

# Initiation of Maternal Behavior in the Rat: Possible Involvement of Limbic Norepinephrine<sup>1</sup>

MARIANNE K. STEELE,<sup>2</sup> DAVID ROWLAND<sup>3</sup> AND HOWARD MOLTZ

*Committee on Biopsychology, Department of Behavioral Sciences, The University of Chicago  
Chicago, IL 60637*

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STEELE, M. K., D. ROWLAND AND H. MOLTZ. *Initiation of maternal behavior in the rat: Possible involvement of limbic norepinephrine.* PHARMAC. BIOCHEM. BEHAV. 11(2) 123-130, 1979.—The dorsal norepinephrine (NE) fiber system was manipulated in pregnant female rats. Brainstem lesions of the dorsal bundle, depleting NE in cortex and hippocampus, resulted in deficits in maternal-behavior onset in primiparous rats. Similarly, fornix-bundle transections, depleting only hippocampal NE, were associated with an absence of pup care. Hypothalamic NE levels, as well as dopamine and serotonin concentrations in cortex, hippocampus and hypothalamus, were not significantly affected by these manipulations. The data are discussed in terms of behavioral specificity, possible hormonal involvement and interactions with diencephalic mechanisms controlling the onset of maternal behavior in the female rat.

Maternal behavior      Limbic norepinephrine      Behavioral specificity      Hormones

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THE initiation of maternal behavior in the parturient rat involves a complex interaction of neural and hormonal events [15,32]. For example, the termination of gestation and the onset of pup-related activities are associated with increasing plasma levels of estrogen and decreasing plasma levels of progesterone [22,39]. The initiation of maternal behavior has also been demonstrated to be under the control of such neural structures as the hippocampus [11], cingulate cortex [30], septum [31], nucleus accumbens [33], medial preoptic area [24], and the paraformal hypothalamus [3].

In addition to the neural and hormonal variables just mentioned, there are reports in the literature [21,26] which indicate that central nervous system (CNS) monoamines may be involved in the initiation of maternal behavior. Furthermore, these data suggest that hypothalamic norepinephrine (NE), in particular, may be important in the onset of maternal responsiveness.

However, the relationship between neurochemistry and maternal behavior has not been investigated in brain areas other than the hypothalamus. Indeed, extrahypothalamic structures have been implicated in the control of maternal behavior by a number of studies [11, 30, 31, 33]. The following experiments, therefore, were designed to investigate the possible role of extrahypothalamic NE in the control of pup care in the rat. CNS concentrations of dopamine (DA) and serotonin (5-HT) were also determined, as were levels of NE

in the hypothalamus. In addition, so as to ensure specificity, measures of ingestive behavior and sensory-motor function were gathered. In Experiment 1, the dorsal NE bundle was lesioned in primiparous female rats to assess the effects of telencephalic and limbic NE depletion upon the onset of maternal responsiveness.

## EXPERIMENT 1

### METHOD

#### *Animals*

Virgin female rats of the Wistar strain were born and raised in the authors' laboratory under the day-night cycle of 12:12 (lights on 8 a.m.). Each female was mated between 90 and 120 days of age. Vaginal smears were taken daily, the presence of sperm marking Day 0 of pregnancy. Upon the discovery of sperm, females were housed singly in standard laboratory cages with ad lib access to food and water until surgery was performed.

#### *Surgical Procedure*

To allow for complete cellular loss of neurotransmitters by the time of parturition and to allow the acute effects of the

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<sup>2</sup>Present address: Department of Physiology, University of Texas Health Science Center at Dallas, Dallas, TX 75235.

<sup>3</sup>Present address: Department of Behavioral Science, Millikin University, Decatur, IL 62522.

surgery to dissipate by the time of behavioral testing, all operations were performed between Days 5 and 8 of gestation. Animals were anesthetized with Nembutal, supplemented by ether when necessary during surgery.

Bilateral dorsal bundle (DB) lesions (N=9) were made with a stainless steel electrode (No. 1 insect pin) insulated except for the tip, stereotaxically placed at coordinates obtained from deGroot's [7] atlas of the rat forebrain (A: 1.0; L: 1.1; H: -1.0), according to the descriptions of Ungerstedt [38] and Palkovits and Jacobowitz [25]. Destruction of the NE tracts was produced by passing a 0.8 mA anodal current down the electrode for 12 seconds. In sham-operated animals (N=9), the electrode was lowered but no current was passed.

### Observations

Postsurgically, animals were housed singly in large maternity cages measuring 22×20 in. and equipped with a front panel of clear Plexiglas to provide an unobstructed view of the interior. Food and water were available ad lib.

At 21 days from the time of impregnation, each female was supplied with nesting material consisting of a packet of thinly cut newspaper strips. As soon as a birth was discovered, the condition of the young and the mother, as well as the presence or absence of a nest, were noted. Mother and litter were then left undisturbed until the following day when the litter was culled to six in number. Thereafter, mother and litter were observed daily. If on any test day, dead or moribund pups were discovered in the cage they were removed and foster pups of an appropriate age (1-5 days old) from the colony were added to the litter. At no time did a litter consist of less than three pups.

### Behavioral Testing

Testing continued for 12 days. Daily observations included: *nursing*—nipple attachment of the litter to the dam; presence of milk in the stomach of the pups; *nest building*—presence or absence of a nest, if present, the condition of the nest was rated—Good (a tight, compact nest, at least partially covering dam and young), Fair (loosely constructed nest utilizing all the paper strips available), Poor (flat wading of paper strips gathered to one area), None (nest material scattered around cage). *Retrieving of pups*—latency in minutes up to 20 min for all the pups to be returned to the nest; *body weight*—mother and litter. Moreover, to demonstrate that any behavior deficit observed in these lesioned animals was relatively specific to maternal behavior rather than to some general sensory or motor deficit, a battery of tests was given on Days 5 and 10 post-partum. These *neurological tests*, adopted from Marshall and Teitelbaum [17], are designed to measure visual, auditory and olfactory senses, pain perception, righting responses and muscle tone and control.

### Neurochemical Assay and Histology

Females were guillotined at about 1300 hr and the brain regions were dissected as follows: *Cortex* frontal, parietal, occipital and temporal lobes plus the caudate-putamen complex; *Hippocampus* the entire hippocampal formation lifted from the ventral telencephalon; *Hypothalamus* the preoptic, tuberal and mammillary regions located between two coronal sections, one rostral at the level through the

optic commissure and one caudal at the level just behind the mammillary bodies; both the medial and lateral hypothalamus located between two sagittal sections on the medial border of the internal capsule on each side; the dorsal limit of the hypothalamic tissue sample was on a horizontal plane continuous with the anterior commissure. The thalamus and cerebellum were discarded. The remainder of the brain caudal from the mammillary bodies to the brainstem was placed in 10% Formalin for at least one week. They were then sectioned at 50  $\mu$ m in the area of the lesion and stained with cresylechtviolet.

When a sufficient number of brain regions had been accumulated (tissue samples were stored in liquid nitrogen), amines were simultaneously extracted by means of ion-exchange chromatography (Amberlite CG 50) as described by Anden and Magnusson [1]. NE and DA were measured spectrophotofluorometrically by the method of Anton and Sayre [2], modified by Barchas, Erdelyi and Angwin [4]. 5-HT concentrations were determined according to the method of Maikel, Cox, Sallent and Miller [16]. Both internal and external standards were included in such assay.

## RESULTS AND DISCUSSION

### Maternal Behavior

Prior to parturition only one difference was observed between lesioned and sham-operated animals: four experimental females displayed feeding deficits lasting from 1 to 5 days. A supplemental diet, consisting of food chow powder, sugar and water, was therefore made available ad lib. Subsequently, weight gains were comparable across all groups, and the birth process, assessed by the timing parturition and absence of dead and/or crushed pups, appeared normal in all animals.

Females sustaining lesions of the dorsal bundle displayed clearcut deficits in maternal behavior as compared with sham-operated (control) mothers (see Tables 1 and 2). Experimental animals built poorer nests and retrieved less often and with longer latencies than did control animals. Two non-maternal females never constructed a nest or retrieved young during the entire testing period. Moreover, the pups of the DB-lesioned mothers were rarely found to be nipple-attached, in contrast to those of control mothers. As might be expected, no weight gains were seen for the pups of non-maternal mothers. The large number of cold and uncared-for pups, as well as the high incidence of pup mortality (mean=7.7 dead pups/mother), made any attempts to measure growth or weight increases pointless.

Mothers in both experimental and control groups exhibited variable individual weight gains over the observation period. Non-maternal females gained an average of 9.3 g, while control mothers increased their weight by an average of 19.9 g. The differences in bodyweight gain between the two groups may be due to the physiological demands of lactation experienced by maternal-control mothers. Body weight (and food intake) increases are typically observed during lactation [9]. Non-maternal animals, on the other hand, may have ceased to lactate due to a lack of pup stimulation and, therefore, did not evidence such weight gains. All animals appeared healthy and well-groomed and no systematic deficit in either sensory or motor functions were observed.

TABLE 1

	A		B	
	DB-lesioned n=9	Control n=9	Fornix Cut n=12	Control n=8
Nursing	11	100	0	100
Good Quality Nest Building	22	100	0	100
Pup Retrieval Within 10 Mins	22	100	16	100
Sensory-Motor Tests	100	100	92	87

Behavioral Observations: Percent of females exhibiting components of normal maternal behavior and adequate sensory-motor function over all days of testing.

A: Dorsal Bundle (DB) lesioned females vs. controls; B: Fornix-cut females vs. controls.

TABLE 2

	A		B	
	DB-lesioned n=9	Control n=9	Fornix Cut n=12	Control n=8
$\bar{X}$ Female Weight Change (gms)	+ 9.3	+ 19.9	- 2.0	+ 18.2
Litter Weight Gain ( $\bar{X}$ gms)	—	103.0	—	97.0
$\bar{X}$ Nbr Dead Pups/Mother	7.7	—	4.5	—

Further data contrasting A: Dorsal Bundle (DB) lesioned females vs controls; B: Fornix-cut females vs controls.

Neurochemical Assay

Concentrations of NE, DA and 5-HT in cortex, hippocampus and hypothalamus for DB-lesioned and control (sham-operated) animals are presented in Table 3. Non-maternal mothers with damage to the dorsal NE bundle sustained significant losses of NE from both the cortex ( $t=6.5$ ,  $p<0.001$ ) and the hippocampus ( $t=5.2$ ,  $p<0.001$ ). Hypothalamic NE levels were not affected in these animals ( $t=0.06$ , n.s.).

Neither 5-HT in any brain area assayed nor DA either in the cortex or hippocampus showed any significant change in levels when values from non-maternal and maternal animals were compared. There was, however, a statistically significant increase in hypothalamic DA concentrations in the non-maternal subjects as compared to maternal animals ( $t=4.49$ ,  $p<0.05$ ).

Histology

As can be seen in Fig. 1, lesions that resulted in deficits in pup care were confined to the dorso-medial tegmentum at the level of the interpeduncular nucleus and the superior

colliculus. Tissue damage produced by the surgery extended from the caudal border of the diencephalon to the more rostral portions of the medulla.

In the present study, lesions of the dorsal NE bundle, depleting cortical and hippocampal NE, resulted in deficiencies in pup care. It is unclear at present if the statistically significant increase in hypothalamic DA is also related to the lack of maternal responsiveness seen in our DB-lesioned females. 5-HT concentrations in all brain areas appeared normal in lesioned non-maternal females, as did DA levels in cortex and hippocampus. It therefore appears that the initiation of maternal behavior in the rat is unrelated to 5-HT in whole brain and DA in cortex and hippocampus.

Since it is generally agreed that cortical structures are not critically involved in the control of maternal behavior in the rat ([32], p. 629), the results of Experiment 1 suggest that it is NE in the hippocampus (rather than cortex) that plays a role in the induction of rodent pup care. The involvement of this system is further supported by the data of Kimble *et al.* [11], wherein dorsal hippocampal aspiration resulted in aberrant maternal responsiveness in female rats.

Prior studies in the author's lab have indicated that tran-

TABLE 3

	Hypothalamus		Hippocampus		Cortex	
	DB-Lesioned	Control	DB-Lesioned	Control	DB-Lesioned	Control
NE	1447 ± 82	1454 ± 86	127 ± 28	422 ± 45*	109 ± 14	337 ± 29*
DA	1421 ± 18	1085 ± 73 <sup>†</sup>	478 ± 53	556 ± 86	942 ± 119	1096 ± 112
5-HT	781 ± 116	815 ± 49	460 ± 114	324 ± 42	336 ± 23	357 ± 24

\*difference between lesioned and control values,  $p < 0.01$ .

<sup>†</sup>difference between lesioned and control values,  $p < 0.05$ .

Mean concentrations ± SEM (ng/g) of NE, DA and 5-HT in brain areas of dorsal bundle (DB) lesioned females (n=9) and in control animals (n=9).

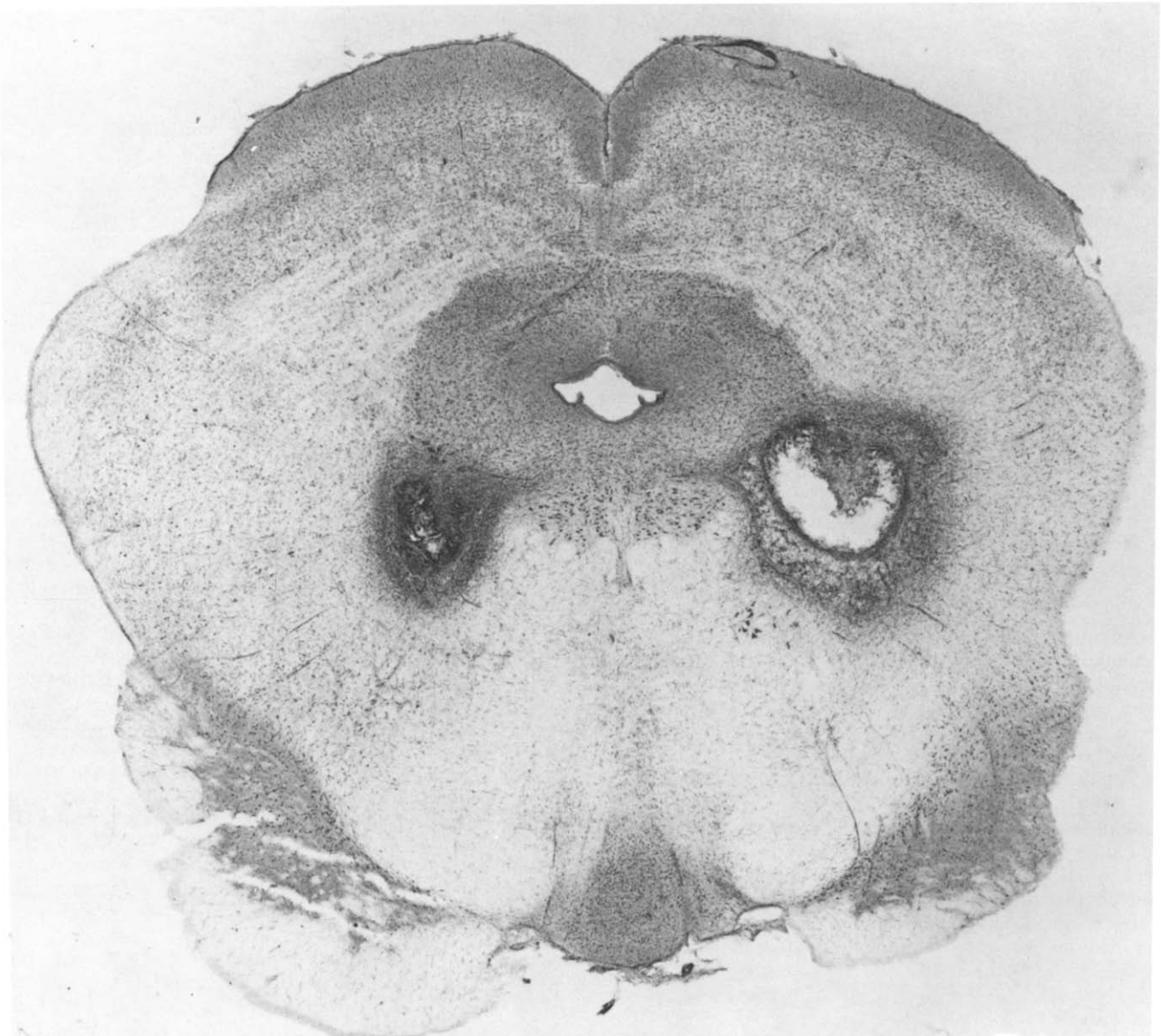


FIG. 1. Typical dorsal bundle lesion resulting in deficits in maternal behavior (A: 1.0, deGroot, 1959).

section of the fornix, a major fiber bundle connecting the hypothalamus and the hippocampus, depletes NE in the hippocampus while leaving cortical and hypothalamic NE levels virtually normal. The following experiment then utilizes this surgical technique to test the hypothesis that hippocampal NE, rather than cortical NE, is related to the deficits in maternal behavior observed in Experiment 1.

EXPERIMENT 2

METHOD

Animals

Virgin female rats of the Wistar strain were raised and mated under conditions identical to Experiment 1.

Surgical Procedures

With the following exceptions, all procedures were the same as those described previously. The fornix was transected by a horizontal cut made by a knife assembly similar to that described by Sclafani and Grossman [27] and used by Numan [23]. The guide shaft of the knife assembly was stereotaxically implanted at the coordinates A: 7.0; L: 1.0; H: +1.0 [7]. When the assembly was in position, the blade was extended and the assembly rotated medially so that a 180° cut was produced. The blade was then retracted and the assembly withdrawn. This procedure was followed on both sides of the brain so that the cuts were overlapping at the site of the fornix (n=12). Sham-operated animals were subjected to a similar surgical procedure except that the blade was not extended nor was the knife assembly rotated (n=8).

Observations and Behavioral Testing

Maternal behavior and sensory-motor functions were assessed in the manner described for Experiment 1.

Neurochemical Assay and Histology

At the completion of testing, animals were chosen at random and either guillotined for assay (fornix cut, n=8; sham, n=5) or perfused for histology (fornix cut, n=4; sham, n=3). In the case of those females selected for assay, NE, DA and 5-HT levels were determined in cortex, hippocampus and hypothalamus by the methods described earlier. Those animals selected for histology were killed with an overdose of Nembutal and then perfused through the heart with 0.9% saline followed by 10% Formalin. The brains were removed and allowed to remain in Formalin for at least one week. They were then sectioned at 50 μm in the area of the cut and stained with cresylechtviolet.

RESULTS AND DISCUSSION

Clear deficits in pup care were seen in animals with fornix bundle transections as compared with females that had undergone the sham operation. Without exception, experimental mothers displayed no nursing, crouching or licking behavior toward their young (see Tables 1 and 2). Nipple attachment was never seen in these females and the pups were always cold, unlicked and without milk in the stomach. Only one fornix-transected female exhibited any type of nest building behavior, and the nest that was constructed was of a very poor quality. Retrieving of young was displayed by two non-maternal mothers. However, with these females, as with other animals in this group, pups were typically found scattered around the cage floor at the start of daily testing.

In contrast to the above, the complete spectrum of maternal behaviors was exhibited by sham-operated animals: they retrieved and nursed their young and built excellent nests.

Both experimental and control animals performed equally well on all tests evaluating sensory and motor functions. Hyperirritability was observed in one experimental and two control females, suggesting that the septum may have been injured during surgery. However, the control animals exhibited excellent maternal behavior indicating that the hyper-reactivity is unrelated to the onset of maternal responsiveness.

Neurochemistry

Deficits in maternal behavior in fornix-transected females were associated with significant losses of NE from the hippocampus (t=2.96, p<0.01). As can be seen in Table 4, hypothalamic and cortical NE were somewhat depressed when compared to control levels; however, neither of these differences was statistically significant (hypothalamus: t=1.4, p<0.20, cortex: t=1.6, p<0.10). Differences in 5-HT and DA concentrations between experimental and control animals were not significant in any of the brain areas assayed.

Histology

Figure 2 depicts a typical knife cut of the fornix which resulted in deficits in pup care. The lateral and ventral aspects of the transections were similar in all experimental animals. The cuts extended, on the average, 1.5 mm medial to the guide cannula implantation. Portions of the cut could be seen as anterior as 8.6 mm, extending caudally to anterior 5.6 mm. In females receiving sham-knife cuts, the tracks of the guide cannula could be seen; however, no tissue damage to the fornix or septum was observed.

TABLE 4

	Hypothalamus		Hippocampus		Cortex	
	Fornix Cut	Control	Fornix Cut	Control	Fornix Cut	Control
NE	2133 ± 143	2492 ± 236	310 ± 19	416 ± 35*	261 ± 38	356 ± 36
DA	X	X	X	X	1455 ± 101	1699 ± 228
5-HT	1248 ± 85	1193 ± 188	317 ± 110	359 ± 101	376 ± 11	413 ± 35

\*difference between lesioned and control values, p<0.01.

X no values available.

Mean concentrations ± S.E.M. (ng/g) of NE, DA and 5-HT in brain areas of females receiving

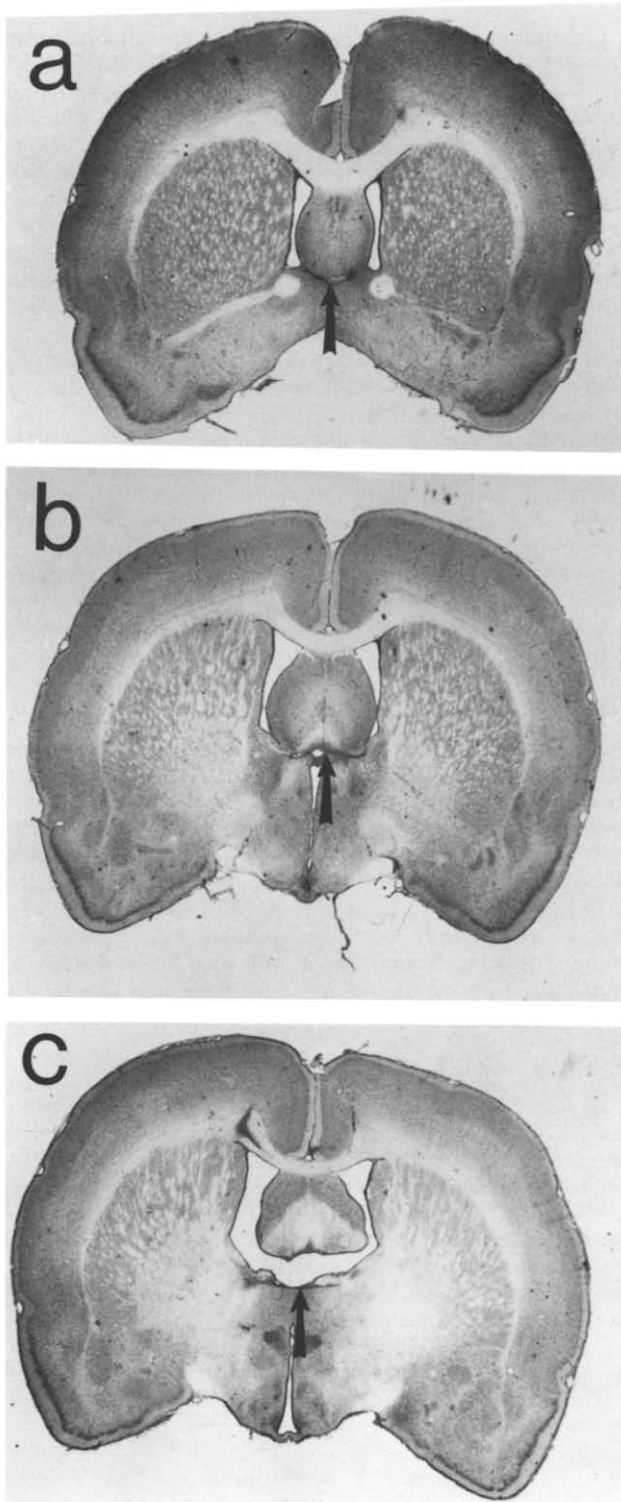


FIG. 2. Typical knife cut of the fornix associated with deficits in maternal behavior (a: A 7.8; b: A 7.0; c: A 6.2, deGroot, 1959).

The results of Experiment 2 demonstrate that fornix transection, resulting in depletion of hippocampal NE, results in dramatic deficits in maternal responsiveness. Compared to sham-operated maternal animals, non-maternal females sustained significant losses of NE from the hippocampus; concentrations of this neurotransmitter in the hypothalamus and cortex, however, were not significantly affected by the surgery.

No significant differences in brain levels of 5-HT were noted between maternal and non-maternal animals. It is likely, then, that the observed deficits in maternal responsiveness are independent of the serotonin-neurochemical system. Due to the variable levels of DA in hypothalamic and hippocampal samples, no conclusion can be drawn regarding the necessity of functional DA neurons for the initiation of pup care. However, the data from the present experiment, as well as data from Experiment 1 and a previous study [12], suggest that telencephalic, diencephalic and limbic DA are probably not essential for the onset of normal maternal behavior.

#### GENERAL DISCUSSION

The present series of experiments indicate that limbic system NE may be involved in the initiation of maternal behavior in the female rat. Specifically, depletion of hippocampal NE, via either DB lesions or fornix transection, results in deficits in pup care.

The behavioral deficits seen in the present series of studies appear to be relatively specific to maternal behavior: hippocampal lesions have little detrimental effect upon female sexual responses [11,19]. Sensory-motor tests were performed on all experimental and control groups and indicated, in general, normal functioning of gross sensory and motor capacities. In addition, manipulations were performed far in advance of behavioral testing to control for any acute effects of surgery upon pup care. Body weights were monitored in all females and appeared normal across all groups. Research now being completed indicates that sexual behavior and estrus cyclicity are normal in fornix-transected females that behave non-maternally toward their pups.

It is possible that hormones of ovarian, adrenal or pituitary origin may interact with hippocampus in controlling pup-care induction. The hippocampus influences the secretion of pituitary hormones [8,13], which in turn modulate the dynamics of adrenal and ovarian steroids. Steroids have been demonstrated to affect the induction of maternal responsiveness [20,29] and, consequently, may play a role in the hippocampal regulation of pup care. Work in progress is investigating this possibility.

Previous studies [3, 21, 23, 26] have suggested that the hypothalamus is involved in the initiation of pup care in the rat. It is interesting to speculate how our data, relating deficits in maternal behavior to hippocampal NE loss, can be integrated with the hypothalamic studies. In the first place, the hippocampal and hypothalamic NE systems may both influence maternal behavior, i.e., interact as in the case of control over pituitary hormone release [13]. Damage to either one of these CNS structures (hippocampus or hypothalamus) could disrupt a functional relationship between them such that the expression of maternal behavior is deficient. Similar interactional hypotheses have been invoked to describe the control of feeding behavior in rats [18], the symptoms of Parkinsonism [5,10] and the development of visual function in cats [6,28].

On the other hand, while the hypothalamus may be involved in pup care, hypothalamic NE may not, since in the only two neurochemical studies of maternal behavior [21,26], brain areas other than the hypothalamus were not assayed and therefore, levels of NE in cortex and hippocampus were not determined. Indeed, in the absence of data to the contrary, hippocampal NE may have been the critical variable (rather than hypothalamic NE) influencing maternal behavior onset in these studies.

Interestingly, lateral-ventricular infusion of 6-OHDA (a catecholaminergic neurotoxin) has been reported to result in both impaired [26] and normal [35,36] pup care in the female rat. Steele [36] found that infusion of 6-OHDA into the ventro-lateral tegmentum was compatible with full and complete maternal responsiveness. The critical variable in determining whether 6-OHDA infusion will result in deficient or normal pup care appears to be the time interval between drug administration and behavioral testing. 6-OHDA infusion at the time of parturition results in deficits in maternal behavior which appear to partially recover over seven days of testing [26]. 6-OHDA infusion two months to

three weeks prior to parturition and behavioral observations, on the other hand, does not interfere with normal pup-care onset [35,36]. Supersensitivity is a typical outcome of 6-OHDA administration [14] and behavioral recovery can often be observed within several days of drug injection [34,37]. It may be that whole-brain depletion of NE by 6-OHDA results in a disruption of maternal behavior, but that the behavior recovers as neuronal supersensitivity develops.

The above discussion of 6-OHDA effects upon pup care still leaves open the question of just where in the brain NE influences maternal behavior. A role for hypothalamic NE, while suggestive, is still inconclusive due to the lack of NE data from other brain areas. In contrast, based on the results of the present studies, hippocampal NE has been strongly implicated in the initiation of pup care in the rat. However, the possibility exists that neurotransmitters other than monoamines (e.g., acetylcholine, histamine, GABA) could also be involved in the onset of maternal behavior in the female rat.

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