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BRIEF COMMUNICATION

Dorsal Hippocampal Lesion Does Not Affect Dopaminergic Indices in the Basal Ganglia

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LIPSKA, B. K., G. E. JASKIW, F. KAROUM, I. PHILLIPS, J. E. KLEINMAN AND D. R. WEINBERGER. *Dorsal hippocampal lesion does not affect dopaminergic indices in the basal ganglia.* PHARMACOL BIOCHEM BEHAV **40**(1) 181–184, 1991.—To determine the influence of intrinsic neurons of the dorsal hippocampus on dopamine (DA) turnover in other limbic areas, DA and its metabolites were assayed in several brain areas 14 and 28 days after bilateral ibotenic acid (IA) lesions of the dorsal hippocampus in the rat. The locomotor response to d-amphetamine was also assessed. Spontaneous locomotion was increased 14 but not 28 days postoperatively. There was no change in d-amphetamine-induced locomotion at any time. Presynaptic indices of DA turnover in the medial prefrontal cortex, anteromedial striatum and nucleus accumbens were not affected by the lesion. Unlike lesions of the medial prefrontal cortex, deefferentation of the dorsal hippocampus does not increase DA turnover in the basal ganglia.

Dorsal hippocampus Dopamine Ibotenic acid Amphetamine Locomotor response Nucleus accumbens

FUNCTIONAL interdependence may be a property common to several DA terminal fields (3,14). The hippocampus is a mesocortical DA terminal field (1,19) whose role in regulating other DA systems has not been well examined. Hippocampal lesions have been reported to reduce DA utilization in the nucleus accumbens (17), to increase the density of DA type-2 receptors in the nucleus accumbens and/or corpus striatum (15) and to affect exploratory behavior (13). Inferences based on these studies must be made cautiously, however. Anatomical and functional heterogeneity of the hippocampus precludes comparisons between studies where different hippocampal subregions were disturbed. Secondly, the ablative lesioning techniques used in many studies destroy axons of passage as well as intrinsic neurons. In contrast, excitotoxins demonstrate axon-sparing properties in several brain areas (2), including the hippocampus (8). Recently, we found that ibotenic acid (IA) lesions of the medial prefrontal cortex transiently increased amphetamine-induced locomotion and biochemical indices of presynaptic DA turnover in the basal ganglia (6). In the current study we tested the hypothesis that IA lesions of the dorsal hippocampus would affect DAergic transmission in the nucleus accumbens or corpus striatum in a similar fashion.

METHOD

Adult male Sprague-Dawley rats (Zivic Miller Labs, 200–250 g) were housed 3 to a cage under standard conditions (6). After induction of anesthesia with Equithesin 3 cc/kg (IP), animals were placed in a Kopf stereotaxic frame (tooth bar −2.5 mm from interaural line). Ibotenic acid (Sigma Chemical Co.) (5 μg/0.5 μl over 2.5 min) or vehicle (0.1 M phosphate-buffered saline, pH 7.4) was infused (Harvard Apparatus pump) through bilateral 26-gauge stainless steel cannulae (AP −3.0 mm, ML ±2.2 mm, VD −3.9 mm, with respect to bregma), which remained in place for an additional 5 min after infusion. Animals were tested between 9:00 a.m. and 1:00 p.m., 14 or 28 days after the surgery. Each animal was tested once only. Animals were transported in their home cages and immediately placed in clear Plexiglas activity monitors (42 × 42 × 30 cm) (Omnitech model RXYZCM 16). Spontaneous locomotor activity was measured during a 60-min habituation period. Each rat then received a saline injection (1 ml/kg IP) and was replaced in the photocell monitor for an additional 60-min period. At that point 1.5 mg/kg of D-amphetamine (Sigma) was administered and locomotor activity was recorded for a final 90 min.

Other, testing-naive rats with IA or sham lesion were sacrificed on the 14th or 28th postoperative days. These animals were acclimatized to the dissection area for 24 h prior to decapitation. Brain regions (anteromedial caudate, nucleus accumbens and medial prefrontal cortex) were dissected over wet ice from 2-mm thick sections as reported previously (6) and frozen at −70°C until analysis by mass fragmentography (9). Sixteen rats with ibotenic acid and 4 with sham injections were randomly selected

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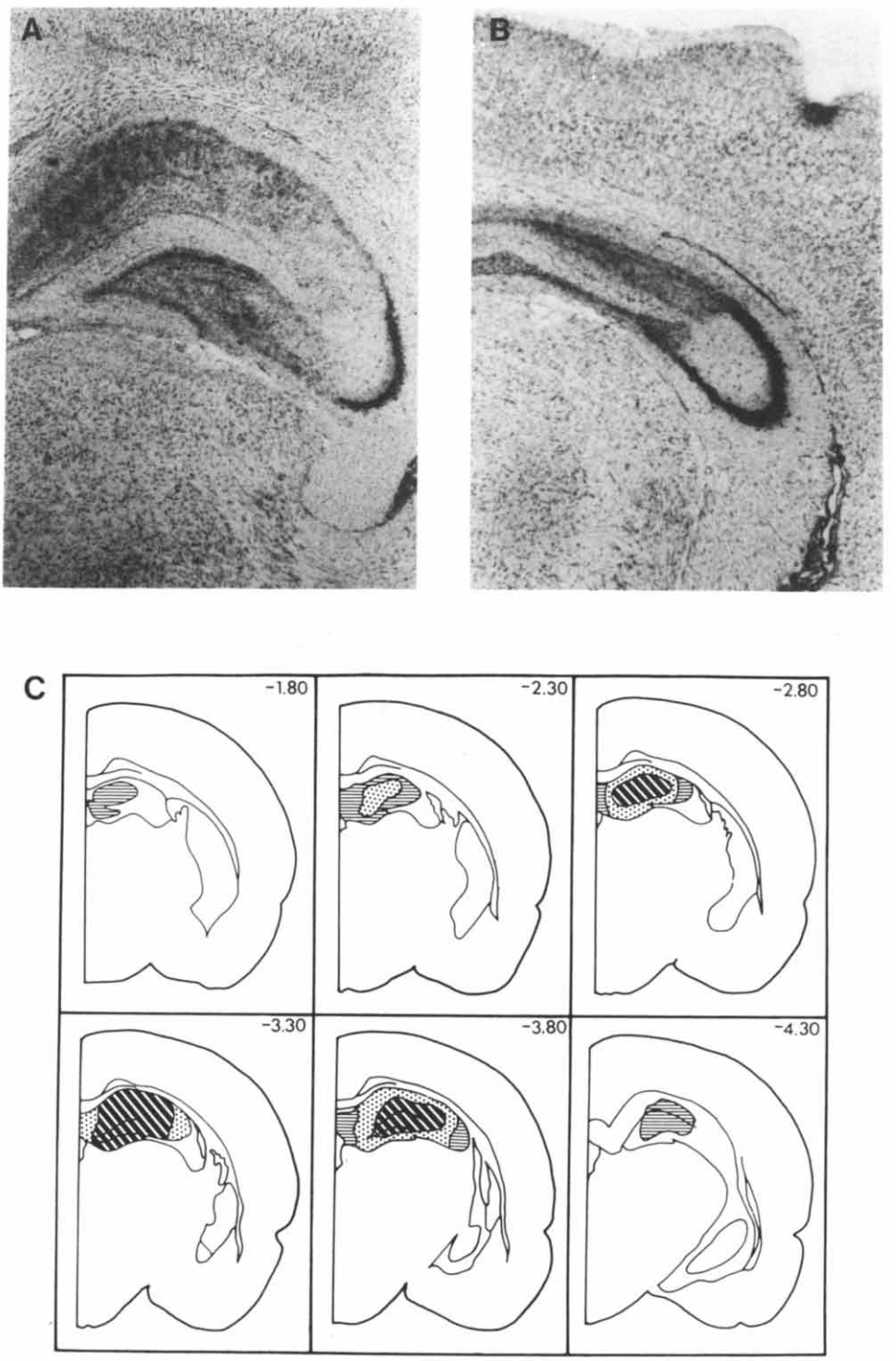

FIG. 1. Photomicrographs of cresyl violet-stained coronal sections through the dorsal hippocampus of the rat. (A) Rat sacrificed 14 days after surgery; (B) 28 days after surgery. Note the shrinkage of the lesioned hippocampus and sparing of pyramidal cells in the subfield CA2 and CA3. (C) Lesion boundaries defined as the area of neuronal absence and determined from cresyl violet-stained coronal sections from 16 rats with IA lesions of the dorsal hippocampus. Horizontal bars and the diagonal bars indicate the largest and smallest lesions, respectively. Stippling indicates the area encompassing the lesion boundaries in 10 rats.

14 and 28 days after the lesion and decapitated. The brains were quick frozen on dry ice. Cryostat sections were prepared and stained with cresyl violet. The outermost area of neuronal cell loss as determined by light microscopy was used to define the lesion boundaries. An average lesion was reconstructed that included the lesioned area within 10 rats. Data were expressed as

TABLE 1

CONCENTRATIONS OF DA AND METABOLITES AFTER IA LESION OF DORSAL HIPPOCAMPUS

	14 Days Postoperatively		28 Days Postoperatively	
	SHAM	IBO	SHAM	IBO
MPFC				
DA	0.92 ± 0.17(11)	0.94 ± 0.22(12)	1.15 ± 0.48(12)	0.92 ± 0.22(12)
DOPAC	0.54 ± 0.18	0.49 ± 0.13	0.54 ± 0.15	0.53 ± 0.19
HVA	0.88 ± 0.23	0.76 ± 0.21	0.74 ± 0.21	0.86 ± 0.23
DOPAC/DA	0.59 ± 0.13	0.54 ± 0.15	0.50 ± 0.15	0.59 ± 0.25
MCS				
DA	123.7 ± 14.0 (12)	126.6 ± 14.6 (12)	118.6 ± 11.4 (12)	113.8 ± 7.3 (12)
DOPAC	16.2 ± 2.5	15.4 ± 2.3	14.1 ± 1.8	14.2 ± 2.2
HVA	7.6 ± 1.6	7.5 ± 1.7	6.8 ± 1.6	7.5 ± 2.0
DOPAC/DA	0.13 ± 0.01	0.12 ± 0.01	0.12 ± 0.02	0.13 ± 0.02
NAS				
DA	66.0 ± 11.1 (11)	65.5 ± 16.7 (11)	79.8 ± 5.6 (11)	74.9 ± 8.0 (11)
DOPAC	18.0 ± 4.7	16.0 ± 1.8	19.9 ± 2.6	19.3 ± 4.4
HVA	3.9 ± 1.2	3.9 ± 1.1	4.3 ± 1.7	3.6 ± 0.8
DOPAC/DA	0.28 ± 0.08	0.26 ± 0.06	0.25 ± 0.03	0.26 ± 0.06

All values are expressed as ng/mg protein ± SD. Numbers in parentheses denote the number of animals used in the assay for a given brain area. Abbreviations: MPFC—medial prefrontal cortex; MCS—medial corpus striatum; NAS—nucleus accumbens.

mean ± standard error of the mean (SEM) and were analysed by a computer based Statistical Analysis System (SAS Institute Inc.). Behavioral and biochemical results were analysed by ANOVA and MANOVA respectively, followed by post hoc Newman-Keuls tests where appropriate.

RESULTS

There was neuronal loss and gliosis but no cavitation in the IA-lesioned dorsal hippocampus in fields CA1 and CA4, 14 and 28 days postoperatively. At both times a sharp boundary in the subfield CA2–CA3 in the most posterior sections, separating intact from degenerated cells, was observed. The IA-lesioned dorsal hippocampus was markedly reduced in volume by day 28. There were no histological changes in adjacent structures, in the ventral hippocampus and particularly in the subiculum (Fig. 1).

There were no main effects of time or lesion demonstrated by a two-way ANOVA of distance traveled on day 14, though a time × lesion interaction was evident, $F(4,15)=5.84$, $N=12$ per group, $p<0.05$. Newman-Keuls' comparisons showed that the distance traveled by the IA-lesioned rats during the 60-min acclimatization period was significantly greater than that of sham-lesioned animals (2879 ± 1834 cm vs. 1340 ± 803 cm, $p<0.01$). This effect was not present 28 days postoperatively ($F=1.6\times10^{-4}$, $N=12$ per group, $p=0.99$). At either 14 or 28 days after surgery, locomotion subsequent to saline or D-amphetamine injection was not significantly different between IA- and sham-lesioned animals. There was, however, a tendency towards increased locomotion after D-amphetamine administration in IA-lesioned rats on the 28th day postoperatively (14808 ± 4053 cm vs. 12093 ± 2930 cm, $F=3.4$, $N=12$ per group, $p=0.07$).

The concentrations of DA, DOPAC, HVA or the DOPAC/DA ratio in the anteromedial caudate, nucleus accumbens and medial prefrontal cortex did not differ between IA lesioned as compared to control animals either on the 14th or 28th day after surgery (Table 1).

DISCUSSION

As intended, the area of neuronal loss induced by IA was limited to the dorsal part of the hippocampus (CA1, CA2–CA3, CA4, dentate gyrus). Other investigators have demonstrated that such lesions do not damage axons passing through or afferents terminating in the hippocampus (8). The lesion induced a transient increase in spontaneous locomotor exploration but not in amphetamine-induced locomotion. While an augmentation of amphetamine-induced behaviors has been reported following hippocampal lesions (24), the earlier studies employed a different postoperative interval and testing modality, and induced ablative lesions that affected areas beyond the dorsal hippocampus. Behavioral effects appear also to be critically dependent on the location and extent of hippocampal lesions (12). Spontaneous locomotion has been found to be permanently increased after ventral or combined dorsal-ventral hippocampal lesions but only transiently augmented after dorsal hippocampal lesions (12). These results are consistent with our findings.

Our IA lesion did not affect presynaptic DA indices in the nucleus accumbens, anteromedial striatum or medial prefrontal cortex, limbic regions known to receive hippocampal afferents (4). One group has reported a transient decrease in nucleus accumbens DA utilization and in NE levels 7 days after hippocampal aspiration, but these indices normalized by day 28 (17). Striatal DA utilization was not affected at either time. In another investigation, no effect could be attributed to the hippocampal lesion per se (25). Thus aspiration lesions of different regions of the hippocampus have not in general been associated with consistent changes in presynaptic DA indices within limbic regions. Our data extend these observations to IA lesions confined to the dorsal hippocampus.

Our largely negative findings are surprising in light of numerous investigations linking the hippocampus and the basal ganglia. Uptake studies after transection of the fimbria/fornix, implicate glutamate (GLU) as the neurotransmitter in hippocampal projections to the corpus striatum (22) and nucleus accumbens (20–22). Our dissection provided tissue predominantly from the dorsomedial striatum and from the anterior accumbens (6), regions that on the basis of glutamate uptake studies after transection of the fimbria-fornix, are believed to receive glutamatergic innervation from the hippocampus (20–22). It is noteworthy, however, that the data provided by glutamate uptake

changes have not been uniformly supported by anatomic tracing studies (10,11). Recent evidence for convergence of DAergic and hippocampal afferents on common neuronal targets in the medial nucleus accumbens implicate primarily ventral hippocampus (16).

Insofar as IA lesions of the MPFC have been studied as an animal model of some aspects of schizophrenia, i.e., limbic DA dysregulation and a prefrontal defect (23) and the hippocampus has also been implicated in schizophrenia (18), a comparison of the effects of hippocampal lesion with the MPFC lesion was of interest. Notwithstanding the limitations noted above, we conclude that the short-term effects of excitotoxic dorsal hippocampal lesions appear to be quite different from those of the MPFC, though both are mesocortical DA terminal fields and both probably project to striatum and accumbens. Whether loss of the dorsal hippocampus is followed by a more subtle stress-dependent DA dysregulation, as is the case for the MPFC (5,7), remains to be determined.

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