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Differential Effects of Neurotoxic Lesions on Psychoneuroendocrine Functions[1,2]

TIMOTHY R. KING AND DWIGHT M. NANCE

Department of Anatomy, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, B3H 4H7, Canada

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KING, T. R. AND D. M. NANCE. *Differential effects of neurotoxic lesions on psychoneuroendocrine functions.* PHARMACOL BIOCHEM BEHAV **24**(1) 107–114, 1986.—The use of neurotoxic agents has provided new insight into the functions of the septal region. The psychoneuroendocrine effects of kainic acid (KA) lesions in the lateral septum (LS) have been confirmed, and we have compared the effects of these lesions to those following lesions of the medial septum (MS) and hippocampus (HP). In addition, the effects of the cytotoxin ibotenic acid (Ibo), have been studied. The alterations in psychoneuroendocrine functions resulting from the cytotoxic lesions have been compared to those from electrolytic septal lesions (DCLS) and sham operations. KA and Ibo lesions of the LS resulted in extensive bilateral loss of neurons in the LS; however, KALS lesions also resulted in cell loss in the CA3–CA4 cell regions of the HP. In contrast, KA and Ibo lesions of the MS did not produce any obvious cell loss in the MS. KA lesions of the HP produced extensive CA3–CA4 cell loss and a reduction in the size of the fornix and rostral septum. The behavioral and endocrine effects of these lesions were, relative to controls: the KALS group exhibited fewer percent days of vaginal estrus, increased ovarian compensatory hypertrophy (OCH), increased body weight (BWt), attenuation in the anorexic effects of estrogen, and decreased female sexual behavior. The KAMS group exhibited a transitory increase in BWt and increased male sexual behavior. IboLS group demonstrated a greater percent days of vaginal estrus and increased female sexual behavior whereas the IboMS group exhibited a decrease in OCH. The KAHP group exhibited a partial attenuation in the anorexic effects of estrogen on food intake and BWt gain. The DCLS group demonstrated increased female sexual behavior. These results indicate that the septal region is involved in both facilitatory and inhibitory modulation of a variety of estrogen responsive processes and further suggest that the MS and LS have different psychoneuroendocrine functions.

Sexual behavior Ovarian function Feeding behavior Kainic acid Ibotenic acid Septum Hippocampus

UNDERSTANDING of the role of the septal area in psychoneuroendocrine functions is based largely upon electrolytic lesions or knife cut techniques [11, 12, 22]. With respect to the hormone dependent display of female sexual behavior, it has been demonstrated that electrolytic lesions or deafferentations of the septal area increase the behavioral sensitivity to sex steroids [11,22]. Recently, the use of neurotoxins has contributed new insights into septal function [2, 5, 10, 13]. Kainic acid (KA) lesions have been reported to produce alterations in ovarian function [2,13], female sexual behavior [5,13], and body weight (BWt) regulation [10,13]. However, results from these KA studies [2, 5, 10, 13] have not been in total agreement with respect to the extent of neurological damage nor the behavioral consequences of these lesions. A related problem is the observation that hippocampal CA3–CA4 cell loss is generally found following KA lesions of the septum [5,13]. Since the neurotoxin Ibotenic acid (Ibo) has been reported to produce more restricted lesions than KA [8], it would be of interest to examine the effects of Ibo lesions in the septal area.

We report here an examination of the effects of KA and Ibo lesions on several psychoneuroendocrine functions and have extended these observations to include specific regions of the septum as well as hippocampus. These new results show that the septum exerts both excitatory and inhibitory control over a variety of diverse psychoneuroendocrine functions and these divergent functions reside in different anatomical regions.

GENERAL METHOD

Female S/D rats (Simonsen Lab., Gilroy, CA) weighing 140–170 g were housed in gang cages and allowed ad lib access to water and Purina Rat Chow. Animals were anaesthetized with Brietal (sodium hexobarbital; 50 mg/kg) for surgical procedures. Seven groups of rats received the following treatments. KA (0.5 μl; 2 μg/μl saline, Sigma) was infused bilaterally into the lateral septum (KALS) and hippocampus (KAHP) and 1.0 μl unilaterally into the medial septum (KAMS). Ibo (0.5 μl; 5 μg/μl saline, supplied by Dr.

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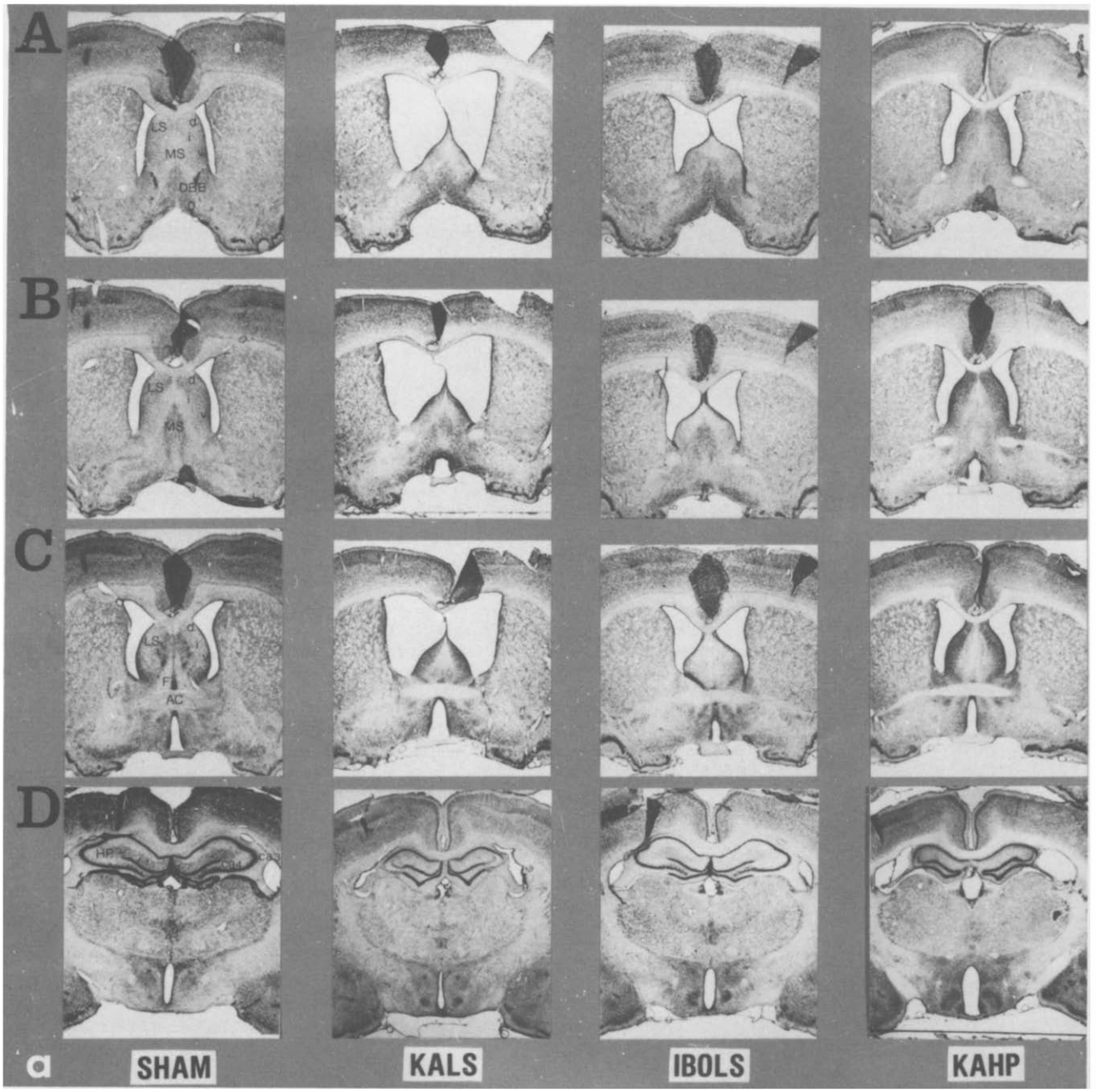

FIG. la,b. Representative microphotographs at various levels (rostral to caudal, A–D) of the septum and hippocampus of rats following KA lesions of the LS, MS, and HP, Ibo lesions of the LS and MS, electrolytic (DC) lesions of the LS, and sham surgeries.

C. H. Eugster) was infused bilaterally into the lateral septum (IboLS) and medial septum (IboMS). The neurotoxins were infused using a Hamilton microsyringe at a rate of 0.1 μl per minute and the needle was left in place for an additional 10 minutes post infusion. DC lesions of the LS (DCLS) were obtained by passing a 2.5 mA current for 20 seconds through a stainless steel electrode which was insulated except for 0.5 mm at the tip. Sham surgeries consisted of an electrode lowered but no current passed or saline injections. The DeGroot [3] stereotaxic coordinates were: lateral septum (LS) 1.5 mm anterior to bregma, 0.65 mm lateral, and 4.5 mm below the dura; medial septum (MS), 2.6 mm anterior, 0.07 mm lateral, and 6.0 mm below the dura; hippocampus (HP) −3.6 mm posterior to bregma, 5.0 mm lateral, and 5.0 mm below the dura.

Histology

All groups were perfused with 4.0% paraformaldehyde-0.5% glutarylaldehyde in phosphate buffer (pH 7.2–7.4) and brains removed for histology. Brains were cut on a freezing microtome at 40 μm and stained with cresyl violet.

Statistical Analysis

All data involving repeated measures on the same subjects were analyzed using the BMDP2V statistical program

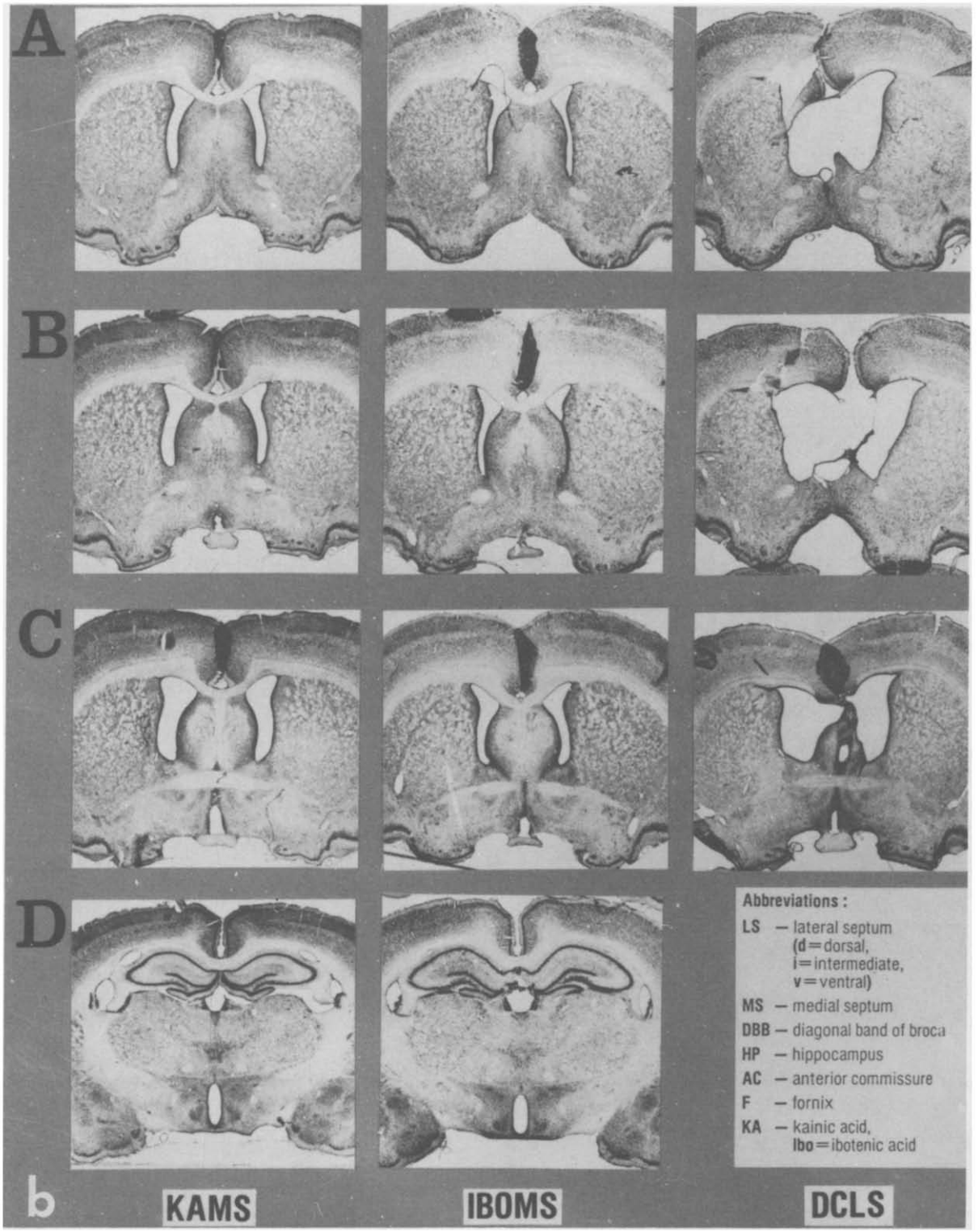
A
B
C
D
Abbreviations :
LS — lateral septum (d=dorsal, i=intermediate, v=ventral)
MS — medial septum
DBB — diagonal band of broca
HP — hippocampus
AC — anterior commissure
F — fornix
KA — kainic acid, Ibo=ibotenic acid
b
KAMS
IBOMS
DCLS

FIG. 1b.

TABLE 1

MEAN (±SE) PERCENT DAYS OF VAGINAL ESTRUS (E), OVARIAN WEIGHT (mg), AND PERCENT OVARIAN COMPENSATORY HYPERTROPHY (OCH) FOLLOWING NEUROTOXIC OR ELECTROLYTIC LESIONS AND SHAM SURGERIES IN VARIOUS BRAIN AREAS OF ADULT FEMALE RATS

Group	N	% Days E	1st Ovary	2nd Ovary	% OCH
KALS	8	17.4±1.9*	28.6± 2.9	40.4±2.4	46.3±10.2*
KAMS	7	27.3±2.3	32.5± 1.9	41.9±1.8	30.2± 5.6
KAHP	7	21.3±2.4	32.2±11.1	43.6±2.8	30.3± 6.1
DCLS	10	22.7±2.4	30.3± 1.4	39.5±1.6	31.7± 5.7
IboLS	5	34.2±3.4*	30.3± 3.3	35.7±2.7	20.5± 8.3
IboMS	4	23.0±0.0	32.2± 3.2	38.7±1.3	8.9± 4.2†
SHAM	19	26.9±0.8	31.5± 1.3	37.8±1.1	21.3± 5.5

*Significantly different from sham $p<0.05$.
†$p<0.1$ compared to sham.

TABLE 2

EFFECTS OF NEUROTOXIC OR ELECTROLYTIC LESIONS AND SHAM SURGERIES ON FEMALE SEXUAL BEHAVIOR (MEAN LQ ± SE) FOLLOWING VARIOUS HORMONE INJECTIONS WITH ESTRADIOL BENZOATE (EB), PROGESTERONE (P), AND TESTOSTERONE PROPIONATE (TP) IN ADULT FEMALE RATS

		Mean L.Q. ± SE			
Group	N	EB alone	EB + P	EB + P 24 hr	TP + P
KALS	8	24.0± 9.9	75.0±11.8	6.7± 4.9*	3.7± 1.8*
KAMS	7	30.4± 9.0	95.0± 3.2	60.4± 8.7	46.4± 8.7
KAHP	7	30.4±13.4	94.7± 2.0	11.5± 5.5	27.5± 4.2
DCLS	10	59.2±10.2*	97.4± 1.7	55.2± 7.2	62.4± 8.5
IboLS	5	22.5±10.3	92.8± 1.8	68.2± 9.7*	47.8±10.8
IboMS	4	35.7±17.9	96.0± 2.3	52.0±18.5	48.0±15.1
SHAM	19	19.4± 3.7	94.1± 2.0	38.5± 6.8	53.8± 6.7

*Significantly different from shams $p<0.05$.
EB alone (2 μg × 3, test on day 4), EB + P (2 μg × 3 followed 24 hr later by 0.5 mg P, tested 4–6 hr later), EB + P 24 hr (2 μg EB × 1 followed 24 hr later by 0.5 mg P, tested 4–6 hr laters), and TP + P, (150 μg × 3 followed 24 hr later by 0.5 mg P, tested 4–6 hr later).

for analysis of variance with repeated measures and then Duncan's multiple range test for comparisons of individual means or comparing all means with control. All other data were statistically analyzed using Student's *t*-test. Probabilities less than 0.05 were regarded as statistically significant.

EXPERIMENT 1A. EFFECTS OF NEUROTOXINS AND DC LESIONS ON OVARIAN FUNCTION

KA lesions of the LS have been shown to produce a significant increase in ovarian compensatory hypertrophy (OCH) and to alter vaginal cyclicity [13]. We have replicated these observations and have examined the possible effects of neurotoxic lesions in additional extrahypothalamic regions on ovarian function.

Method

Daily vaginal smears were performed for 8 days prior to brain surgeries. Animals were then allowed an 11 day recovery period before smears were re-initiated. Vaginal smears were monitored for an additional 21 days (days 12–33 post surgery) at which time animals were anaesthetized with ether, hemi-ovariectomized and the ovary weighed. The remaining ovary was removed 10 days later (day 43) and weighed. Mean percent days of vaginal estrus and mean percent ovarian compensatory hypertrophy (OCH) were calculated.

EXPERIMENT 1B. EFFECTS OF NEUROTOXIC AND DC LESIONS ON FEMALE SEXUAL BEHAVIOR

It has been shown that electrolytic lesions of the LS markedly increase female sexual behavior of female rats following priming with sex steroids [11,12]. Consistent with this, both KA and DC lesions of the MS produce an increase in lordosis behavior ([5]; King, unpublished observation). However, in marked contrast, it has been reported that KA lesions of the LS produced a decrement in lordosis behavior [13]. A possible basis for these reported differences is the extent and/or location of neuronal damage. Gorzalka and Gray [5] reported that KA lesions of the MS produced extensive cell loss in the MS and major cell loss in the LS whereas Nance [13] reported that KA lesions of the LS produced minimal neuronal damage. These results appear to be inconsistent with recent reports that the LS is more sensitive to the neurotoxic effects of KA than the MS [8]. We have re-examined the effects of KA lesions on female sexual behavior using a more toxic concentration. Based upon previous observations of extensive CA3–CA4 cell loss in the HP following KA lesions of the septum, we have also examined the effects of neurotoxic lesions in the HP plus the additional lesion groups described in the general procedure.

Method

Beginning day 59 post brain surgery, a series of female sexual behavior tests was initiated. The animals were tested 4 times for lordosis behavior after treatment with the following hormone regimens; 2 μg estradiol benzoate (EB) for 3 days and tested 24 hours later (EB alone). Immediately following the first test, animals were injected with 0.5 mg progesterone (P) and tested 4–6 hours later (EB+P). In all subsequent tests animals were tested 4–6 hours after the last injection. On day 73 post brain surgery, animals received a single injection of 2 μg EB followed 24 hours later by a single 0.5 mg P injection and subsequently tested (EB+P 24 hr). On day 87, animals received 150 μg of testosterone propionate (TP) for 3 days followed 24 hours later by a single injection of 0.5 mg P (TP+P). All tests consisted of placing the test animal in a Plexiglas arena with 2–4 Long-Evans stud males until 10–15 vigorous mounts had occurred. A lordosis quotient (LQ) was calculated by dividing the number of positive lordotic responses by the total number of mounts and multiplying by 100.

EXPERIMENT 1C. EFFECTS OF NEUROTOXINS AND DC LESIONS ON MALE SEXUAL BEHAVIOR

The preoptic area is a focal region for the regulation of male sexual behavior [1, 9, 15] and the medial forebrain bundle appears to comprise an essential pathway for its expression [1,6]. Since the septal area has major efferent pro-

TABLE 3

EFFECTS OF NEUROTOXIC OR ELECTROLYTIC LESIONS, AND SHAM SURGERIES IN VARIOUS BRAIN AREAS ON MALE SEXUAL BEHAVIOR (MEAN NUMBER OF MOUNTS ± SE) IN ADULT FEMALE RATS DURING CHRONIC TESTOSTERONE PROPIONATE (TP) TREATMENT (150 μg/DAY)

		Days TP Test		
Group	N	6 TP	14 TP	21 TP
KALS	7	0.0±0.0†	0.1±0.1	0.1±0.1
KAMS	7	6.3±2.6*	10.3±4.4*	8.2±3.0
KAHP	7	0.3±0.3	2.7±1.9	2.8±1.3
DCLS	10	1.5±1.0	2.0±1.1	3.6±1.4
IboLS	5	1.2±1.2	0.6±0.6	1.8±1.3
IboMS	4	3.0±2.6	1.5±0.9	2.5±2.5
SHAM	19	0.7±0.3	1.2±0.6	3.8±1.6

†Means number mounts (±SE).
*Significantly different from shams $p<0.05$.

jections in the medial forebrain bundle which pass through the preoptic area and lateral regions of the hypothalamus [19], we have examined the possible effects of the present neurotoxic lesions on the regulation of male sexual behavior in female rats.

Method

Two weeks following the last female sexual behavior test (day 108 post surgery) animals were tested 3 times for male sexual behavior. The test animals received daily injections of 150 μg TP over a period of 21 days and were tested on days 6, 14, and 21. Each test consisted of placing a test animal in a Plexiglas arena and following a 2 min adaptation period, a hormonally primed receptive female rat was introduced. The test period was 15 minutes in duration and the stimulus female was replaced after 7½ minutes by a second stimulus female. The total number of mounts and latency to the first mount were recorded for each animal.

Results and Discussion

Histology. Figure 1 shows representative photomicrographs of the various lesions made in the present study. Sections A–D represent rostral to caudal levels of the septal area as well as the dorsal HP. Following saline injection, the overall morphology of the septal area and HP appeared normal. Both KA and Ibo lesions of the LS resulted in symmetrical loss of major portions of the LS (Fig. 1, sec. A–C) but there were some morphological differences between the KA and Ibo lesions of the LS. First, only the KALS lesions resulted in the bilateral loss of CA3–CA4 cells in the HP (Fig. 1, sec. D). Secondly, the size of the fornix in the septal area appeared to be reduced after KALS lesions but not after IboLS lesions (Fig. 1, sec. B–C). In contrast, KA and Ibo lesions of the MS produced little or no detectable damage to this area or the HP (Fig. 1, sec. A–C). KAHP lesions resulted in the bilateral loss of CA3–CA4 cell groups (Fig. 1, sec. D), and there appeared to be a reduction in the overall size of the fornix and rostral septal area (Fig. 1, sec A–D). DCLS lesions resulted in complete loss of the LS and major portions of the MS (Fig. 1, sec. A–C). A number of DCLS lesions also impinged on the cingulate cortex.

Ovarian function. The effects of various lesions on ovarian function are illustrated in Table 1. Compared to shams, KALS lesions resulted in significantly fewer days of vaginal estrus whereas IboLS lesions produced a significant increase in the days of vaginal estrus. With respect to OCH, the KALS group demonstrated a significant increase in OCH compared to shams. No other significant differences were observed. However, there was a trend for the IboMS group to exhibit a decrease in OCH compared to the shams ($p<0.1$). The effects of KALS lesions on ovarian function confirms earlier results reported by Nance [13]. IboLS lesions appear to exert opposite effects on vaginal cyclicity relative to KALS lesions.

Female sexual behavior. The effects of various lesions on female sexual behavior are shown in Table 2. Considering the LQ scores across all 4 tests, the KALS group demonstrated an overall decrement in lordosis behavior ($p<0.05$) compared to the sham operated group. Considering the individual tests, for EB alone the DCLS group exhibited significantly higher levels of lordosis behavior compared to shams. Following EB+P 24 hr, KALS group demonstrated a significant decrement in lordosis behavior whereas IboLS lesions produced a significant increase in female sexual behavior, relative to controls. Following injections of TP+P, the KALS group again showed a significant decrement in lordosis behavior as compared to shams. These results confirm the previous findings reported by Nance [13], and further demonstrate opposite behavioral consequences of KA and Ibo lesions. However, contrary to the results of Gorzalka [5], no difference was found between KAMS and sham groups. The important difference in these two studies may be the extent of neuronal damage. The complete MS cell loss and extensive LS cell loss reported by Gorzalka and Gray [5] was not observed in the present study. Thus, the present results verify that alterations in psychoneuroendocrine functions can be produced by KA even in the absence of observable neuronal loss [13]. This conclusion is further strengthened by the male sexual behavior tests.

Male sexual behavior. Table 3 summarizes the effects of various lesions on male sexual behavior in the female rat. Analysis of total number of mounts across all tests indicated that the KAMS group exhibited significantly higher levels of mounting behavior compared to shams ($p<0.05$). All other groups were equivalent to shams across the three tests. Differences in mount latency among the various groups did not reach statistical significance.

EXPERIMENT 2. EFFECTS OF NEUROTOXIC AND ELECTROLYTIC LESIONS ON THE ESTROGENIC CONTROL OF FOOD INTAKE (FI) AND BWT

It is well established that estradiol has anorexic effects in the female rat [20] and the hypothalamus appears to be one of the major sites for the anorexic action of estrogen [16]. Recently, Nance has reported that the LS may be involved in energy balance as indicated by a significant increase in weekly BWt gains and an attenuation in the anorexic effects of estrogen following KA lesions of the LS [13]. Also, KA lesions of the MS in female rats are reported to produce a transitory period of hyperphagia without altering BWt [10]. In this experiment we have re-examined the effects of the various neurotoxic and electrolytic lesions on BWt gains. Subsequently, the anorexic effects of estrogen on FI and BWt were tested in several groups.

TABLE 4

MEAN (±SE) ABOLUTE GAIN IN BWt (g) FOLLOWING NEUROTOXIC OR ELECTROLYTIC LESIONS AND SHAM SURGERIES IN VARIOUS BRAIN AREAS OF ADULT FEMALE RATS

		Weeks Post-Surgery				
Group	N	1	4	8	12	16
KALS	7	2.3±1.7	56.6±2.4*	93.1±8.3*	106.4±16.8*	143.6± 9.0*
KAMS	7	9.4±1.6	49.6±3.7	78.3±3.8*	100.2± 5.2*	119.1± 5.6*
KAHP	7	−4.5±1.8	35.9±4.3	62.9±6.4	82.9± 7.0	92.3±10.4
DCLS	10	9.6±1.0	41.2±3.1	72.9±8.4	82.9± 4.8	96.5± 5.6
IboLS	5	8.8±3.6	38.5±5.2	61.0±8.7	73.9± 8.8	94.5± 9.9
IboMS	4	16.0±2.4	41.4±2.0	67.8±6.0	81.9± 8.9	104.4±10.4
SHAM	19	4.5±1.1	34.4±1.9	58.8±2.5	78.5± 2.9	101.3± 3.9

*Significantly different from shams $p<0.05$.

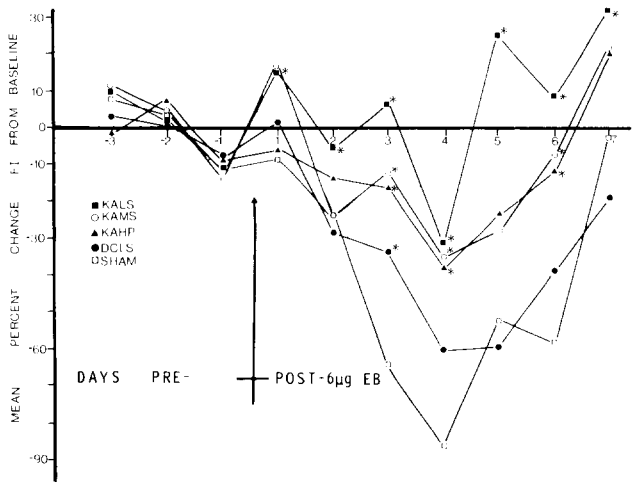

FIG. 2. Mean percent change in daily food intake (FI) from baseline of sham operated, Kainic acid (KA) lesions of the lateral septum (LS), medial septum (MS), and hippocampus (HP), and electrolytic (DC) lesions of the LS for 3 days prior and 7 days following a 6 μg injection of estradiol benzoate (EB). Baseline was computed as the mean FI for the 3 days prior to EB injection. *Significantly different from sham $p<0.05$.

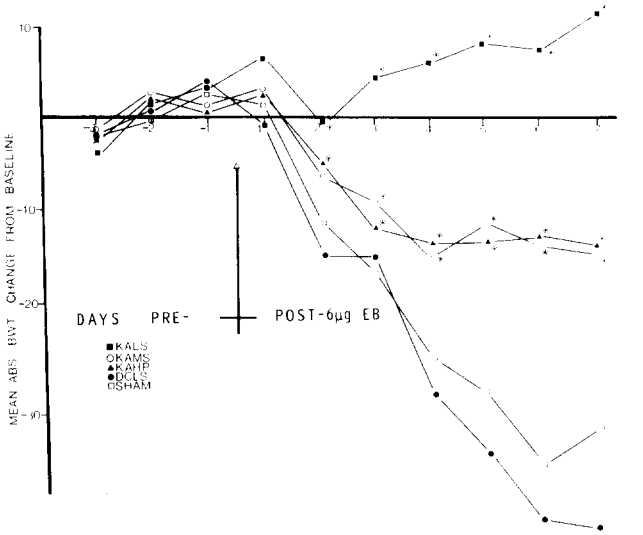

FIG. 3. Mean absolute change in body weight (BWt) from baseline in animals with neurotoxic, electrolytic or sham operated surgeries (same groups as shown in Fig. 2) for 3 days prior and 7 days following a 6 μg injection of estradiol benzoate (EB). Baseline was computed as the mean BWt gain for the 3 days prior to EB injection. *Significantly different from sham $p<0.05$.

Method

Throughout the experiment, BWts were monitored weekly and subsequently relative and absolute BWt gains were calculated. For the groups involved in the food intake study (KALS, KAMS, KAHP, DCLS, and shams), animals were placed in individual cages and given ad lib access to water and a high fat diet of Crisco and Purina Rat Chow (1:2) and BWt and food intake (FI) recorded daily. Following a 7 day baseline period, test animals received a single 6 μg injection of EB and FI and BWt were monitored for an additional 12 days. Daily changes in BWt from baseline and mean percent change in FI from baseline were calculated for each animal.

Results and Discussion

The weekly BWt gains post surgery for all seven groups of animals are shown in Table 4. Over a 16 week period both KALS and KAMS groups gained significantly more weight compared to shams. The KALS group continued to gain significantly more weight, compared to the shams, up to at least 20 weeks whereas by this time all other groups were comparable to shams (data not shown). Effects of the various lesions on the estrogenic control of daily FI and BWt gains are illustrated in Figs. 2 and 3. Prior to estrogen treatment (baseline), no differences in BWt gains or FI were observed between the groups. However, significant group differences were observed after the EB injection with respect to both BWt and FI. The typical anorexic effects of estrogen were confirmed in the shams which showed a significant decrease in BWt and FI. Likewise, the DCLS group exhibited a decrease in BWt and FI from baseline comparable to the sham animals. Both the KAMS and KAHP groups showed a significant decrease in BWt and FI from baselines;

however, these relative decreases were significantly less than those demonstrated by the shams. The KALS rats did not respond to the anorexic effects of EB and continued to gain in BWt and showed no significant change in FI from baseline following EB treatment.

The weekly BWt results reconfirm the previous finding by Nance [13] with respect to KALS lesions, and partially replicate the observation of Munoz and Grossman [10] with reference to the effects of KA lesions of the MS on energy balance. The most interesting result was the almost complete attenuation of the anorexic effects of estrogen shown by the KALS group. Thus the loss in behavioral responsiveness to estrogen shown by the KALS animals may account for the persistent increase in BWt shown by this group following brain surgery.

GENERAL DISCUSSION

In summary, the KALS group demonstrated (1) increase in OCH, (2) fewer percent days of vaginal estrus, (3) decrease in female sexual behavior, (4) increase in BWt, and (5) attenuation of the estrogenic control of FI and BWt regulation. The KAMS group exhibited (1) increase in male sexual behavior, (2) transitory increase in BWt, and (3) partial attenuation of the estrogenic control of FI and BWt regulation. KAHP animals, similar to the KAMS group, demonstrated a partial attenuation of the estrogenic control of FI and BWt regulation. IboLS rats exhibited (1) greater percentage of days of vaginal estrus, and (2) increase in female sexual behavior whereas the IboMS group exhibited a trend towards a decrease in OCH. The DCLS group demonstrated an increase in female sexual behavior.

The variety of behavioral alterations resulting from septal lesions appear to be correlated with the extent and/or location of septal damage as well as the specific neurotoxin. With regard to septal damage, extensive septal lesions (both LS and MS destroyed) have been shown to produce an increase in the behavioral sensitivity of female rats to sex steroids [5, 11, 12]. However, these alterations are limited to an increase in female sexual behavior. We have observed similar results in the present study following DCLS lesions. Contrary to these findings [5, 11, 12], we report here that more localized septal lesions (i.e., LS only) produce a variety of behavioral alterations which include a neurotoxin specific increase or decrease in the behavioral sensitivity to estrogen. Importantly, this finding demonstrates that more definitive KA lesions of the LS produce the same psychoneuroendocrine changes as less toxic doses of KA which do not produce obvious lesions of the LS [13].

The behavioral differences resulting from KA and Ibo septal lesions were surprising in view of the similar gross morphological damage produced by the neurotoxins (Fig. 1). In general, both Ibo and KA alter the overall sensitivity of female rats to estrogen and these changes are in the opposite direction. Three possibilities may account for these observed differences. First, it has been suggested that these neurotoxins affect different glutamate preferring receptor sites [18]. That is, KA primarily affects the excitatory receptors and Ibo the inhibitory receptor sites. Perhaps correlated with this, immediately following brain surgeries, KA induced a transitory hyperactivity whereas Ibo produced a transitory catatonic state in the rats. Secondly, these neurotoxins may selectively destroy different neuronal populations within the same area. In support of this, it has been shown that KA destroys pyramidal cells in the HP while Ibo destroys both pyramidal and granular cells in the same area [7]. Finally, the concurrent loss of neurons on the HP following KA infusions in the LS, but not Ibo, may contribute to the behavioral differences reported [5, 10, 13]. However, the present study suggests the the HP cannot be implicated in all the alterations in psychoneuroendocrine functions following KALS lesions. Therefore, a major site of action of the neurotoxins would appear to be receptor sites of a specific neuronal population or selective destruction of different neuronal populations within the septal area and/or hippocampus. One possible site of action for one or both of these neurotoxins may be the estrogen sensitive neurons located in the LS [17].

These neurotoxins have added new insight into the regulation of endocrine function. Until recently, it was accepted that the central nervous system control of the endocrine organs was mediated entirely through the pituitary. For example, it has been shown that complete septal ablations which altered uterine weight in the rat were associated with changes in FSH levels [21]. However, several findings now suggest a possible direct neural connection between the hypothalamus and the peripheral endocrine organs [4,14]. Recently, it has been suggested that the LS may also be involved in the neuronal control of the ovary [13]. The present study confirms the LS is involved in ovarian control and further suggests that the LS has a dual role in this modulatory process. The results also suggest a role for the MS in the control of ovarian function.

The neuronal control of gonadotropins, lordotic behavior, male sexual behavior, and feeding behavior is believed to be mediated by relatively discrete neural systems. The present data, combined with previous results, indicate that the MS has a dual role in the modulation of both male and female sexual behavior whereas the LS exerts both excitatory and inhibitory control on female sexual behavior. The increased BWt gains and the attenuation in the estrogenic control of FI and BWt following KA lesions of the LS suggest that the LS is a primary extrahypothalamic site involved in hormonal control of energy balance.

In conclusion, the present study illustrates the importance of the septum in the modulation of various psychoneuroendocrine functions. One common feature of all these systems is a hormone-brain interaction and one function of the septal area may be to modulate the action of sex steroids on brain function. Furthermore, the use of different neurotoxins in the present study indicates that the septal area may be involved in both inhibitory and excitatory modulation of various psychoneuroendocrine processes.

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