Pergamon

Pharmacology Biochemistry and Behavior, Vol. 48, No. 4, pp. 1053–1057, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)E0074-R

BRIEF COMMUNICATION

The Effects of Combined Prefrontal Cortical and Hippocampal Damage on Dopamine-Related Behaviors in Rats

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Received 8 July 1993

LIPSKA, B. K., G. E. JASKIW AND D. R. WEINBERGER. *The effects of combined prefrontal cortical and hippocampal damage on dopamine-related behaviors in rats.* PHARMACOL BIOCHEM BEHAV **48**(4) 1053–1057, 1994.—The effects of excitotoxic damage to both the medial prefrontal cortex (MPFC) and the ventral hippocampus (VH) on behaviors related to mesolimbic/nigrostriatal dopamine (DA) transmission were investigated in the rat. Locomotor activity in a novel environment, after injection of saline, and after *d*-amphetamine was assessed 2 and 4 weeks after ibotenic acid lesion of both MPFC and VH in adult rats. In addition, stereotypic behaviors and locomotion after apomorphine were evaluated 8 weeks after the lesion. Locomotor activity was significantly enhanced in all testing conditions in lesioned rats as compared with sham-operated animals, while oral stereotypic behaviors elicited by apomorphine were attenuated possibly because they were eclipsed by excessive locomotion. These data indicate that coexisting lesions of the MPFC and VH in adult rats produce potent and long-lasting effects on behaviors believed to be dependent primarily on the mesolimbic DA system. The profile of changes resembles more closely that observed after excitotoxic lesions of the VH alone rather than that after separate MPFC lesion.

Prefrontal cortex Hippocampus Exploration *d*-Amphetamine Stereotypy Apomorphine Dopamine

BOTH the medial prefrontal cortex (MPFC) and the ventral hippocampus (VH) participate in regulation of subcortical DA transmission (7,8,17,20,26,31,38). While MPFC innervates dorsal and ventral aspects of the striatum (5,15,23) as well as the substantia nigra (SN) and ventral tegmental area (VTA), the sources of striatal dopaminergic innervation (16,30), VH projects mainly to the ventral striatum (6,13,24,29,32). We have previously suggested that differential effects of excitotoxic lesions of the MPFC or VH in adult rats on behaviors related to striatal DA transmission may be attributed to the differences in their projection sites (21).

We have also previously shown that excitotoxic damage of the VH in adult rats decreases DA turnover in the MPFC (20), and that the magnitude of this reduction is related to the enhancement of DA concentration in the nucleus accumbens. Thus, it seemed conceivable that the VH lesion may also exert its effects on the nucleus accumbens indirectly through the MPFC. If the latter were true, then MPFC lesions superimposed on VH lesions should significantly change the effects of VH lesions. We tested this hypothesis by evaluating the effects of combined excitotoxic VH and MPFC lesions.

METHOD

Surgery

Male Sprague–Dawley rats (Zivic Miller), weighing 220–240 g at the beginning of the study, were maintained under 12L : 12D cycle with food and water provided ad lib. After

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induction of anesthesia (Equithesin 3 ml/kg IP) and immobilization in a stereotaxic frame (Kopf Instruments), each rat received three infusions on each side of the brain. Vehicle (artificial CSF, pH = 7.4) in control rats (sham) or ibotenic acid (Sigma Chemical Co.) (10 μg/μl) in lesioned rats (lesion) was injected at a rate of 0.2 μl/min bilaterally into the medial prefrontal cortex (5 μg/0.5μl, AP +3.2 mm, ML ±0.7 mm, VD −3.4 mm) and ventral hippocampus (at two sites: 6 μg/2 × 0.3 μl, AP −4.4 mm, ML ±5.0 mm, VD −8.0 and −6.0 mm) through stainless steel cannulae by means of a microinfusion pump. The cannulae remained in place for 3 min after each injection.

Behavioral Testing

Two different cohorts of rats (n = 8 per sham or lesion group) were tested 2 and 4 weeks after surgery (total n = 32). On the day of testing, rats were moved to the testing area in their home cages. Animals were weighed and placed in Plexiglas cages equipped with photocell monitors (Omnitech model RXYZCM) for a 60-min habituation period (hab). Rats then received an injection of saline (1 ml/kg, IP) and their motor activity was recorded for another 60 min (saline). After that time, each rat was injected with *d*-amphetamine sulfate (amphetamine) (Sigma Chemical Co., 1.5 mg/kg, IP) and placed again in a monitored cage for 90 min. Locomotor activity (total distance traveled in cm) was recorded during each testing session.

Both cohorts tested in the first experiment were used again for assessement of apomorphine-induced stereotypic behavior 2 months after the lesion (n = 16 per sham or lesion group, total n = 32). Rats were transferred from their home cages to individual hanging metal cages (25 × 30 × 25 cm) with wire bottoms and faces. After a 3 h acclimatization, freshly prepared apomorphine (APO) (Sigma Chemical Co.) (0.75 mg/kg, SC) in distilled water was injected at 1300 h. Starting 10 min after injection, each rat was observed for 15 s at 5 min intervals during the 60-min period after injection. Locomotion, sniffing, licking, biting, and gnawing were scored during each interval. The intensity of stereotypic behavior was scored as follows: 1—fixed sniffing; 2—single short occurrence, 3—occasional bursts, 4—intermittent intense performance, 5—continuous intense performance of either licking, biting, or gnawing (oral stereotypies).

Following behavioral testing, randomly chosen rats from sham and lesion groups (n = 6/group) were euthanised by decapitation. Brains were removed and frozen on dry ice. Cresyl violet sections (20 μm) were evaluated by light microscopy.

Statistical Analysis

In the first experiment, two-way ANOVA with session (hab, saline, amphetamine) and status (sham or lesion) as independent factors and locomotor activity (total distance traveled in cm) as a dependent variable was used at each postoperative interval (2 and 4 weeks).

Locomotion data for each rat (present = 1, absent = 0) obtained from the stereotypy experiment were summed for the entire observation period, to yield a cumulative locomotion score (LOC). The scores assigned for the intensity of stereotypy were also summed to yield a total stereotypy score (TSS). Finally, the frequency of expression of high level oral stereotypies (if intensity score ≥3 is present = 1, if absent = 0) was summed for each animal over the entire testing period to yield a high level (oral) stereotypy score (HLS). *t*-Tests were used to compare the mean scores of LOC, TSS, and HLS in sham and lesion groups.

RESULTS

Nissl-stained coronal sections through the lesioned brains illustrated that neural loss and gliosis were confined to the intended regions (Fig. 1), as described previously (8,20). The prefrontal cortex is traditionally defined to be the cortical projection field of the mediodorsal nucleus of the thalamus (35). The MPFC lesion extended from the genu of the corpus callosum, and affected areas of cingulate cortex (Cg1-3), parts of infralimbic cortex, and orbital cortices (20). The VH lesion

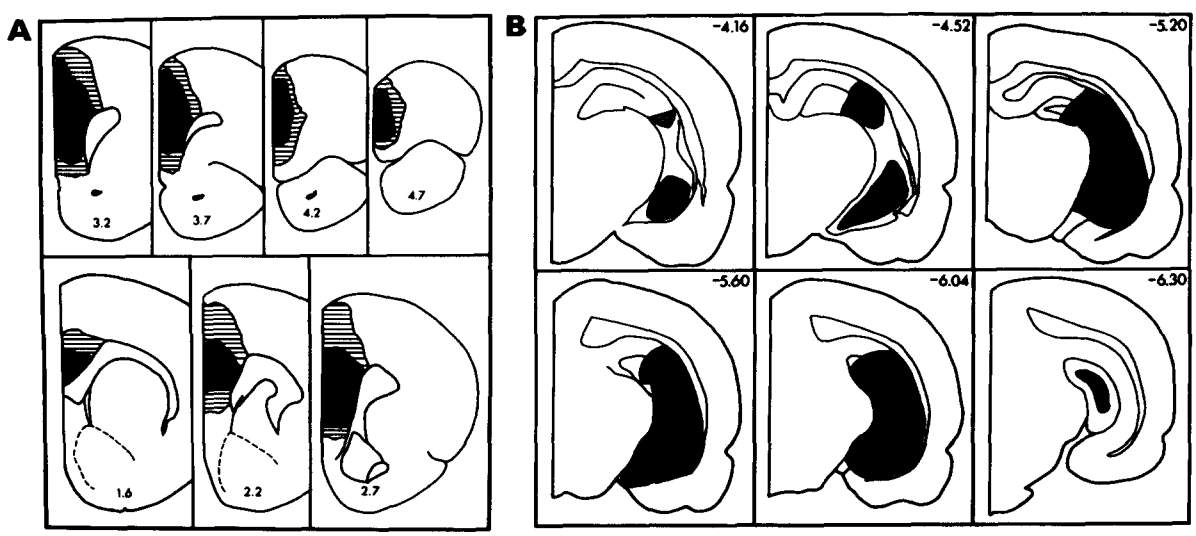

FIG. 1. Lesion boundaries defined as the area of neuronal absence and determined from Nissl-stained coronal sections from rats with combined ibotenic acid lesions of medial prefrontal cortex (A) and ventral hippocampal formation (VH). Lesioned areas do not overlap. Coordinates refer to distance in mm anterior (+) or posterior (−) to bregma. Blackened and striped areas indicate smallest and largest lesions, respectively.

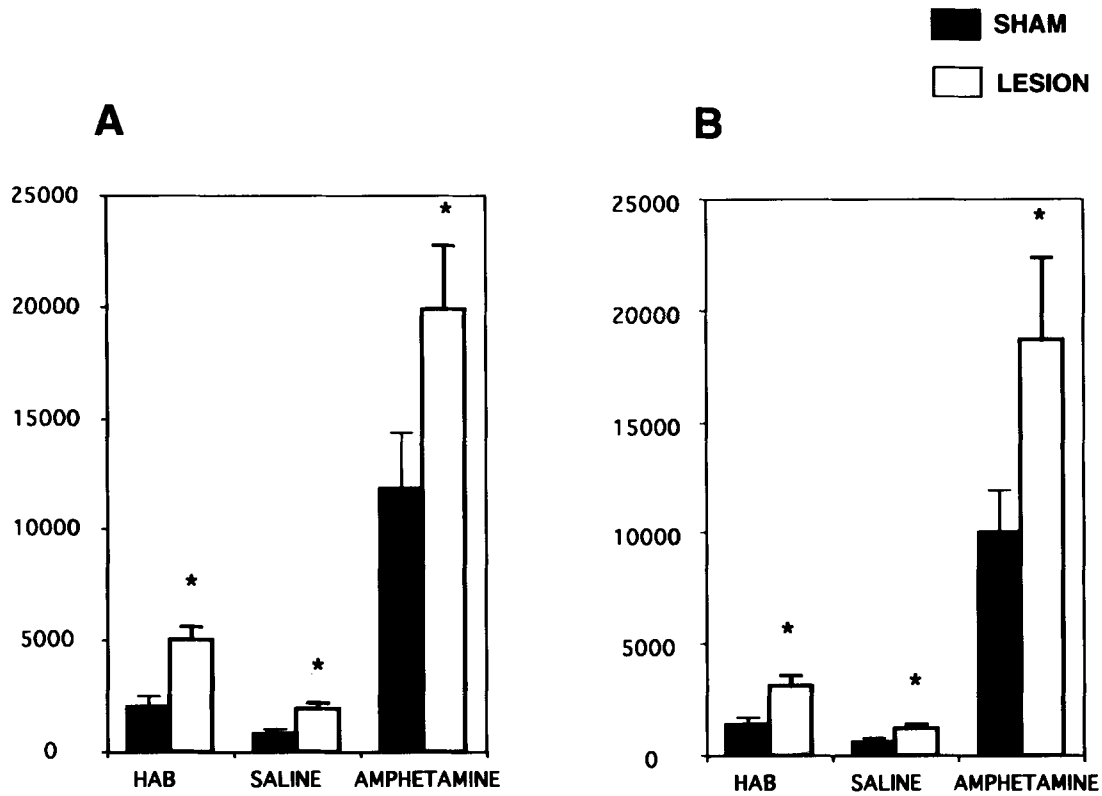

FIG. 2. Locomotor activity (total distance traveled in cm) in rats with combined control (sham) or ibotenic acid (lesion) lesions of medial prefrontal cortex and ventral hippocampus. Rats were monitored for 60 min in a novel environment (hab), for 60 min after injection of saline (saline), and for 90 min after amphetamine (1.5 mg/kg, IP, amphetamine). Testing was performed 2 (A) (n = 8 per group) and 4 weeks (B) (n = 8 per group) postoperatively. *Significantly different from a sham group ($p < 0.05$).

affected ventral-temporal parts of the hippocampal formation including dentate gyrus and subiculum, and spared the dorsal-rostral aspects of the hippocampus. The lesioned areas (MPFC and VH) did not overlap and there was no damage outside MPFC or VH.

Rats with the combined MPFC and VH lesion traveled a greater distance when exposed to a novel environment (hab), after saline injection (saline), as well as following administration of *d*-amphetamine (amphetamine) at both postoperative intervals (2 and 4 weeks after the lesion) as compared with their sham-operated counterparts ($p < 0.05$) (Fig. 2). ANOVA confirmed these differences. At 2 and 4 weeks postoperatively, there were significant main effects of status, $F(1,47) = 10.0$, $p = 0.003$, and $F(1,47) = 7.1$, $p = 0.01$, respectively, and session, $F(2,47) = 50.0$, $p = 0.0001$, and $F(2,47) = 40.5$, $p = 0.0001$, respectively. The status × session interaction was significant at 4 weeks postoperatively, $F(2,47) = 3.3$, $p = 0.05$, and showed a trend towards significance at 2 weeks after the lesion, $F(2,47) = 2.6$, $p = 0.08$. Lesion rats also manifested increased locomotor activity after administration of apomorphine ($p < 0.05$). However, oral stereotypic behavior was significantly attenuated ($p = 0.02$) and total stereotypy score tended to be reduced ($p = 0.1$) in lesion rats following apomorphine administration (Fig. 3).

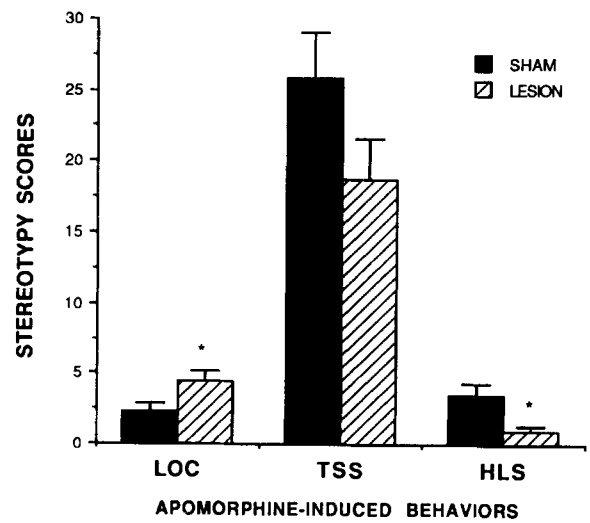

FIG. 3. Behavioral responses to apomorphine (0.75 mg/kg, SC) in rats with control (sham) or ibotenic acid (lesion) combined lesions of medial prefrontal cortex and ventral hippocampus. LOC—locomotion score, TSS—total stereotypy score (intensity of sniffing, biting, licking, or gnawing), HLS—high level oral stereotypy score (frequency of occurrence of intense licking, biting or gnawing). *Significantly different from a sham group ($p < 0.05$), n = 16 per group.

DISCUSSION

These results indicate that concurrent damage to the MPFC and VH produces profound and enduring effects on locomo-

tor activity in all testing conditions—in a novel environment, after saline injection, and after administration of *d*-amphetamine and apomorphine. Lesioned rats manifest, however, attenuated stereotypic responses to apomorphine.

We have previously demonstrated that separate ibotenic acid lesions of the MPFC or VH produce differential effects on these behaviors in adult rats. In particular, MPFC damage results in transient (present at 2 but not at 4 weeks after the lesion) enhancement in spontaneous locomotion, hyperlocomotion induced by the injection of saline or by amphetamine (8), and in enhanced stereotypic response to apomorphine accompanied by a reduction in locomotion evident 4–8 weeks postoperatively (1,21). This is in agreement with the results of other studies showing that desruption of the MPFC, either by deafferentation or deefferentation, results in increased DA transmission in the basal ganglia (7,8,19,22,25,26,28,34), potentiated apomorphine-induced stereotypies (28,36,39) and exaggerated responsiveness to stress (4,9,11) The VH lesion, in contrast, is associated with enduring effects on spontaneous exploratory activity and *d*-amphetamine-induced hyperlocomotion but not with hyperlocomotion after the injection of saline (20). Moreover, apomorphine-induced stereotypic behaviors are reduced in VH lesioned rats, while locomotor activity is markedly increased (21).

The differential modulation of behavioral responses associated with striatal DA-mediated transmission may result from differential output of the MPFC and VH both to the striatum and to the sites of their DA origin, VTA and SN. The MPFC innervates both the nucleus accumbens and anteromedial caudate putamen, and projects also directly to the SN and VTA (16,30). The VH projects almost selectively to the ventral striatum, i.e., nucleus accumbens (5,6,13,15,23,24,29,32) as well as indirectly to the VTA (32). Loss of glutamatergic pathways to the VTA may, in turn, affect DA release in the nucleus accumbens (12). Thus, the nucleus accumbens is the site where the effects of hippocampal and prefrontal cortical lesions overlap. Concurrent deefferentation of both MPFC and VH might then be expected to induce the most profound effects on behaviors dependent primarily on the nucleus accumbens. Present results confirm this assumption. Enhanced exploratory activity, hyperlocomotion induced by mild environmental stress (injection of saline), *d*-amphetamine-induced hyperactivity, and hyperlocomotion in response to apomorphine are all attributable to the increased DA activity predominantly within the nucleus accumbens (2,3,14,24,33). Reduced stereotypic response to apomorphine may also suggest such a possibility. As pointed out by others (27,37), apomorphine-induced locomotor activity and stereotypies may be reciprocally balanced (i.e., increase in expression of one of these behavioral measures results in reduction of the other). In other words, locomotion may interfer with stereotypic behaviors, and vice versa. If, as is believed, stereotypy is mediated within the dorsal striatum and exploratory locomotion within the nucleus accumbens (27), then the combined MPFC and VH lesion-induced enhancement in DA transmission primarily in the latter region would result preferentially in increased locomotion and, consequently, in blunting of stereotypic behaviors. Our data are consistent with this possibility.

These data indicate that concurrent damage of hippocampal and prefrontal cortical projections has severe consequences on the behavioral responses mediated by DA transmission within the nucleus accumbens, and that the profile of changes resembles most closely that observed after VH lesion alone. It is conceivable that the compensatory mechanisms either counteracting the effects of damage or leading to eventual normalization of at least some functions over time after separate lesions, fail in the case of more profound or more generalized insults (10,18).

In summary, a combination of MPFC and VH excitotoxic damage results in robust and enduring increases in behavioral measures linked primarily to the mesolimbic DA system. These results also indicate that the striatally mediated effects of adult VH lesions are not dependent on an intact MPFC.

REFERENCES

1. Braun, A. R.; Jaskiw, G. E.; Vladar, K.; Sexton, R.; Kolachana, B.; Weinberger, D. R. Effects of ibotenic acid lesion of medial prefrontal cortex on dopamine agonist-related behaviors in the rat. Pharmacol. Biochem. Behav. 46:51–60, 1993.
2. Clarke, P. B. S.; Jakubovic, A.; Fibiger, H. C. Anatomical analysis of the involvement of mesolimbocortical dopamine in the locomotor stimulant actions of *d*-amphetamine and apomorphine. Psychopharmacology (Berlin) 96:511–520; 1988.
3. Cools, A. R. Mesolimbic dopamine and its control of locomotor activity in rats: Differences in pharmacology and light/dark periodicity between the olfactory tubercle and the nucleus accumbens. Psychopharmacology (Berlin) 88:451–459; 1986.
4. Deutch, A. Y.; Clark, W.A.; Roth, R. H. Prefrontal cortical dopamine depletion enhances the responsiveness of mesolimbic dopamine neurons to stress. Brain Res. 521:311–315; 1990.
5. Fonnum, F.; Storm-Mathisen, Y.; Divac, I. Biochemical evidence for glutamate as neurotransmitter in corticostriatal fibers in rat brain. Neuroscience 6:863–873; 1981.
6. Groenewegen, H. J.; Vermeulen-Van der Zee, E.; Te Kortschot, A.; Witter, M. P. Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of phaseolus vulgaris leucoagglutinin. Neuroscience 23: 103–120; 1987.
7. Haroutunian, V.; Knott, P.; Davis, K. L. Effects of mesocortical dopaminergic lesions upon subcortical dopaminergic function. Psychopharmacol. Bull. 24:341–344; 1988.
8. Jaskiw, G. E.; Karoum, F.; Freed, W. J.; Phillips, I.; Kleinman, J. E.; Weinberger, D. R. Effect of ibotenic acid lesions of the medial prefrontal cortex on amphetamine-induced locomotion and regional brain catecholamine concentrations in the rat. Brain Res. 534:263–272; 1990.
9. Jaskiw G. E.; Weinberger D. R. Ibotenic acid lesions of the medial prefrontal cortex potentiate FG-7142-induced attenuation of exploratory activity in the rat. Pharmacol. Biochem. Behav. 36: 695–697; 1990.
10. Jaskiw, G. E.; Tizabi, Y.; Lipska, B. K.; Kolachana, B.S.; Wyatt, R. J.; Gilad, G. M. Evidence for a frontocortical-septal glutamatergic pathway and compensatory chnges in septal glutamate uptake after cortical and fornix lesions in the rat. Brain Res. 550: 7–10; 1991.
11. Jaskiw, G. E.; Weinberger, D. R. Ibotenic acid lesions of medial prefrontal cortex augment swim-stress-induced locomotion. Pharmacol. Biochem. Behav. 41:607–609; 1992.
12. Kalivas, P. W., Duffy, P.; Barrow, J., Regulation of mesocorticolimbic dopamine system by glutamic acid receptor subtypes. J. Pharmacol. Exp. Ther. 251:378–387; 1989.
13. Kelley, A. E.; Domesick, V.B. The distribution of the projection from the hippocampal formation to the nucleus accumbens in the rat: An anterograde andretrograde-horseradish peroxidase study. Neuroscience 7:2321–2335; 1982.
14. Kelly, P. H.; Seviour, P. W.; Iversen, S. D. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of

the nucleus accumbens septi and corpus striatum. Brain Res. 94: 507–522; 1975.
15. Kim, J. S.; Hassler, R.; Hang, P.; Paik, K. S. Effect of frontal cortex ablation on striatal glutamic acid levels in rat. Brain Res. 132:370–374; 1977.
16. Kolb, B. Functions of the frontal cortex of the rat: A comparative review. Brain Res. Rev. 8:65–98; 1984.
17. Lanier, L. P.; Isaacson, R. L. Activity changes related to the location of lesions in the hippocampus. Behav. Biol. 13:59–69; 1975.
18. Lashley, K. S. Brain mechanisms and intelligence. A quantitative study of injuries to the brain. New York: Dover Publications, Inc.; 1963.
19. Leccese, A. P.; Lyness, W. H. Lesions of dopamine neurons in the medial prefrontal cortex: Effects on self-administration of amphetamine and dopamine synthesis in the brain of the rat. Neuropharmacology 26:1303–1308; 1987.
20. Lipska, B. K.; Jaskiw, G. E.; Chrapusta, S.; Karoum, F.; Weinberger, D. R. Ibotenic acid lesion of the ventral hippocampus differentially affects dopamine and its metabolites in the nucleus accumbens and prefrontal cortex in the rat. Brain Res. 585:1–6; 1992.
21. Lipska, B. K.; Jaskiw, G. E.; Braun, A. R.; Weinberger, D. R. Prefrontal cortical and hippocampal modulation of haloperidol-induced catalepsy and apomorphine-induced stereotypic behaviors in the rat. (submitted).
22. Martin-Iverson, M. T.; Szostak, C.; Fibiger, H. C. 6-Hydroxydopamine lesions of the medial prefrontal cortex fail to influence intravenous self-administartion of cocaine. Psychopharmacology (Berlin) 88:310–314; 1986.
23. McGeer, P. L.; McGeer, E. G.; Scherer, U.; Singh, K. A glutamatergic corticostriatal path? Brain Res. 128:369–373; 1977.
24. Mogenson, G. J.; Nielsen, M. A. A. A study of the contribution of hippocampal-accumbens-subpallidal projections to locomotor activity. Behav. Neural Biol. 42:38–51; 1984.
25. Oades, R. D.; Taghzouti, K.; Rivet, J. M.; Simon, H.; LeMoal, M. Locomotor activity in relation to dopamine and noradrenaline in the nucleus accumbens, septal and frontal areas: 6-hydroxydopamine study. Neuropsychobiology 16:37–42; 1986.
26. Pycock, C. J.; Kerwin, R. W.; Carter, C. J. Effect of lesion of cortical dopamine terminals on subcortical dopamine in rats. Nature 286:74–77; 1980.
27. Robbins, T. W.; Mittleman, G.; O'Brien, J.; Winn, P. The neuropsychological significance of stereotypy induced by stimulant drugs. In: Cooper, S. J.; Dourish, C. T., eds. Neurobiology of stereotyped behaviour. Oxford: Clarendon Press; 1990:25–63.
28. Scatton, B.; Worms, P.; Lloyd, K. G.; Bartholini, G. Cortical modulation of striatal function. Brain Res. 232:331–343; 1982.
29. Sesack, S. R.; Pickel, V. M. In the rat medial nucleus accumbens, hippocampal and catecholaminergic terminals converge on spiny neurons and are in apposition to each other. Brain Res. 527:266–279; 1990.
30. Sesack, S. R.; Pickel V. M. Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. J. Comp. Neurol. 320:145–160; 1992.
31. Springer, J. E.; Isaacson, R. L. Catecholamine alterations in basal ganglia after hippocampal lesions. Brain Res. 252:185–188; 1982.
32. Swanson, L.; Cowan, W. M. An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. J. Comp. Neurol. 172:49–84; 1977.
33. Swerdlow, N.; Koob, G. The neural substrates of apomorphine-stimulated locomotor activity following denervation of nucleus accumbens. Life Sci. 35:2537–2544; 1984.
34. Tassin, J. P.; Stinus, L.; Simon, H.; Blanc, G.; Thierry, A. M.; LeMoal, M.; Cardo, B.; Glowinski, J. Relationship between the locomotor hyperactivity induced by A10 lesions and the destruction of the fronto-cortical dopaminergic innervations in the rat. Brain Res. 141:267–281; 1978.
35. Van Eden, C. G. Development of connections between the mediodorsal nucleus of the thalamic and prefrontal cortex in the rat. J. Comp. Neurol. 244:349–359; 1986.
36. Warenycia, M. W.; McKenzie, G. M.; Murphy, M.; Szerb, J. C. The effects of cortical ablation on multiple unit activity in the striatum following dexamphetamine. Neuropharmacology 26: 1107–1114; 1987.
37. Whishaw, I. Q.; Fiorino, D.; Mittleman, G.; Castaneda, E. Do forebrain structures compete for behavioral expression? Evidence from amphetamine-induced behavior, microdialysis, and caudate-accumbens lesions in medial frontal cortex damaged rats. Brain Res. 576:1–11; 1992.
38. Woodruff, M. L.; Baisden, R. H.; Fish, B. S. Forebrain catecholamine concentrations in the rat after neocortical and hippocampal lesions. Life Sci. 29:2603–2607; 1981.
39. Worms, P.; Willigens, M. T.; Continsouza-Blanc, D.; Lloyd, K. G. The effect of different types of cortical lesions on drug-induced catalepsy in rats: A pharmacological analysis. Eur. J. Pharmacol. 113:53–59; 1985.