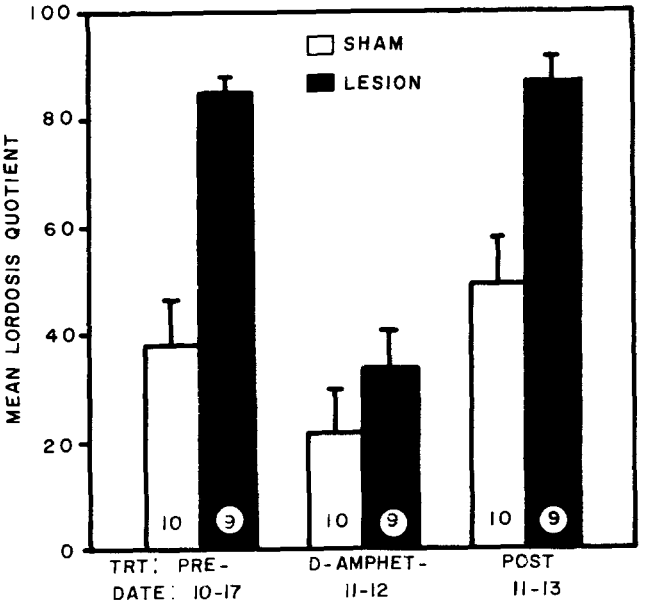


FIG. 5. Effects of d-amphetamine (1.0 mg/kg) on the mean lordosis quotient (± SE) of septal lesioned and sham operated female rats. The first behavior test, indicated as PRE-, was conducted approximately three weeks prior to the amphetamine test and occurred on the fourth day following 2μg estradiol benzoate (EB)/day for three days. For the second test (amphetamine), animals were primed with the same dose of EB for three days and d-amphetamine injected 30–90 min prior to the behavior test on Day 4. Animals were tested a third time the next day (24 hr postamphetamine). Number of animals/group and dates of the behavior test are indicated.

*Discussion*

These data at least suggest that administration of amphetamine can reduce the hyperresponsiveness to estrogen typically shown by septal lesioned female rats. In general, these results are compatible with the possibility that the modifications in lordosis behavior produced by septal lesions may in part be mediated by lesion induced changes in the catecholamines. The last experiment examined the possibility that detectable differences in the levels and turnover of brain amines in various areas would differ between septal lesioned and sham operated rats at a point in time during which reliable behavioral differences would normally be present.

## EXPERIMENT 5. EFFECTS OF SEPTAL LESIONS ON BRAIN AMINE LEVELS AND TURNOVER

Some alterations in brain amine levels have been reported following septal lesions [2,10]. However, these studies utilized male rats and also a relatively short lesion-to-assay interval. Since the effects on lordosis behavior of septal lesions are long-lasting, if not a permanent alteration in a hormone dependent behavior, more long-term changes in brain amine function should also be present if the brain amines are in some manner related to the behavioral effects of septal lesions.

*Method*

In this last experiment we utilized septal lesioned and sham operated female rats which had been tested twice for lordosis behavior and shown to exhibit the septal lesion effect in a preliminary and unrelated experiment. At the time of sacrifice, animals were approximately 150 days old and had been spayed and given septal lesions or sham operations approximately two to three months earlier. Animals had not been tested nor given steroids for at least three weeks prior to the present experiment. All rats were injected with 2 μg EB/day for three days. Instead of receiving a standard behavior test on Day 4, all animals were killed by decapitation, their brains quickly removed for dissection and assay at the same time behavior tests were ordinarily conducted. Two hours prior to sacrifice, animals were randomly divided into two groups and given either saline or 250 mg/Kg alpha-methyltyrosine methylester HCL (AMT) (Sigma), in order to index turnover following synthesis inhibition. After the brains were removed, they were rinsed with ice cold saline, then placed on a saline

soaked paper towel with the dorsal side down. A frontal cut was then made perpendicular to the ventral surface of the brain about 1.0 mm posterior to the optic chiasm. The anterior portion of brain tissue was then placed in 10% Formalin and saved for subsequent histological confirmation of the septal lesions. The posterior section of the brain was placed on solid $CO_2$. This entire procedure took less than one min. The frozen brains were then stored at -40° C.

In order to examine the content and turnover of the brain amines in specific brain areas, the frozen brains were placed on aluminum blocks in an ice bath and allowed to thaw for a few minutes just prior to dissection. A frontal cut was made perpendicular to the ventral surface of the brain just anterior to the mammillary bodies. The following samples were then dissected from this frontal section: dorsal hippocampus, cortex (midline cingulate region), amygdala (including the adjacent pyriform cortex), and medial and lateral hypothalamus. Three additional frontal cuts were made in the remaining posterior section of brain tissue, with one cut being just anterior to the interpeduncular nucleus and two more at 2 mm intervals. From these later sections, the interpeduncular-substantia nigra area and central gray were identified and dissected out.

All tissue samples from individual rats, ranging in size from 5–50 mg, were homogenized in 500 μl 0.4 N perchloric acid, centrifuged at 10,000 X G for 30 min, and the clear supernatant taken for the assay of norepinephrine (NE), DA and 5-HT. The perchloric acid extract was adjusted to pH 7.0 by an equal volume of 0.4 M $K_2HPO_4$/0.2 N NaOH and the $KC10_4$ centrifuged down. The supernatant was extracted with 600 μl 0.1 M diethylhexylphosphoric acid in chloroform. The amines were then eluted from the organic phase with 200 μl 0.2 N perchloric acid. NE and DA were then assayed fluorimetrically using 0.1 the volumes described by Shellenberger and Gordon [21]. The 5-HT was assayed using 0-phthalaldehyde described by McCamen *et al.* [13]. All estimates of amine levels were based upon four to six animals per group.

*Results and Discussion*

No significant differences in brain levels of NE and 5-HT were found between septal lesioned and sham operated animals in all brain areas assayed, and septal lesions had no effect on the rate of decline in NE when measured 2 hr following AMT in any brain loci sampled (*t*-test for independent groups). However, septal lesioned animals were found to have significantly lower mean levels of DA in the amygdala than sham operated animals, 0.67 ± 0.07 vs 1.16 ± 0.15 pmol/mg tissue, respectively, for the saline treated groups. Lesioned animals also showed an apparent slower rate of turnover in DA in the amygdala than sham animals, as indexed by AMT depletion and relative to the brain levels of the saline groups. Mean DA levels 2 hr after AMT were 0.38 ± 0.10 vs 0.18 ± 0.2 pmol/mg for septal lesioned and sham operated animals, respectively. Although there was a tendency for decreased levels and slower turnover rates for DA in the hippocampus and lateral hypothalamus of septal lesioned animals, the low endogenous levels and sensitivity of the assay precluded our detecting any significant group differences in these areas. It should also be noted that the forebrain section that was utilized for histological verification of septal damage contained mesolimbic and striatal areas which are important dopamine containing regions, and may also be modified by septal lesions [4], a possibility currently under investigation.

These preliminary results suggest that further consideration of brain amines may provide a potential biochemical index of lesion-induced changes in hormone sensitive brain areas. We have recently reported additional lesion experiments [18] which indicate a potential facilitatory role for the amygdala region in the effects of septal lesions on lordosis behavior. Thus, the modified DA function in the amygdala reported here provides convergent evidence of a potential role for the amygdala and possibly DA in relation to the effects of septal lesions on behavioral sensitivity to estrogen.

## GENERAL DISCUSSION

The present data indicate that there are at least three factors which can modify the effects of septal lesions on the lordosis behavior of adult rats primed with estrogen. First, presumably as a result of early exposure to endogenous androgens in the male or exogenous injections of a large dose of TP in neonatal female rats, septal lesions do not alter the behavioral responsiveness to estrogen when measured by lordosis behavior. This is in marked contrast to the effects of septal lesions on the lordosis behavior of normal female and androgenized female rats treated with lower doses of TP at later ages ([14], and Experiment 1). Second, the sexually dimorphic effects of septal lesions can be modified in adult male and female rats by chronic treatment with gonadal hormones following septal destruction. Whereas estrogen facilitates the expression of lesion induced changes in the lordosis behavior of male rats [16], androgens attenuate the lesion dependent changes in lordosis behavior normally observed in female rats (Experiment 2). And finally, pharmacological intervention at the time of testing can modify behavioral responsiveness to estrogen induced by septal ablation. Whether these three experimental situations represent independent phenomena, each with its own underlying mechanism, or reflect different types of modulations of a more unitary process of neural, hormonal and behavioral integration or some combination of these two possibilities is presently unknown.

Conceptually, the generation of a viable explanation of these phenoma would be easier if a common mechanism could be discerned. With this bias in mind, some common features among these experimental situations can be recognized. First, and most obvious, is that the analysis of these phenomena has utilized the same dependent variable, lordosis behavior. The expression of lordosis behavior in the rat is entirely hormone dependent, at least as tested in the present experiment. Thus, behavioral differences in lordosis behavior are generally ascribed to differential sensitivity to the activational effects of hormones. At present, it appears that hormones could produce either an

increase in sensitivity to stimuli associated with being mounted [11], selective alterations in motor systems [9], or both. Whatever the neural-humoral dimension that mediates the behavioral action of hormones, it seems reasonable to consider that hormone sensitivity may be a second common feature of all these experimental situations. However, is this modulation in behavioral sensitivity to estrogen a generalized increased state of hormone sensitivity, or a selective effect on certain hormone dependent systems such as those which subserve lordosis behavior?

The effects of septal lesions on androgen and estrogen induced male sexual behavior in both male and female rats has been examined in preliminary experiments (Christensen and Gorski, unpublished data). Much like the lack of any reliable effect of septal lesions on the lordosis behavior of septal lesioned male rats, male sexual behavior is not markedly altered by septal lesions in male rats. In contrast, female rats, which show an increase in lordosis behavior after a septal lesion, also tend to show increased responsiveness to hormones when indexed by male sexual behavior. However, the effects of septal lesions on gonadotropin regulation [14] and hormone induced changes in daily food intake and body weight (additional hormone dependent systems [17]) appear less remarkable than the lesion effects on sexual behavior of female rats (Nance and Gorski, unpublished data). Thus, it is likely that there are both generalized and selective alterations in several hormone sensitive systems, and further analysis of these potentially interrelated neural-behavioral systems may permit some clarification of the neural circuits or hormone sensitive neural sites involved in the mediation of these behaviors as well as their modification by lesions. Also, by comparing males, females and animals treated chronically with hormones after septal destruction in terms of these various hormone dependent variables, it should be possible to determine whether the same or separate neural systems are being modulated by these developmental, postlesion induced and pharmacologically alterable effects of brain lesions on hormone dependent behaviors.

A potential common underlying mechanism is suggested by results of the last two experiments. Some developmental change in brain amine activity has been suggested as an important dimension of neural control for sexually differentiated functions [12]. In addition, modifications in brain amine levels (DA) in adults, although unable to substitute for the priming effects of estrogen, can both facilitate and inhibit the expression of lordosis behavior in both male and female rats [7,22]. Data presented here suggest that septal lesions can modify the content and turnover of DA in selective brain areas, and the expression of lesion dependent changes in lordosis behavior can be pharmacologically modified at the time of behavioral testing. To add to the complexity, however, gonadal hormones can also modify brain levels and turnover of amines [1] and can even interact with drugs at the receptor level in the hypothalamus [3]. Thus, at present, it appears that the activity of certain neurotransmitters in selected brain areas may account for some of the factors which can modify the effects of brain lesions on hormone dependent behaviors. Hopefully a more thorough examination of neurotransmitters will permit a more coherent integration of these divergent phenomena.

ACKNOWLEDGEMENTS

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## REFERENCES

1. Anton-Tay, F., S. M. Anton and R. J. Wurtman. Mechanism of changes in brain norepinephrine metabolism after ovariectomy. *Neuroendocrinology* **6**: 265–273, 1970.
2. Bernard, B. K., J. R. Berchek and D. A. Yutzey. Alterations in brain monoaminergic functioning associated with septal lesion induced hyperreactivity. *Pharm. Biochem. Behav.* **3**: 121–126, 1975.
3. Breuer, H. and G. Köster. Interaction between oestrogens and neurotransmitters at the hypophysial-hypothalamic level. *J. Steroid Biochem.* **5**: 961–967, 1974.
4. Brownstein, M., J. M. Saavedra and M. Palkovits. Norepinephrine and dopamine in the limbic system of the rat. *Brain Res.* **79**: 431–436, 1974.
5. De Groot, J. The rat forebrain in stereotaxic coordinates. *Verh K. ned. Acad. Wet.* **52**: 1–40, 1959.
6. Eriksson, H. and P. Södersten. A failure to facilitate lordosis behavior in adrenalectomized and gonadectomized estrogen-primed rats with monoamine-synthesis inhibitors. *Hormones Behav.* **4**: 89–97, 1973.
7. Everitt, B. J., K. Fuxe, T. Hökfelt and G. Jonsson. Role of monoamines in the control by hormones of sexual receptivity in the female rat. *J. comp. physiol. Psychol.* **80**: 556–572, 1975.
8. Gorski, R. A. Gonadal hormones and the perinatal development of neuroendocrine function. In: *Frontiers in Neuroendocrinology*, edited by L. Martini and W. F. Ganong. New York: Oxford University Press, 1971, pp. 237–290.
9. Gorski, R. A. The neuroendocrine regulation of sexual behavior. In: *Advances in Psychobiology, Vol. 2*, edited by G. Newton and A. H. Riesen. New York: John Wiley and Sons, 1974, pp. 1–58.
10. Heller, A., J. A. Harvey and R. Y. Moore. A demonstration of a fall in brain serotonin following central nervous system lesions in the rat. *Biochem. Pharmac.* **11**: 859–866, 1962.
11. Kow, L. and D. W. Pfaff. Dorsal root recording relevant for mating reflexes in female rats: Identification of receptive fields and effects of peripheral denervation. *J. Neurobiol.* **6**: 23–37, 1975.
12. Ladosky, W. and L. C. J. Gaziri. Brain serotonin and sexual differentation of the nervous system. *Neuroendocrinology* **6**: 168–174, 1970.
13. McCaman, M. W., D. Weinreich and R. E. McCaman. The determination of picomole levels of 5-hydroxy-tryptamine and dopamine in aplysia, tritonia and leech nervous tissues. *Brain Res.* **53**: 129–137, 1973.
14. Nance, D. M., J. Shryne and R. A. Gorski. Septal lesions: Effects on lordosis behavior and pattern of gonadotropin release. *Hormones Behav.* **5**: 73–81, 1974.
15. Nance, D. M., J. Shryne and R. A. Gorski. Effects of septal lesions on behavioral sensitivity of female rats to gonadal hormones. *Hormones Behav.* **6**: 59–64, 1975.

16. Nance, D. M., J. Shryne and R. A. Gorski. Facilitation of female sexual behavior in male rats by septal lesions: An interaction with estrogen. *Hormones Behav.* **6**: 289–299, 1975.
17. Nance, D. M. and R. A. Gorski. Neurohormonal determinants of sex differences in the hypothalamic regulation of feeding and body weight. *Pharmac. Biochem. Behav.* **3**: SUPPL. 1, 155–162, 1975.
18. Nance, D. M., M. McGinnis and R. A. Gorski. Interaction of olfactory and amygdala destruction with septal lesions: Effects on lordosis behavior. Abst. Sixth Annual Meeting, Society for Neuroscience, Toronto, Nov. 1976.
19. Nance, D. M., C. Phelps, J. E. Shryne and R. A. Gorski. Alterations by estrogen and hypothyroidism in the effects of septal lesions on lordosis behavior of male rats. *Brain Res. Bull.* **2**: 49–53, 1977.
20. Seggie, J. and G. M. Brown. Septal lesions and resting adrenal function: A possible explanation of conflicting findings. *Neuroendocrinology* **8**: 367–374, 1971.
21. Shellenberger, M. K. and J. H. Gordon. A rapid simplified procedure for simultaneous assay of norepinephrine, dopamine, and 5-hydroxy-tryptamine from discrete brain areas. *Analyt. Biochem.* **39**: 356–372, 1971.
22. Södersten, P. and S. Ahlenius. Female lordosis behavior in estrogen-primed male rats treated with p-chlorophenylalanine or α-methyl-p-tyrosine. *Hormones Behav.* **3**: 181–189, 1972.
23. Tarttelin, M. F., J. E. Shryne and R. A. Gorski. Patterns of body weight change in rats following neonatal hormone manipulation: A "critical period" for androgen-induced growth increases. *Acta Endocr.* **79**: 177–191, 1975.
24. Winer, B. J. *Statistical Principles in Experimental Design.* New York: McGraw-Hill, 1962, pp. 28–40 and 298–312.