Behavioral effects of lesions to the caudate nucleus or mediodorsal thalamus in neonatal, juvenile, and adult rats

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The prefrontal cortex, caudate nucleus, and mediodorsal thalamus are anatomically and behaviorally related. In the present study, the age-dependent lesion effects of caudate nucleus or mediodorsal thalamus damage were assessed using a spatial delayed alternation task known to be sensitive to prefrontal cortex damage. Bilateral electrolytic lesions were placed in the caudate nucleus or mediodorsal thalamus in rats making up three different age-at-surgery groups: neonatal (8-10 days), juvenile (25-27 days), and adult (150-160 days). All animals were allowed a 110-120-day postoperative recovery interval prior to behavioral testing. The subjects given either caudate nucleus or mediodorsal thalamus lesions as neonates were unimpaired in comparison to the juvenile or adult operates sustaining comparable brain damage. Both caudate nucleus and mediodorsal thalamus lesions produced in both juvenile and adult subjects severely retarded acquisition of the alternation task. The results are consistent with the hypothesis that the subcortical components of the prefrontothalamic system mature earlier than do the cortical components.

The prefrontal cortex, caudate nucleus (CN), and mediodorsal thalamic nucleus (MD) are anatomically (Beckstead, 1979; Divac, 1979; Divac, Kosmal, Bjorklund, & Lindvall, 1978; Krettek & Price, 1977; Leonard, 1969, 1972) and behaviorally (Divac, 1971, 1972; Kolb, 1977; Rosvold, 1972) interrelated. This has led to the suggestion that there is a "prefrontothalamic system" (Divac, 1971; Kolb, 1977; Rosvold, 1972), a system that has been identified in several mammalian orders (Markowitz & Pritzel, 1977).

In adult rats, selective lesions to mediofrontal (MF) or orbitofrontal (OF) cortex result in different behavioral impairments. Damage to the MF subfield impairs performance on several behavioral tasks requiring alternation or reversal of place learning. Lesions to the OF subfield leave place learning relatively unaffected, but they impair performance on tasks which require the animal to alternate or inhibit ongoing operant behavior. In addition, hyperactivity, hypodipsia, and hypophagia are often elicited by OF but rarely by MF cortex lesions. This double dissociation of behavioral functions after damage to the two major subdivisions of rat prefrontal cortex has been extensively documented (Divac, 1971; Johnston,

Hart, & Howell, 1974; Kolb & Nonneman, 1975; Kolb, Nonneman, & Singh, 1974; Nonneman & Corwin, 1981; Wikmark, Divac, & Weiss, 1973).

When lesions are placed in the CN (Divac, 1972; Gross, Chorover, & Cohen, 1965; Hannor & Bader, 1974; Kolb, 1977; Potegal, 1969; Schmaltz & Isaacson, 1968, 1972) or MD of adult rats (Gross et al., 1965; Kolb, 1977; Means, Harrell, Mayo, & Alexander, 1974; Means, Hunt, Whiteside, & Bates, 1973), the constellation of behavioral dysfunction resembles that following damage to the prefrontal neocortex. Although a double dissociation of "prefrontothalamic function" has not yet been clearly identified within the rat CN, it seems likely that such a separation exists, as the afferent and efferent prefrontothalamic fibers course principally through different sectors of CN (Beckstead, 1979; Krettek & Price, 1977; Leonard, 1972). Interconnections between MF cortex and MD travel through the anterodorsal sectors of CN; those between OF cortex and MD pass through more ventrolateral sectors of CN. Thus, anterodorsal CN lesions should produce behavioral impairments resembling those following MF cortex damage, while lesions placed in the ventrolateral CN should result in impairments resembling those seen after OF cortex damage. In a recent study, Thompson, Guilford, and Hicks (1980) reported that deficits in spatial learning ability follow anterodorsal, but not ventrolateral, CN damage. Their results thus suggest that a demonstration of double dissociation of function within CN is possible.

It would be difficult to demonstrate different locus-

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specific lesion effects following MD damage, as the surgical target is small and its projections to the prefrontal cortex arise from partially overlapping fields (Beckstead, 1979; Krettek & Price, 1977).

Not all of the behavioral effects produced by prefrontal cortex damage in adulthood are observed in rats given prefrontal lesions during infancy (Kolb & Nonneman, 1976, 1978; Kolb & Whishaw, 1981; Nonneman & Corwin, 1981). In general, the younger the rat at the time of surgery, the greater the behavioral sparing observed, but the severity of the deficit produced by surgery at a given age depends on the specific behavioral task as well as the prefrontal subfield removed (Kolb & Nonneman, 1976; Nonneman & Corwin, 1981). In fact, juvenile rats receiving MF lesions as late as 25 days of age are unimpaired in spatial alternation learning ability (Nonneman & Corwin, 1981), and no deficit is seen on this same task in infant rats, even after simultaneous removal of both the MF and OF cortex or complete anterior neocortical ablation (Vicedomini, Corwin, & Nonneman, 1982). Thus, following early damage to the cortical components of the prefrontothalamic system, considerable sparing of function occurs on a task that is seriously impaired by such damage in adolescent or adult rats.

In the present study, we examined the possibility that similar sparing of function might occur after early damage to the subcortical components of this system. Rats receiving CN or MD lesions as neonates, juveniles, or adults were tested 4 months later for spatial alternation learning ability.

METHODS

Subjects

Neonatal (8-10 days old at surgery), juvenile (25-27 days old at surgery), and adult (150-160 days old at surgery) Long-Evans hooded rats of both sexes from the Psychology Department's animal colony were used. For subjects in the neonatal or juvenile surgical groups, litters were culled to eight rats within 2 days of birth. All rats were weaned at 21 days of age and thereafter group housed (3-4 per cage) according to sex until about 75 days of age. For the remainder of the experiment the subjects were housed individually. The colony room environment was maintained at a constant temperature ($22^{\circ} \pm 1^{\circ}\text{C}$) and relative humidity ($45\% \pm 5\%$). A 12:12 light-dark cycle was maintained, with light onset at 8 a.m. All surgical procedures and behavioral testing were conducted during the light phase.

Neonatal ($n = 10$), juvenile ($n = 11$), and adult ($n = 13$) rats were given bilateral lesions to CN or MD. Additionally, 7 neonatal and 7 juvenile rats received sham lesions. A split-litter technique was used so that each surgical group was represented in every litter. The neonates were removed from the nest as a litter and returned to their mother as a litter following surgery. All subjects received equivalent postoperative recovery intervals (110-120 days) prior to behavioral testing.

Surgery

Anesthesia was produced in neonates by Ketaset (Ketamine hydrochloride 100 mg/cc), using a 1:12 dilution of the stock solution (.5 mg/kg) injected im. Chloral hydrate (330 mg/kg) was used to anesthetize the juvenile and adult operates.

Bilateral electrolytic (anodal dc) lesions were placed in CN or MD of neonatal and juvenile rats using stereotaxic coordinates obtained from the atlas by Sherwood and Timiras (1970). The stereotaxic coordinates for adult CN or MD lesions were taken from Pellegrino and Cushman's (1967) atlas. For both CN and MD lesions at each age, the following current parameters were used: adult, 1.5 mA, 20 sec; juvenile, 1.5 mA, 15 sec; neonate, 1.5 mA, 10 sec. Lesions produced in CN were intended to destroy only the anterodorsal sector, thus disrupting fibers interconnecting MD and MF cortex. Sham operations produced in neonatal and juvenile rats included all aspects of CN or MD lesions except that current was not passed through the lesioning electrode.

Behavioral Testing

The testing apparatus, a wooden T-maze painted flat gray throughout, has been described in previous studies (Kolb & Nonneman, 1977; Nonneman & Corwin, 1981). A modification of the spatial delayed alternation procedure described by Wikmark et al. (1973) was used. This spatial alternation task was chosen because performance on this task has been shown to be a reliable indicator of MF cortex integrity (Kolb & Nonneman, 1977; Nonneman & Corwin, 1981; Vicedomini et al., 1982).

Prior to initial training, the rats were gently handled daily and allowed to explore the maze. During this 7-10-day adaptation phase, food was not present in the maze, and the animals were allowed free access to food in the home cage. Then the animals were placed on a 23-h food deprivation schedule and pretrained 10 trials per day with food (hydrated Purina Rat Chow) available in both goal arms. During this pretraining phase, consecutive responses to the same arm were followed by forced choice to the previously nonchosen arm. This procedure was intended to discourage the formation of side preferences, and to ensure that the animal experienced reward in both goal arms. Pretraining was terminated when the rats ate readily on all trials for 2 consecutive days, a criterion most animals obtained within a few days.

During behavioral testing, the animals were required to spatially alternate their responses. A noncorrection procedure was used, and the position of the food cup on any trial depended on the animals' previous response. The first trial of each training session was always reinforced. On subsequent trials, a correct choice (alternation) was reinforced by 10 sec access to rat chow, after which the food cup containing the chow was moved to the other goal arm for the next trial. On nonalternation trials, when reinforcement was not obtained, the animal was blocked in the unbaited goal arm for 10 sec. After each trial, the animal was removed from the goal arm and placed into the startbox for the next trial. An error was scored if the animal entered the same goal arm on two consecutive trials; additional consecutive responses to the same goal arm were scored as perseverative errors. Ten trials per day were given until a criterion of 80% correct on 2 consecutive days or a maximum of 200 trials was observed.

Histological Procedures

At the completion of all behavioral testing, the rats were sacrificed with an overdose of chloroform and transcardially perfused with .9% saline followed by 10% Formalin in saline. The brains were removed and kept in 30% sucrose-10% Formalin for 2 weeks, and then cut on a freezing microtome at $35\text{ }\mu\text{m}$, mounted on slides, and stained with cresyl violet. Every fifth section throughout the extent of the CN or anterior thalamus was kept. The lesions were assessed by light microscopy and reconstructed on standardized diagrams adapted from the atlas by Pellegrino and Cushman (1967).

RESULTS

Behavioral

Figure 1 (upper panel) shows median and mean trials to criterion in acquisition of spatial delayed al-

Figure 1. Upper panel shows median trials to criterion in acquisition of spatial alternation; center panel shows median errors to criterion; lower panel shows median perseverative errors to criterion. Mean performance is indicated by solid triangles; performance range is indicated by vertical bars. Statistical results presented to the right of each panel are based on a two-tailed analysis. Group abbreviations: S=sham lesion, NCN=neonatal caudate nucleus lesion, NMD=neonatal mediodorsal thalamus lesion, JCN=juvenile caudate nucleus lesion, JMD=juvenile mediodorsal thalamus lesion, ACN=adult caudate nucleus lesion, and AMD=adult mediodorsal thalamus lesion.

ternation. The center panel shows median and mean errors to criterion, and median and mean perseverative errors to criterion are shown in the lower panel. Statistical comparisons between subjects given similar lesions at different ages and comparisons between lesioned and sham-operated subjects were made using Mann-Whitney U tests. The results of these analyses are shown in the upper right corner of each panel in Figure 1.

The findings of both trials and errors analyses reveal an identical pattern of results. Acquisition performance of neonatal CN or MD operates did not

differ from that of sham operates; however, each one of these groups differed significantly from the groups of subjects given CN or MD lesions as juveniles or adults. The performance of subjects receiving CN or MD lesions as juveniles did not differ reliably from those given comparable lesions in adulthood. The results for perseverative errors were the same, except that subjects receiving neonatal CN lesions differed neither from sham operates nor from subjects receiving CN lesions as juveniles or adults.

Anatomical

Reconstructions of maximum and minimum CN or MD lesions produced in each age group are shown in Figure 2. The smallest CN lesions in each age group were confined to the head of CN and extended caudally to include the medialmost anterodorsal sector of CN bordering the lateral ventricles. The largest CN lesions in each age group extended from the head of CN caudally into the body of CN. In these subjects, damage was confined to the anterodorsal sector of CN, except in one neonatal operate which sustained modest unilateral damage to ventrolateral CN. The smallest MD lesions in each group produced bilateral damage to the lateral and medial segments of MD (terminology of Krettek & Price, 1977). Subjects found to have the largest MD lesions suffered variable damage to the anterior nuclei, the anterior reticular nuclei, and the medial aspects of the ventromedial thalamic nuclei. Additionally, one subject in each age group given MD lesions sustained bilateral damage to the habenula and lateral thalamic nucleus.

Both CN and MD lesions produced in neonates were larger than those produced in juvenile or adult animals. Thus, the behavioral sparing observed in neonatally operated subjects is not dependent on differences in lesion size between neonatal and juvenile or adult operates. That is, behavioral sparing in neonatal operates occurred despite the fact that these subjects had larger CN or MD lesions.

DISCUSSION

The results of this study show that considerable sparing of function occurs following neonatal damage to the subcortical components of the prefrontothalamic system of rats, the caudate nucleus (CN) and the mediodorsal thalamus (MD). Comparable results have been obtained following neonatal damage to either prefrontal cortical subfield of rats (Kolb & Nonneman, 1978; Nonneman & Corwin, 1981).

In contrast, the effects of damage to the cortical components of the prefrontothalamic system of juvenile rats are less severe than the effects of damage to the subcortical components. In the present study, rats receiving CN or MD lesions at 25 days of age were as impaired as adult operates on a spatial alternation learning task. In a previous study

Figure 2. Reconstructions of minimum (shaded area) and maximum (shaded plus striped area) caudate nucleus and mediodorsal thalamus lesions. Group abbreviations are as in Figure 1.

(Nonneman & Corwin, 1981), rats receiving lesions of the mediofrontal (MF) cortex at 25 days of age were not impaired on the same task, whereas rats receiving comparable lesions at 40 days of age or later were seriously impaired. These results are consistent with suggestions that the subcortical components of the prefrontothalamic system mature at an earlier age than do the cortical components (Goldman, 1974; Sahley & Nonneman, 1979).

It does not seem likely that the behavioral sparing observed in this study depends on less complete destruction of the prefrontothalamic system in neonatal operates than in juvenile or adult operates. In fact, the neonatal lesions appeared to be more extensive than those produced in juvenile or adult animals. The CN lesions presumably destroyed the principle interconnections between MD and MF prefrontal cortex as well as the neurons of the anterodorsal caudate. The MD lesions were quite extensive and destroyed most of the afferent and efferent connections between MF and prefrontal cortex. This evidence of behavioral sparing after complete deafferentation of prefrontal cortex in infant rats is consistent with two recent reports of similar sparing following neonatal anterior decortication that caused almost complete degeneration of MD (Kolb & Whishaw, 1981; Vicedomini et al., 1982).

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