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Hyperactivity Following Intradentate Injection of Colchicine: A Role for Dopamine Systems in the Nucleus Accumbens

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EMERICH, D. F. AND T. J. WALSH. *Hyperactivity following intradentate injection of colchicine: A role for dopamine systems in the nucleus accumbens.* PHARMACOL BIOCHEM BEHAV **37**(1) 149–154, 1990.—The role of dopamine systems in the nucleus accumbens (NA) in mediating the hyperactivity following colchicine-induced granule cell damage was investigated. In the first experiment adult Sprague-Dawley rats were bilaterally injected with 6-hydroxydopamine (6-OHDA; 8 μg/2 μl) or 0.5% ascorbate into the NA. Eight days later, rats received intradentate COLCH or CSF and were tested for locomotor activity 2, 4, 6, 8, and 10 days later. Intradentate COLCH produced a significant hyperactivity which was prevented by prior injection of 6-OHDA into the NA. Neurochemical analysis revealed that 6-OHDA decreased dopamine (80%) but not norepinephrine in the NA without altering either catecholamine in the striatum. In the second experiment animals were injected with COLCH or CSF in the dentate gyrus and immediately implanted with bilateral cannulae in the NA. Animals received intraaccumbens injections of CSF or d-ampehtamine (20 μg/1 μl) and were tested for locomotor activity. Amphetamine produced a significant increase in locomotor activity in both CSF- and COLCH-treated animals. However, COLCH produced an exaggerated response to the motor stimulating effects of ampehtamine. These results suggest that the destruction of dentate granule cells following colchicine results in a "functional" hyperactivity of the mesolimbic dopamine input to the NA which might disinhibit locomotor activity.

Hippocampus Nucleus accumbens Dopamine Locomotor activity Limbic system

THE hippocampus (HPC) is a limbic system structure that receives its primary afferent inputs from the polymodal association areas of the entorhinal cortex and from the medial septal nucleus (7). The HPC in turn projects to thalamic, hypothalamic, neocortical, and mesolimbic sites, which have been implicated in the modulation of cognitive, emotional, and locomotor behavior (10, 19, 30). Damage to the HPC, its intrinsic neuronal populations, or its network of afferent and efferent fibers, produces a constellation of behavioral deficits which are likely to reflect the influence of the HPC on a multitude of brain regions and behaviors. Thus, behavioral changes induced by neural damage probably represent the disrupted influence of the damaged structure on its efferent projection sites.

A consistent observation following hippocampal damage is a time-dependent increase in locomotor activity. Hyperactivity is observed following hippocampal ablations [see (7)], disruption of the cholinergic input to the HPC (34), or selective destruction of pyramidal cells in CA3 or granule cells in the dentate gyrus (5, 33, 35). While the neural substrates for this hyperactivity are not well understood, recent anatomical and electrophysiological studies indicate that altered mesolimbic systems might be responsible. Several limbic system structures, notably the HPC and amygdala, send excitatory projections to the nucleus accumbens (NA) (4, 10, 16, 22, 39). The NA is also the recipient of a large projection of dopaminergic fibers which originate in the ventral tegmental area (3). These DA afferents presynaptically inhibit the limbic system input to the NA and might bias limbic input to this structure in favor of either the HPC or the amygdala depending upon prevailing environmental and organismic variables (37–39). Several converging lines of evidence indicate that the NA is critically involved in the coordination and initiation of goal-directed motor behavior as well as the hyperactivity produced by psychomotor stimulants (1, 8, 9, 11, 12, 20, 22). Drugs such as amphetamine increase motor activity by enhancng the release of DA from

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terminals in the NA (11,12). Damage to the HPC might disrupt a critical limbic system-accumbens circuit that modulates motor behavior.

Hippocampal circuitry depends upon a series of synapses from entorhinal cortex to dentate granule cells to CA3 pyramidal cells to CA1 pyramidal cells to the subiculum, which in turn projects to a number of cortical and subcortical regions (19). Due to the sequential nature of information processing in the HPC, damage at any point along this pathway should disrupt the output of the subiculum to the NA and increase motor activity. Biochemical studies have in fact demonstrated that aspirative hippocampal lesions result in persistent alterations in the phosphorylation of membrane proteins as well as catecholamine levels in the NA (2, 6, 28). Therefore, the hyperactivity observed following hippocampal damage might share a common substrate with drug-induced hyperactivity; the alteration of dopaminergic mechanisms in the NA which direct motor behavior. Such a conceptual link would provide important insights into the nature of the behavioral changes observed following hippocampal damage as well as provide a further definition of the neural circuitry involved in goal-directed motor behavior and congitive function.

In the following experiments we examined the role of dopaminergic mechanisms in the hyperactivity induced by intradentate injection of colchicine (COLCH). Previous studies in our laboratory have shown that COLCH produces behavioral alterations, including hyperactivity, which are associated with a loss of granule cells in the dentate gyrus (33,35).

METHOD

Subjects

Male Sprague-Dawley rats (Charles River Breeders, Wilmington, MA) approximately 120 days old and weighing 300 grams were used in the following studies. The animals were individually housed in a temperature- and humidity-controlled colony room which was maintained on a 12-hr light/dark cycle with lights on at 0700 hr. Food and water were continuously available except during testing.

Intrahippocampal Injection of Colchicine

Immediately prior to surgery, rats were anesthetized with sodium pentobarbital (45 mg/kg) and positioned in a Kopf stereotaxic apparatus. Rats were bilaterally infused with either artificial cerebrospinal fluid (CSF = 150 mM NaCl, 2.9 mM KCl, 7.8 mM $MgCl_2$, 35.9 mM HCO_3 and 2.2 mM Dextrose) or 3.5 μg of COLCH (Sigma Chemical Co., St. Louis, MO) dissolved in CSF according to a previously described protocol (33), at the following coordinates: rostral = 2.0 mm posterior to bregma, 1.5 mm lateral to the sagittal suture, and 3.8 mm below the cortical surface: caudal = 3.8 mm posterior to bregma, 4.4 mm lateral, and 5.5 mm below the cortical surface (24). A total volume of 0.5 μl (0.125 μl/min) was delivered per site and the injection cannula was left in place for a period of two min following injection. Previous work from this laboratory has shown that this dose of COLCH produces an extensive and selective loss of dentate granule cells while sparing pyramidal neurons, basket cells, and local circuit neurons throughout the HPC (33,35).

Motor Activity

In Experiment 1 locomotor activity was measured in 6 annular activity chambers which were individually housed in light- and sound-attenuated chambers. Each activity chamber consisted of a circular runway 9 cm wide with 20 cm high walls and an outside diameter of 31 cm. Six pairs of photocell sensors were mounted in the outer wall of the runway at equal distances 1 cm above the wire mesh floor. The cumulative frequency of photocell interruptions was automatically recorded for 10-min intervals for a period of 60 min.

Neurochemical Analysis

At the conclusion of behavioral testing animals were sacrificed by decapitation, their brains were removed, and striata and NA dissected on ice. Individual brain areas were homogenized in 2 ml of dibasic sodium phosphate. From this homogenate, 1 ml was removed and placed in 500 μl of 0.4 N perchloric acid and frozen for subsequent analysis of DA and norepinephrine.

Concentrations of DA and norepinephrine in the striatum and NA were determined by reverse-phase high performance liquid chromatography with electrochemical detection using 5-hydroxy-N-methyltryptamine and dihydroxybenzylamine as the internal standard (14,18). Protein content of tissue was determined according to Lowry *et al.* (17).

Statistical Analysis

Overall treatment effects were assessed with either a one- or two-way analysis of variance (ANOVA), depending on the occurrence of multiple factors or repeated measures, according to a mixed-model ANOVA (36). Appropriate pair-wise comparisons were performed with a Fisher's Least Significant Difference (LSD) test (13). Acceptable statistical significance was established as $\alpha < 0.05$.

Experiment 1

The first experiment examined whether destroying the dopaminergic innervation of the NA would alter the expression or time course of COLCH-induced hyperactivity. The increased locomotor activity induced by such psychomotor stimulants as amphetamine is related to an enhanced release of DA in the NA (9, 11, 12, 15). As previously discussed, disruption of the hippocampal output to the NA might alter the influence of dopaminergic afferents from the ventral temental area and lead to changes in locomotor activity. To address these questions the first experiment examined whether 6-OHDA-induced depletion of DA in the NA would alter the degree or temporal characteristics of hyperactivity following intradentate injection of COLCH. If this pharmacological manipulation was able to attenuate the hyperactivity associated with hippocampal damage this could suggest that a common neural substrate subserves the hyperactivity induced by hippocampal damage as well as that produced by psychomotor stimulants.

The rats were tested in a series of experiments involving the following sequence of events. 1) Presurgery locomotor activity levels were recorded for 30 min 2) Twenty-four hr later rats were stereotaxically injected with either 6-OHDA or artificial CSF into the NA. Prior to surgery rats received an intraperitoneal injection of the norepinephrine reuptake blocker desmethylimipramine (25 mg/kg). Thirty min following DMI rats were bilaterally injected with either 6-OHDA (8 μg free base/2 μl prepared in a solution of 0.5% ascorbate in CSF) or the ascorbate vehicle into the NA at the following coordinates: 3.4 mm anterior to bregma, 1.7 mm lateral to the sagittal suture and 7.2 mm below the cortical surface. Pilot experiments verified that these coordinates and injection parameters produced a selective and extensive decrease of DA in the NA. 3) Seven days following surgery locomotor activity was assessed for 30 min. Immediately following this assessment of postoperative baseline activity rats were removed from the chambers

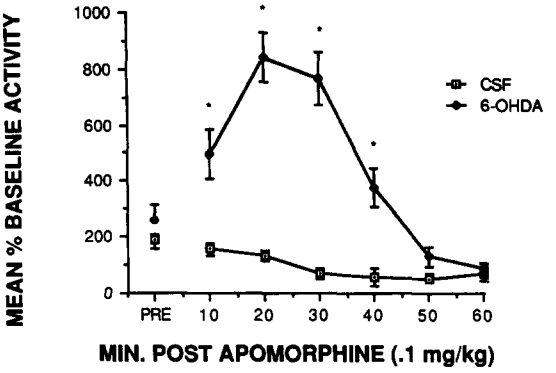

FIG. 1. The effects of apomorphine (0.1 mg/kg) on locomotor activity 7 days following injection of 6-OHDA or artificial CSF into the nucleus accumbens. Data are presented as mean (± SEM) activity counts. *$p<0.05$ vs. CSF controls, Fisher's LSD test.

injected with 0.1 mg/kg apomorphine hydrochloride or vehicle and returned to the activity chambers for an additional 60-min period. This dose of apomorphine has been shown to produce an accentuated locomotor response commensurate with the degree of DA loss in the NA. Six hydroxydopamine-treated animals which exhibited a significantly enhanced response to this apomorphine challenge were used in the subsequent experiments. 4) Twenty-four hr following the apomorphine challenge rats were bilaterally injected with either COLCH (CSF-COLCH; 6-OHDA-COLCH) or CSF (CSF-CSF; 6-OHDA-CSF) into the dentate gyrus using the surgical protocol previously described. 5) Locomotor activity was assessed for a 30-min test period on days 2, 4, 6, 8 and 10 following COLCH. 6) Twenty days following surgery all rats were sacrificed by decapitation and the striatum and NA were removed and subsequently analyzed for DA and NE content.

RESULTS

Apomorphine Challenge

The groups injected with 6-OHDA exhibited a significantly enhanced locomotor response to the apomorphine challenge. A two-factor repeated ANOVA revealed significant treatment [$F(1,27)=42.55$; time, $F(5,135)=39.17$; and treatment by time, $F(5,135)=30.54$, effects, all p's<0.0001]. Post hoc analyses, using a Fisher's LSD test, revealed that the 6-OHDA group was significantly ($p<0.05$) more active (3–10-fold) than the control group up to 40 min following injection of apomorphine. In contrast, the group injected with CSF into the NA exhibited no increase in motor activity following this low dose of apomorphine (see Fig. 1).

TABLE 1

EFFECTS OF 6-HYDROXYDOPAMINE ON REGIONAL LEVELS OF DOPAMINE AND NOREPINEPHRINE

Group	Dopamine	Norepinephrine
	Nucleus Accumbens	
CSF-CSF	38.98 (4.66)	6.54 (2.00)
6-OHDA-CSF	7.49 (1.06)*	10.60 (2.87)
CSF-COLCH	42.82 (5.68)	13.67 (3.42)
6-OHDA-COLCH	9.52 (2.40)*	10.18 (2.49)
	Corpus Striatum	
CSF-CSF	61.89 (6.84)	4.85 (0.55)
6-OHDA-CSF	62.22 (5.73)	4.89 (0.52)
CSF-COLCH	78.61 (11.85)	3.96 (0.65)
6-OHDA-COLCH	65.98 (14.44)	4.99 (0.50)

Data are presented as mean ng/mg protein (± SEM) concentrations of compound. Rats were sacrificed 20 days following intradentate injection of CSF or COLCH (28 days following intraaccumbens CSF or 6-OHDA).
*$p<0.01$ vs. the appropriate control group, Fisher's LSD test.

Effects of 6-OHDA on Colchicine-Induced Hyperactivity

COLCH produced a significant increase (65–126% over control values) in locomotor activity that was evident 2, 4, and 6, but not 8 or 10 days following surgery. At the later two time points, the CSF-COLCH group was 65% more active than the CSF-CSF group but this was not significant due to a high degree of variability. Prior administration of 6-OHDA into the NA blocked the development of the hyperactivity. A two-way repeated ANOVA demonstrated a significant treatment effect, $F(3,12)=4.96$, $p<0.01$, but insigificant time, $F(4,100)=1.02$, $p>0.10$, effect. The results of the post hoc analyses are represented in Fig. 2. The 6-OHDA-COLCH group exhibited no hyperactivity and in fact the activity of this group was comparable to that observed in the control groups. 6-OHDA alone (6-OHDA-CSF) had no effect on locomotor activity. Thus, selective reduction of DA in the NA prevented the development of hyperactivity observed following intradentate injection of COLCH.

Neurochemistry

Bilateral injection of 6-OHDA into the NA produced an

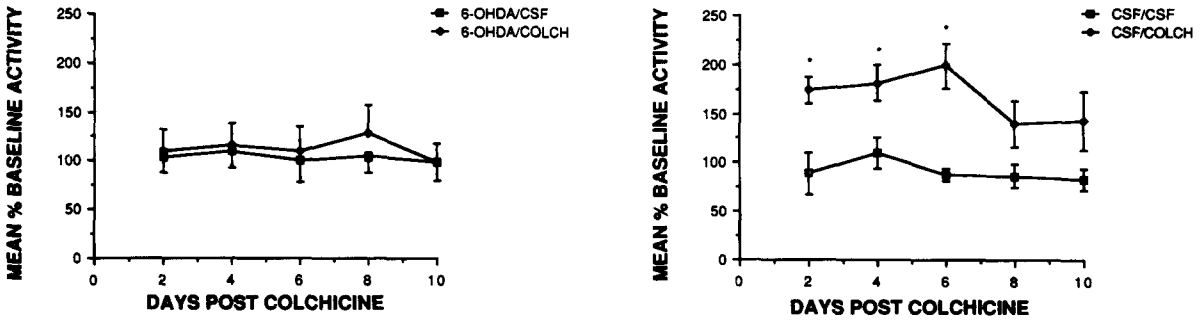

FIG. 2. Prevention of colchicine-induced hyperactivity (right panel) by prior injection of 6-OHDA into the nucleus accumbens (left panel) assessed 2, 4, 6, 8, and 10 days following colchicine. Data are expressed as mean (± SEM) of activity counts. *$p<0.05$ vs. CSF/CSF controls, Fisher's LSD test.

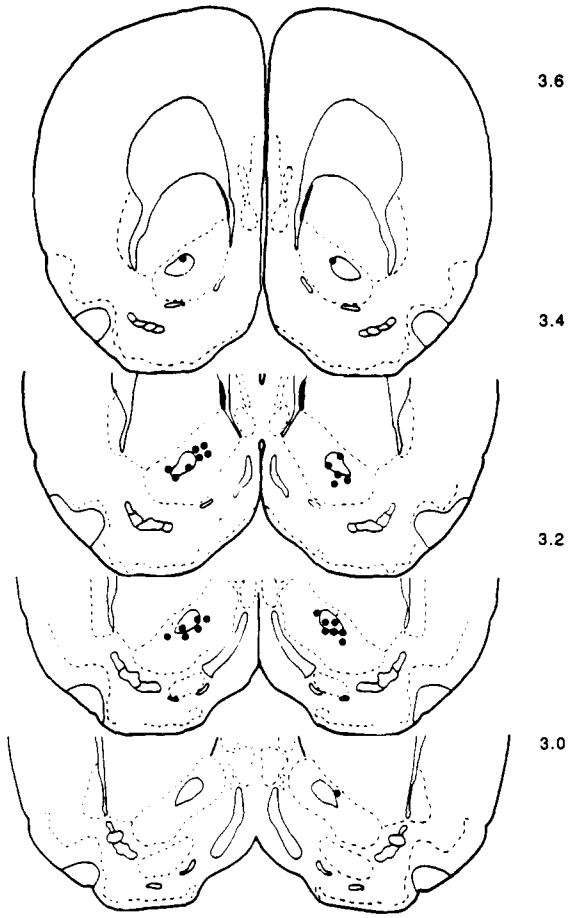

FIG. 3. Representative sections through the rat brain indicating the location of cannula placements into the nucleus accumbens. Each circle represents the location of the cannula tip in a single animal. Numbers represent the distance from bregma. See text for details.

extensive (80%) and specific decrease of DA in this structure in both CSF- and COLCH-treated groups (Table 1). A one-way ANOVA revealed a significant treatment effect for DA concentrations in the NA, $F(3,26) = 19.09$, $p<0.001$. Post hoc analyses using Fisher's LSD test demonstrated that both groups injected with 6-OHDA (6-OHDA-CSF and 6-OHDA-COLCH) had significantly ($p<0.05$) lower concentrations of DA in the NA than the two control groups (CSF-CSF and CSF-COLCH). The degree of DA loss was comparable in the 6-OHDA-CSF group and the 6-OHDA-COLCH group ($p>0.10$). There were no concurrent decreases of NE in the NA, $F(3,27) = 1.12$, $p>0.10$, or of either DA, $F(3,27) = 0.57$, $p>0.10$, or NE, $F(3,27) = 0.72$, $p>0.10$, in the corpus striatum.

Experiment 2

The second experiment examined whether the microinjection of d-amphetamine, a drug that promotes the release of DA, into the NA would produce a significantly enhanced locomotor response in rats previously receiving intradentate COLCH. If the hippocampal damage induced by COLCH functionally disinhibits dopaminergic mechanisms in the NA, then the injection of amphetamine into this terminal region should further exaggerate the relevant behavioral response.

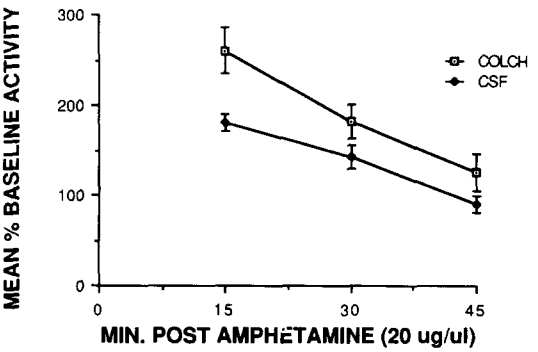

FIG. 4. Effects of injections of amphetamine (20 μg/1.0 μl) into the nucleus accumbens on locomotor activity 14–17 days following intradentate injections of colchicine or artificial CSF. Data are expressed as mean (±SEM) of activity counts. *$p<0.05$ vs. CSF controls.

In the following experiment rats were implanted with bilateral guide cannulae in the NA and housed individually throughout the course of the experiment.

Locomotor activity was assessed in 4 rectangular photocell chambers. Each chamber was made of black Plexiglas and measured 43 cm long, 21 cm wide and 18 cm high. One row of photocells (5.5 cm high) divided the chamber into seven equal sections. Each interruption of a photobeam constituted one activity count and the cumulative frequency of photocell interruptions was automatically recorded by a Commodore 64 computer. Pilot studies verified that the degree of locomotor activity observed in these boxes in controls and COLCH-treated rats was comparable to that previously observed in the annular activity devices.

Seven days following the assessment of motor activity, rats were bilaterally injected with COLCH or CSF into the dentate gyrus according to the previously described protocol. Immediately following the stereotaxic injections bilateral stainless steel cannulae prepared from stainless steel tubing (outer diameter = 0.018 in., internal diameter = 0.004 in.) were placed into the NA at the following coordinates: 3.4 mm anterior to bregma, 1.7 mm lateral to the sagittal suture and 6.2 mm ventral to the surface of the brain. Animals received intraaccumbens injections of CSF (14 days postsurgery) and 20 μg of d-amphetamine 3 days later (20 days postsurgery). Bilateral intracerebral microinjections were performed using injector cannulas which extended 1 mm beyond the cannula tip. Injectors were connected to a 10 μl Hamilton syringe by PE-10 tubing and all drugs were administered in a volume of 1 μl over a 3-min period. Following infusion the injection cannula was left in place for two min to allow for diffusion of the perfusate. Locomotor activity was assessed for 15 min prior to the intraaccumbens injections. Following this baseline assessment the rats were removed, injected with CSF (Day 14) or 20 μg of d-amphetamine sulfate (Day 17) and returned to the activity chambers for 45 min. Three days later all rats were injected with 1 μl of cresyl violet for verification of cannulae placements.

RESULTS

Figure 3 illustrates that all cannula placements were within the NA.

The bilateral injection of d-amphetamine into the NA produced a significant time-dependent increase in locomotor activity which was evident in both the CSF- and the COLCH-treated groups. The COLCH group, however, exhibited an enhanced response to d-amphetamine (Fig. 4). A two-way repeated ANOVA revealed significant treatment, $F(1,13) = 13.66$, $p<0.01$, and time effects,

$F(2,26) = 17.96$, $p<0.05$, but a nonsignificant treatment by time interaction, $F(2,26) = 0.88$, $p>0.10$. Post hoc analysis of the individual time blocks, using a Fisher's LSD test, revealed that the COLCH group exhibited a significantly ($p<0.05$) greater increase in motor activity during the first 15 min following injection. The COLCH group remained 26–46% more active than the CSF group during the later time blocks, but these differences were not statistically significant. The lack of a treatment by the time interaction indicates that the time course of d-amphetamine-induced hyperactivity was comparable in both groups.

DISCUSSION

The present series of experiments indirectly examined the involvement of the mesolimbic DA system in the hyperactivity induced by intradentate injection of COLCH. This treatment produced a time-dependent increase in locomotor activity that was blocked by the selective destruction of DA terminals in the NA by 6-OHDA. While baseline levels of motor activity were not affected by 6-OHDA the hyperactivity induced by intradentate COLCH was abolished. The 6-OHDA regimen produced a selective (80%) decrease of DA in the NA without altering the concentrations of NE in this structure or either DA or NE in the striatum. Intradentate COLCH also produced a significantly enhanced locomotor response to the injection of the indirect DA agonist d-amphetamine into the NA. While all animals exhibited a persistent increase in activity following intraaccumbens amphetamine, the COLCH-treated group exhibited an exaggerated response. Taken together, these observations could indicate that destruction of granule cells in the dentate gyrus by COLCH results in a "functional" hyperactivity of the mesolimbic DA input to the NA which disinhibits locomotor activity.

These data further reinforce the concept that the limbic system in general and the HPC in particular modulates goal-directed motor behavior through their interaction with the ventral striatum. Furthermore, it is suggested that alterations in the relative balance of excitatory limbic system inputs to the NA might bias the system in favor of the relatively stronger input. A disruption of the subicular projection to the NA following intradentate COLCH might enhance the influence of other limbic system (i.e., amygdala) or cortical inputs on this structure and this might be manifested as increased motor activity. It might further be suggested that destruction of the DA input to the NA blocks hyperactivity induced by COLCH by reestablishing a balance or nonbias condition for limbic system inputs to the NA.

Several lines of evidence support the hypothesis that the NA and its dopaminergic innervation is a critical neural substrate for the initiation of motor behavior. For example, 1) the direct administration of DA or dopaminergic agonists into the NA increases locomotor activity (25), 2) the increases in activity following the administration of psychomotor stimulants including cocaine and amphetamine are prevented by injections of 6-OHDA into the NA (9, 11, 12), 3) the locomotor effects of compounds such as caffeine or heroin, which do not interact with central DA systems, are not affected by intraaccumbens 6-OHDA (31), 4) 6-OHDA-induced NA damage attenuates the motor activating effects of nonpharmacological manipulations including stress, schedule-induced polydipsia and food deprivation (31) and 5) 6-OHDA produces a compensatory increase in the density of dopaminergic receptors which is paralleled by an exaggerated locomotor response to DA receptor agonists such as apomorphine (29).

It is well established that damage to the HPC proper or to pyramidal cells in CA3 or granule cells in the dentate gyrus produces increased locomotor activity (5, 33, 35). Several indirect lines of evidence indicate that this hyperactivity might result from an altered relationship between the HPC and motor systems within the ventral striatum, in particular the NA. Anatomical studies have shown that the subiculum sends a large excitatory projection to the NA (4, 10, 30, 37, 38). Due to the sequential nature of the synaptic circuitry in the HPC, in which information travels from dentate gyrus to CA3 to CA1 to the subiculum, it is likely that damage at any point along that pathway will disrupt the output of the HPC which is mediated by the subiculum.

The physiological relationship of the HPC to the NA is not well understood. The convergence of glutamate fibers originating in the HPC onto the same neurons as dopmainergic efferents from the ventral tegmental area (32) may serve as a locus for the initiation and modulation of motor behavior. Injections of glutamate antagonists into the NA have been reported to decrease exploratory behavior and locomotion produced by psychomotor stimulants (26). While these data indicate that glutamate is probably involved in the initiation of locomotor activity, the exact mechanism underlying this interaction is unclear. Furthermore, the NA receives excitatory inputs from other limbic sites, in particular the amygdala, and these also might converge with DA inputs from the VTA (39). Based upon these physiological and anatomical considerations Oades proposed that the DA innervation of the NA might act to gate or regulate the relative influence of the HPC and amygdala on the NA (23).

It is evident that further study is requried to delineate the anatomical and functional asepct of the limbic system-ventral striatal interface. Such an understanding should prove useful for elucidating the neurobiology of goal-directed motor behavior, congitive function, and the substrates of neuropsychiatric disorders and addictive behavior (31).

ACKNOWLEDGEMENT

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