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Alterations in Brain Monoaminergic Functioning Associated with Septal Lesion Induced Hyperreactivity[1]

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BERNARD, B. K., J. R. BERCHEK AND D. A. YUTZEY. *Alterations in brain monoaminergic functioning associated with septal lesion induced hyperreactivity.* PHARMAC. BIOCHEM. BEHAV. 3(1) 121–126, 1975. – Thirty male albino rats, individually housed and receiving food and water ad lib were rated on 3 consecutive days for reactivity to handling. The animals were then assigned to behaviorally equivalent groups and received either bilateral septal lesions or a sham operation. Following two days of recovery, all animals received an additional behavioral testing session. Immediately following this last test, norepinephrine (NE) and dopamine (DA) levels, instantaneous rate constants (k), turnover times (TT) and utilization rates (K) as well as the levels of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in the hypothalamus, limbic system, cortex and pons-medulla were determined fluorometrically. Postoperatively, animals with septal lesions were significantly more reactive to handling, while the behavior of sham-operated controls remained essentially unchanged. Significant reductions in hypothalamic NE and DA and limbic DA were observed in the septal lesion animals. Catecholamine levels in other brain parts were unaffected as were 5-HT and 5-HIAA levels in all brain areas. Ratios of NE/5-HT in the limbic system were significantly reduced in animals which received septal lesions. Measures of catecholamine dynamics (k, TT, K) were unaltered by septal lesions. These results support the hypothesis of a catecholaminergic involvement in affective behavior but do not demonstrate any alteration in the functional dynamics of the brain monoamines associated with the hyperreactivity induced by septal lesions.

Septal lesions Hyperreactivity Hypothalamus Limbic system Cortex Pons-medulla Norepinephrine Dopamine Catecholamine dynamics Serotonin 5-Hydroxyindoleacetic acid

BRADY and Nauta [9] demonstrated that extensive damage to the rat forebrain septum results in a striking increase in reactivity to sudden and intense stimulation. Yet, in the twenty years which have passed, a structure-function explanation for the appearance for this septal syndrome has remained elusive (see Fried [13] for a review). Harrison and Lyon [14] attempted to localize the anatomical substrate for septal hyperreactivity by a structure-by-structure analysis of rat brains containing large septal lesions. From that study, it was concluded that hyperreactivity was not consistently related to any specific pattern of brain damage. More recently, other investigators have produced more discrete lesions within the forebrain septal region in an attempt to determine whether the appearance of hyperreactivity can be correlated with the destruction of one specific anatomical system. Turner [25], for example, has reported that damage to the nuclei and tracts of the stria terminalis is responsible for the syndrome. Schnurr [23], in a study with lesions within the anterior, middle, or posterior thirds of the septal region (apparently excluding the strial complex), observed that hyperreactivity was most commonly associated with damage to the anterior-dorsal area of the septum. These and other independent attempts at localization confirm the original conclusion of Harrison and Lyon that no single site of damage within the septum of the rat brain can completely account for the hyperreactivity syndrome.

Schildkraut and Kety [22] suggest that catecholamines, particularly norepinephrine, are implicated in emotional states and behavior. Recent developments in the biochemistry of aggression provide some evidence for the hypothesis that the emotional reactivity produced by brain damage may also involve catecholaminergic systems. Research by one of us (B.K.B.) has revealed correlations between brain catecholamine levels and dynamics, and different models of aggression: (1) shock-induced, con-

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specific aggression in rats [7], (2) isolation-induced conspecific aggression in mice [5], (3) spontaneous muricide (mouse killing) aggression in the wild rat [6], and (4) ranacide (frog killing) behavior in laboratory rats [2,3]. Similarly, septal lesions have been associated with increased aggressiveness as indicated by measures of: (1) shock-induced fighting [26], (2) shock-induced fighting following isolation [1], (3) reflexive fighting [8], and (4) muricide behavior [20]. Unfortunately, a simple equation relating emotional reactivity and aggression on the one hand, and catecholamine changes and brain damage on the other, is not possible since in several of these studies the appearance of, or recovery from the hyperreactivity syndrome has not been consistently associated with observed changes in aggressive behavior.

The indole monoamine, serotonin, has similarly been implicated in abnormal fluctuations of emotionality and mood [18]. Heller, *et al.* [15] found a 12–14 percent decrease in serotonin levels following septal lesions. This may not be surprising since histochemical findings indicate that the septal region is one of the serotonin rich parts of the brain [17]. It is possible that the lowering of brain serotonin levels, a postulated inhibitory transmitter [24], mediates the effects of septal lesions upon increased emotional behavior. However, two facts would seem to argue against such a proposal for animals with septal lesions: (1) parachlorophenylalanine, a depleter of brain serotonin, reduces hyperreactivity in septal rats [11,12], and (2) lowered levels of serotonin have been observed following recovery intervals sufficiently long to allow the dissipation of hyperreactivity [16].

The present study was undertaken to determine if the hyperreactivity induced by septal lesions was correlated with an alteration in the levels or dynamics of the brain monoaminergic systems. Since Bernard and Paolino [4] have demonstrated that whole-brain analyses of brain monoamines mask region-specific alterations, biochemical evaluations of physiologically distinct brain regions were undertaken. Regional levels of serotonin (5-HT), its metabolite 5-hydroxyindoleacetic acid (5-HIAA), norepinephrine (NE) and dopamine (DA) were obtained together with the rate constants and utilization rates of the catecholamines. This battery of neurochemical indices was expected to provide some indication of the effect of septal lesions on the central monoaminergic neuronal systems.

METHOD

Animals

Thirty male Wistar rats (90–110 days old), bred in our laboratory were weaned at 25 days and reared in pairs in stainless steel cages. Animals were housed in rooms maintained at 23°C and with a 12 hr light–dark cycle (light from 0600–1800). Two days prior to behavioral testing, and for the remainder of the experiment, animals were housed individually. Emotional reactivity was rated at 0700 on 3 consecutive days preceding surgery on a scale of 0 to 5 in each of 6 categories [19]. These categories were: (1) reaction to object presentation; (2) reaction to tap on back; (3) resistance to capture; (4) resistance to handling; (5) vocalization; and (6) urination and defecation.

Procedure

Final preoperative ratings were used in forming 2 behaviorally equivalent treatment groups for surgery. All animals were anesthetized with sodium pentobarbital (45 mg/kg i.p.). Septal lesion rats received bilateral electrolytic lesions which were produced by a 2 mA anodal current of 16 sec duration passed through a stainless steel insect pin, insulated except for 0.5 mm at the tip. The electrode was placed in the septal region at AP 7.6 mm, ML ± 0.5 mm, and DV 1.5 mm, using a head orientation with the incisor bar raised 5 mm above the interaural line in the stereotaxic instrument. Sham control animals underwent identical surgical procedures but no current was passed.

Two days postoperatively, all animals were again tested for emotional reactivity. Immediately following the behavioral test, one-third of each treatment group was decapitated. The remaining rats received an injection of alpha-methyl-para-tyrosine (200 mg/kg in 5% Tween 80, i.p.), and were then decapitated either 2 or 4 hr later. Possible group differences due to diurnal variation in brain monoamine levels were eliminated by sacrificing animals from the three subgroups in rotating order. Subgroups of each treatment group were also balanced with respect to postoperative emotionality.

Immediately upon decapitation, the brain was removed and the hypothalamus punched out using a cylindrical tool 5.04 mm in diameter. The remaining tissue was separated into cerebral cortex (supra-collosal tissue), limbic system (remaining sub-collosal tissue), and the pons-medulla (cerebellum excluded). Brain parts were stored on dry ice for not more than 4 days prior to fluorometric analysis by the method of Bernard and Paolino [4]. Levels of norepinephrine (NE), dopamine (DA), serotonin (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA) were determined for each brain region. Measures of the dynamic catecholamine neuronal functioning were also obtained using the enzyme inhibitor alpha-methyl-para-tyrosine [10]. These indices included the quantity of NE and DA turned over per hour (instantaneous rate constant, k), the time for the entire amine pool to turn over (turnover time, TT) and the utilization rate (rate constant multiplied by initial amine levels, K).

Standard errors of these measures were calculated using the derivations described by Bernard and Paolino [4]. Statistical evaluation of monoamine levels consisted of two-way analyses of variance [27] followed by Newman-Keuls analyses for pairs of means (Koehn, personal communication).

RESULTS

The effect of septal lesions on emotionality ratings can be seen in Table 1. Repeated measures analysis of variance indicated significant main effects for both lesion treatment, $F(1,28) = 130$, $p<0.001$, and test day $F(1,28) = 82$, $p<0.001$ and for the interaction between these two factors, $F(1,28) = 105$, $p<0.001$. Newman-Keuls analyses for pairs of means indicated that postoperatively, animals with septal lesions were significantly more emotional than either postoperative sham controls or their own preoperative emotionality ratings ($p<0.01$). The emotionality scores of the sham animals were unaltered by the experimental procedures.

The biochemical effects of septal lesions were analyzed in several ways. First, regional brain monoamine levels of control animals were compared to those with septal lesions. The analyses of the whole-brain amine levels (right hand column of Table 2) indicate a significant reduction in NE

TABLE 1

EMOTIONALITY RATINGS IN RATS BEFORE AND AFTER BILATERAL ELECTROLYTIC SEPTALS LESIONS*

Treatment	Test Days† Last Preoperative	Postoperative
Septal Lesion	4.97 ± 0.24	15.15 ± 0.91‡
Sham Operation	5.13 ± 0.16	5.66 ± 0.24

*Data analyzed using a two way, repeated measures ANOVA followed by Newman-Keuls analysis for pairs of means. Data expressed as Mean ± Standard Error (N = 15 per treatment)

†Table values are for ratings taken 24 hr prior to and 48 hr following surgery

‡$p<0.01$ (preop. septals vs postop. septals, postop. septals vs postop. shams)

TABLE 2

MONOAMINE LEVELS IN DISCRETE RAT BRAIN REGIONS 48 HR FOLLOWING SEPTAL LESIONS

	Limbic (783)	Hypothalamus (69)	Cortex (551)	Pons-Medulla (205)	Whole-Brain (1608)
Norepinephrine Levels*					
Septal Lesion	307 ± 16	1353 ± 64‡	274 ± 19	456 ± 27	358 ± 20†
Sham Operation	374 ± 26	1532 ± 56	325 ± 13	510 ± 38	426 ± 24
Dopamine Levels					
Septal Lesion	2689 ± 50‡	934 ± 30†	698 ± 138	176 ± 19	1574 ± 76†
Sham Operation	3317 ± 158	1214 ± 83	676 ± 121	167 ± 8	1924 ± 123
Serotonin Levels					
Septal Lesion	513 ± 24	846 ± 81	924 ± 48	692 ± 23	691 ± 35
Sham Operation	497 ± 33	939 ± 24	896 ± 51	754 ± 20	685 ± 37
5-Hydroxyindoleacetic Acid Levels					
Septal Lesion	521 ± 49	921 ± 67	253 ± 16	518 ± 40	446 ± 37
Sham Operation	491 ± 74	870 ± 28	303 ± 21	483 ± 52	442 ± 51

*Data expressed as ng/g tissue; Mean ± Standard Error (4<N<5); Weight of brain tissue (mg) in parentheses.

†$p<0.05$ (septal vs sham)

‡$p<0.01$ (septal vs sham)

and DA ($p<0.05$) in the septal group, while the levels of 5-HT and 5-HIAA were unaffected. Analysis of variance of monoamine levels in individual brain parts (remaining columns of Table 2) indicated a decrease in overall brain levels of NE, $F(1,32) = 11.39$, $p<0.005$, and DA, $F(1,32) = 16.81$, $p<0.001$, in the septal compared to sham animals. Newman-Keuls analyses for pairs of means indicated significant reductions of hypothalamic NE ($p<0.05$) and hypothalamic and limbic system DA ($p<0.01$ and $p<0.05$ respectively) in the septal group. A nonuniform distribution of the monoamines is evident from Table 2 where NE and DA are most highly concentrated in the hypothalamus and limbic system respectively. Although 5-HT concentrations were highest in the cortex and hypothalamus, the range of concentrations of this monoamine in the various brain regions was less than that observed for the catecholamines. The mean level of NE and DA in the cortex and pons-medulla as well as 5-HT and 5-HIAA levels in all brain areas under investigation were not significantly different in animals receiving septal lesions.

Since animals with septal lesions show a decrease in the mean group levels of NE and DA (within brain parts) while levels of 5-HT remain the same (Table 2), it might be suspected that a relative decrease in NE/5-HT or DA/5-HT ratios occurs in septal as compared to sham operated animals. However, when scores consisting of a ratio between NE or DA and 5-HT within each animal were analyzed using a two-way analysis of variance (Table 3), the results indicated that only the NE/5-HT ratio in the limbic region was significantly decreased by septal lesions ($p<0.05$). The hypothalamic NE/5-HT and DA/5-HT ratios in septal animals were not significantly different from the respective control values, despite differences in catecholamine levels for these regions.

While septal lesions significantly altered some regional brain levels of NE and DA, regional catecholamine dynamics as indicated by instantaneous rate constants were unaltered by brain damage (Table 4). The differences in instantaneous rate constants across brain regions and amines were the same across groups of animals. Similarly, septal lesions failed to alter catecholamine turnover times or utilization rates in any brain region studied (Table 5).

TABLE 3

REGIONAL CATECHOLAMINE TO SEROTONIN RAT BRAIN RATIOS 48 HR FOLLOWING SEPTAL LESIONS*

	Limbic System	Hypothalamus
NE/5-HT		
Septal Lesion	0.591 ± 0.038†	1.64 ± 0.11
Sham Operation	0.755 ± 0.039	1.63 ± 0.06
DA/5-HT		
Septal Lesion	5.29 ± 0.27	1.15 ± 0.13
Sham Operation	6.69 ± 0.57	1.30 ± 0.11

*Data are expressed as Mean ± Standard Error (N = 5)
†$p<0.05$ (sham vs septal)

DISCUSSION

These experiments demonstrate that hyperreactivity induced by septal lesions in rats is associated with decreases in whole-brain norepinephrine and dopamine levels. As suggested by Bernard and Paolino [7], however, the more region-specific alterations in brain monoamines may be masked in whole-brain analyses. Therefore, a further unique contribution of the present study is the finding that in septal rats, the reductions in hypothalamic NE, and hypothalamic and limbic DA are the major contributors to changes in whole-brain determinations as well. Alterations in catecholamine levels in the other brain regions under investigation were not significant. A recent article [21] suggested that septal lesions failed to alter whole-brain NE levels 6 days following surgery. They did report a small average decrease, which was not statistically significant because of the proportionally large variability in their data. The NE values obtained in the sham animals in the two studies were not significantly different. However, since their septal animals had lower whole-brain NE levels after 6 days of recovery (297 ng/gm) than did ours after only 2 days (358 ng/gm), it may be that the effect of septal lesions results in a time-dependent decline within the noradrenergic system.

The reduction in hypothalamic NE and DA and limbic DA did not uniformly affect NE/5-HT and DA/5-HT ratios. In fact, only limbic NE/5-HT ratios were significantly decreased thereby indicating an increase in the relative serotonergic dominance. According to the hypotheses of Tagliamonte *et al.* [24] and Bernard and Paolino [4] these results would be interpreted as indicating normal aminergic functioning in the hypothalamus and the possibility of NE acting as an inhibitory transmitter in the limbic region for this behavioral paradigm.

Yet, the functional significance of these alterations in brain amine levels remains obscure since alterations in the dynamics of the neuronal system did not accompany the

TABLE 4

FAILURE OF SEPTAL LESIONS TO ALTER DISCRETE RAT BRAIN REGION CATECHOLAMINE DYNAMICS*

	Limbic System	Hypothalamus	Cortex	Pons-Medulla
NE Instantaneous Rate Constant (k)				
Septal Lesion	0.216 ± 0.033	0.235 ± 0.023	0.234 ± 0.038	0.174 ± 0.018
Sham Operation	0.218 ± 0.039	0.204 ± 0.027	0.237 ± 0.023	0.206 ± 0.022
DA Instantaneous Rate Constant (k)				
Septal Lesion	0.222 ± 0.027	0.375 ± 0.046	0.151 ± 0.067	0.088 ± 0.052
Sham Operation	0.223 ± 0.029	0.491 ± 0.066	0.197 ± 0.045	0.182 ± 0.031

*Data expressed as Mean ($hour^{-1}$) ± Standard Error.

TABLE 5

FAILURE OF SEPTAL LESIONS TO ALTER CATECHOLAMINE TURNOVER TIMES (TT) OR UTILIZATION RATES (K) IN DISCRETE REGIONS OF RAT BRAIN

	Limbic System	Hypothalamus	Cortex	Pons-Medulla
Norepinephrine				
Septal Lesion				
TT*	4.63 4.02–5.46	4.26 3.88–4.71	4.28 3.68– 5.10	5.74 5.20– 6.41
K†	0.066 ± 0.009	0.318 ± 0.087	0.064 ± 0.010	0.079 ± 0.013
Sham Operation				
TT	4.59 3.89–5.59	4.90 4.34–5.64	4.22 3.84– 4.68	4.84 4.39– 5.41
K	0.082 ± 0.013	0.313 ± 0.086	0.077 ± 0.007	0.105 ± 0.020
Dopamine				
Septal Lesion				
TT	4.50 4.00–5.13	2.67 2.37–3.05	6.63 4.58–11.98	11.30 7.13–27.25
K	0.598 ± 0.134	0.350 ± 0.018	0.105 ± 0.097	0.016 ± 0.006
Sham Operation				
TT	4.48 3.96–5.16	2.04 1.80–2.35	5.09 4.14– 6.60	5.05 2.75– 6.63
K	0.740 ± 0.524	0.596 ± 0.105	0.133 ± 0.082	0.030 ± 0.006

*Turnover Times expressed as Mean (hours) ± limits for the 67% confidence interval.
†Utilization Rates expressed as Mean (μg/g/hr) ± Standard Error.

changes in levels. Bernard and Paolino [4] have demonstrated alterations in amine levels without changes in instantaneous rate constants or utilization rates as well as the reverse, that is, changes in amine dynamics without alterations in the levels of brain monoamines. The results of this study further confirm and extend these findings in that septal lesions failed to alter any measure of catecholamine dynamics, instantaneous rate constants, turnover times or utilization rates in any brain region despite changes in the levels of amines in some regions. It is possible that the decrease in catecholamine levels in the hypothalamus and limbic system was induced simply by septal lesion destruction of neuronal tissue. It would appear that the catecholamine neurons not destroyed by the lesion maintained their functional integrity as indicated by unaltered rate constants, turnover times and utilization rates.

Although the present study does demonstrate region-specific alterations in catecholamine levels, the serotonergic system was not affected by septal lesions. Previous research [15,16] which employed septal lesions to investigate monoaminergic functioning, reported decreased brain 5-HT, while no such changes were found in the present study. An explanation for these apparently contradictory results may be found in the recent work of Bernard and Paolino [4]. These authors reported a time-dependent increase in brain serotonin following castration which was just barely significant after 3 weeks but was quite marked by 6 weeks. Since a surgery-to-sacrifice interval of only 2 days was used in the present study, while the interval for the other lesion studies [15,16] was 25–50 days, these results are probably not contradictory. Again, the serotonergic effects of septal lesions, like the time-dependent catecholamine changes previously proposed, may depend on the postoperative recovery interval.

Varying the postoperative recovery interval for the purpose of investigating time-dependent biochemical changes has implications beyond the effects of brain damage upon brain biochemistry. The septal rat preparation if given sufficiently long periods of recovery (21 days or greater, depending upon treatment and strain), will no longer show the striking emotional reactivity characteristic of immediate postoperative observations [28,29]. Whether brain catecholamine levels return to normal, or whether increases in serotonin following long-term recovery from septal lesions are a function of the behavioral state of the animal at the time of sacrifice, are two questions inviting further investigation. In a series of studies by one of us (D.A.Y.) and co-workers [28,29] (Yutzey and Lieb, unpublished observations), it has been repeatedly noted that the return of normal behavioral reactivity after long recovery intervals is prevented if septal lesions are accompanied by additional damage to cortical or subcortical areas. This phenomenon appears to be nonspecific to any of the several anatomical loci of additional destruction attempted in these experiments. It remains to be seen whether principles of recovery of function, derived from the investigation of monoamine activity in animals with septal lesions alone, may also be applied to animal preparations having multiple brain lesions which postpone the recovery from the septal hyperreactivity syndrome.

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