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Attenuated extracellular dopamine levels after stress and amphetamine in the nucleus accumbens of rats with neonatal ventral hippocampal damage

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Summary. In vivo microdialysis was used to study the effects of restraint stress (30 min) and amphetamine (AMPH) (5 mg/kg, i.p.) in awake adult male rats with neonatal ventral hippocampal (VH) damage. Extracellular levels of dopamine (DA), dihydrophenylacetate (DOPAC), homovanillate (HVA) and 5-hydroxyindolacetate (5-HIAA) were measured in the nucleus accumbens (NA). There were no differences in the baseline levels of DA, DOPAC, HVA or 5-HIAA in the lesioned as compared to the sham rats. Release from restraint resulted in increased extracellular levels of DA in the sham but not in the lesioned animals. AMPH increased DA release in both sham operated and lesioned animals, but this increase was significantly attenuated in the lesioned rats. Our data suggest that this developmental lesion alters function of the dopaminergic system in response to environmental and pharmacological challenge.

Keywords: Hippocampus, microdialysis, dopamine, amphetamine, ibotenic acid, 5-HIAA.

Abbreviations

DA dopamine, *NA* nucleus accumbens, *MPFC* medial prefrontal cortex, *AMPH* amphetamine, *VH* ventral hippocampus.

Introduction

In an earlier series of experiments, we have shown that rats with neonatal (postnatal day 7, PD7) excitotoxic damage of the ventral hippocampus (VH) express behavioral abnormalities that appear relatively late in development, i.e. after puberty (PD56), and that implicate increased mesolimbic/nigrostriatal dopamine (DA) activity. These behavioral abnormalities can be blocked with antipsychotic drugs (Lipska et al., 1993; Lipska and Weinberger,

1993). Adult rats with the neonatal VH lesion express also exaggerated locomotor responses to amphetamine (AMPH) (Lipska et al., 1993), diminished haloperidol-induced catalepsy, augmented apomorphine-induced stereotypy (Lipska and Weinberger, 1993), impaired prepulse inhibition of the acoustic startle response (Lipska et al., 1995) and increased locomotion following acute stressful situations such as a single saline injection or exposure to novelty or a swim test (Lipska et al., 1993). This work has been confirmed and extended by others (Wan et al., 1996; Flores et al., 1996; Black et al., 1996).

In contrast to the evidence that hyperlocomotion expressed under these conditions is linked to increased dopaminergic action in the mesolimbic system (Costall and Naylor, 1977; Kelly et al., 1975), we have found that in vitro tissue concentrations of 3-methoxytyramine (3-MT), a DA metabolite indicative of DA release, is decreased after mild chronic stress in the lesioned as compared to the sham operated rats in the MPFC, striatum and nucleus accumbens (NA) (Lipska et al., 1995). We have also recently shown that AMPH induced expression of c-fos mRNA, an immediate early gene transcript induced in response to AMPH challenge via DA D_1 receptor stimulation (Graybiel et al., 1990; Merchant et al., 1994), is attenuated in the MPFC, cingulate cortex and ventral striatum in the lesioned rats (Lillrank et al., 1996). These data raise the question of whether neurotransmitter systems other than dopamine, receptors other than DA receptors, or post-receptor signaling events are responsible for the behavioral findings of hyperlocomotion after stress and AMPH in neonatally VH lesioned rats or whether the previously used technique to measure DA release (tissue levels of 3-MT) did not adequately reflect functionally relevant changes.

In order to clarify this issue, we studied the effect of AMPH and restraint stress on extracellular levels of DA, its metabolites and 5-HIAA in the NA using in vivo microdialysis. Responses to AMPH and to restraint stress involve both the dopaminergic and the serotonergic system. In vivo microdialysis allows continuous monitoring of the extracellular levels of neurotransmitters for prolonged time in awake rats and causes relatively small damage to brain tissue. The levels of neurotransmitters collected from the extracellular space quite reliably reflect neurochemical events occuring in the synaptic region (Zetterström et al., 1983; Westerink et al., 1987). In the present study, in vivo microdialysis was used to determine if restraint stress and AMPH differentially affect extracellular dopamine, its metabolites and 5-HIAA levels in the NA in rats with the neonatal VH lesions and the sham operated controls.

Materials and methods

Surgery

Pregnant Sprague-Dawley rats obtained at 12–15 days of gestation (Zivic-Miller Labs) were housed individually in breeding cages with a 12 h light/dark cycle and fed ad libitum. Litters of 4–8 male pups were formed. On the 7th day of age (PD7, weight 17–18 g), pups were randomly assigned to LESION (n = 12) and SHAM (n = 11) status and anesthe-

tized by hypothermia (placed on ice for 10–20 minutes). The pups were taped to a platform fixed to a stereotaxic Kopf instrument. An incision was made in the skin overlying the skull. Ibotenic acid (0.3 μl), (Sigma, 10 μg/μl) (in LESION rats) or artificial cerebrospinal fluid (in SHAM rats) was infused bilaterally into the ventral hippocampal formation (AP −3.0 mm, ML ±3.5 mm, VD −5.0 mm, relative to Bregma) through a Hamilton needle using an infusion pump at a rate of 0.15 μl/min. On the 25th day of age, rats were weaned and separated by lesion status and grouped two to three to a cage. At PD56, the microdialysis probes were implanted. Anesthesia was induced with Equithesin (26.2 g chloral hydrate and 6.48 g Na-pentobarbital, total volume 770 ml, i.p.). The animals were placed in a stereotaxic frame with an incisor bar set at −2.4 mm. A microdialysis probe (CMA11, CMA Microdialysis, outer diameter 0.24 mm, a 2 mm dialyzing membrane at the tip), was implanted in the right nucleus accumbens (AP −1.6 mm, L +0.8 mm, VD −7.8 mm (Paxinos and Watson, 1986). The microdialysis probe was attached to the bone with dental cement using three small stainless steel screws.

Microdialysis

The rats were allowed to recover from the surgery overnight. On the next day, they were placed in a hemispheric bowl and the implanted microdialysis probe was connected to a microinfusion pump (CMA100, CMA Microdialysis) via a liquid swivel. The dialysis probe was perfused with Ringer solution (NaCl 147 mM; $CaCl_2$ 1.5 mM; KCl 4 mM, pH 6, and 0.15 mM ascorbic acid to prevent DA breakdown) at a constant flow rate of 2 μl/min. The perfusate was discarded during the first 60 min and then collected at 15-min intervals for analysis of dopamine and amine metabolities. Four fractions were collected in the beginning of the experiment to establish the stable baseline levels, whereupon each rat was restrained for 30 min and then released. Perfusate samples were collected for a further 90 min. At the end of the experiment, each rat received amphetamine sulphate (5 mg/kg) intraperitoneally and perfusate samples were collected for a final 45 minutes (total time from restraint to the end of the experiment 165 min).

Chromatography

DA, dihydrophenylacetate (DOPAC), homovanillate (HVA), and 5-hydroxyindolacetate (5-HIAA) were assayed using high pressure liquid chromatography (HPLC) coupled to electrochemical detection. Twenty μl of dialysate was injected onto a reversed phase HPLC column (Spherisorb, PhaseSep Inc., 2 mm × 10 cm, C-18, 3 μm particle size) using an automated refrigerated injection unit. Catecholamine metabolites were separated by eluting the column with mobile phase (5% acetonitrile, 0.1 mM monosodium phosphate, 0.1 mM EDTA, 0.6 mM sodium octyl sulfate, pH 2.95). A pulse free solvent delivery system allowed 120 μl/min at a constant flow rate. All samples were analyzed in the same HPLC assay. Peak heights were measured to determine the levels of the chemicals. External standards of all measured chemicals were periodically injected to identify the peaks. Detection limits of our analysis system for DA ranged between 8–15 fmols per injection, and for the metabolites 50–70 fmols/injection.

Statistical methods

The levels of transmitters and their metabolites are expressed as percentages of baseline values defined as the average of the last two samples before restraint stress. The restraint and AMPH data were analyzed separately using a two-way analysis of variance (ANOVA) with treatment (lesion status) as an independent variable and time (15 min samples after the beginning of treatment) as a repeated measure. If significant ($p < 0.05$) effects or interactions were detected, the data were subjected to LSD post-hoc comparison.

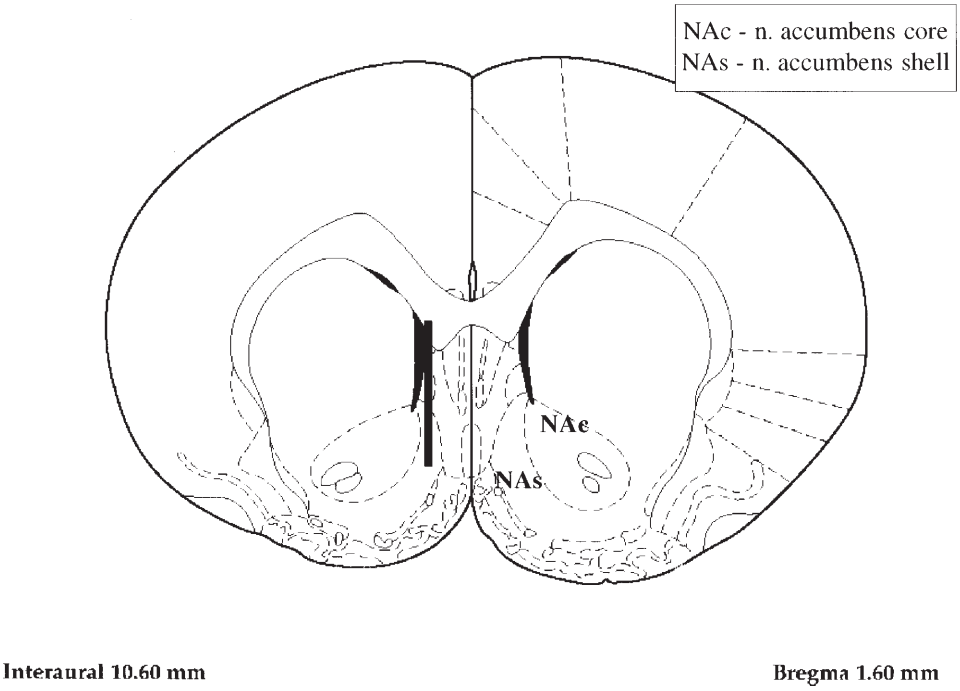

Fig. 1. A drawing showing the location of a microdialysis probe (a black vertical bar) in the nucleus accumbens (NA). *NAc* nucleus accumbens core, *NAs* nucleus accumbens shell (from Paxinos and Watson, 1986)

Results

Histology

All brains were examined to verify the location of the ibotenic acid lesion in the VH and microdialysis probes in the NA using Nissl stained sections. The lesion criterion was defined as neuronal loss and gliosis confined to the VH, with all the cytoarchitectural divisions in the ventral aspects of the hippocampus (CA1-CA4) as well as parts of the subiculum affected and no discernible damage outside the hippocampus as previously reported (Lipska et al., 1993). Three animals were deleted from further analysis due to improper location of the lesion. In these cases the lesion was either unilateral or encroached on the adjacent neocortex. The probe aimed at nucleus accumbens was in 70% of the cases in the shell region and in the remaining 30% in the core region (Fig. 1). Three animals had to be deleted from further analysis due to improper location of a probe or signs of excessive bleeding around a probe.

Baseline levels

The baseline extracellular levels of DA, DOPAC or HVA were not altered in the lesioned as compared to the sham operated rats (Table 1 and Fig. 2). Although the baseline levels of 5-HIAA tended to be lower in the lesioned

Table 1. Baseline levels of DOPAC, HVA and 5-HIAA (mean ± S.E.M. in fmol/20μl, n = 5) in microdialysates of the nucleus accumbens in awake freely moving rats

	Lesion	Sham
DA	61.61 ± 17.19	35.76 ± 2.47
DOPAC	5433.4 ± 990.2	5034.1 ± 1369.4
HVA	1802.1 ± 341.0	1732.9 ± 375.5
5-HIAA	1755.8 ± 444.6	2657.0 ± 357.2

as compared to the sham operated rats, the change was not statistically significant ($F_{(1,8)} = 1.98$, $p = 0.19$).

Effect of restraint

Restraint differently affected the extracellular levels of DA in the lesioned and control rats (main effect of lesion $F_{(1,8)} = 5.26$, $p < 0.05$). In the sham operated animals, there were no significant changes during restraint but DA levels increased by 30% above baseline ($p < 0.05$) 60 min after the release of the animals from restraint (i.e., 90 min from the beginning of the experiment). The lesioned animals showed a decrease of 23% below baseline at 30 min during restraint ($p < 0.05$), whereupon DA levels returned to baseline (Fig. 3). There were no significant changes in DOPAC levels (Time $F_{(8,64)} = 1.69$, $p = 0.12$, Lesion $F_{(1,8)} = 0.87$, $p = 0.38$) (data not shown). For HVA values,

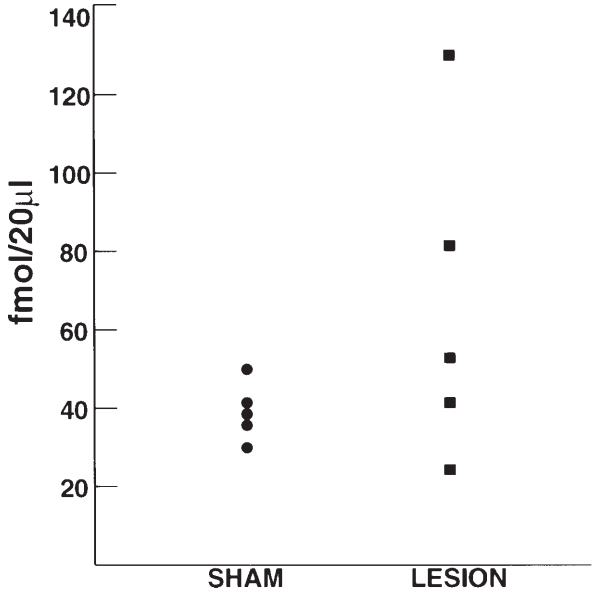

Fig. 2. Distribution of baseline levels of extracellular dopamine in the nucleus accumbens in the sham and lesioned rats

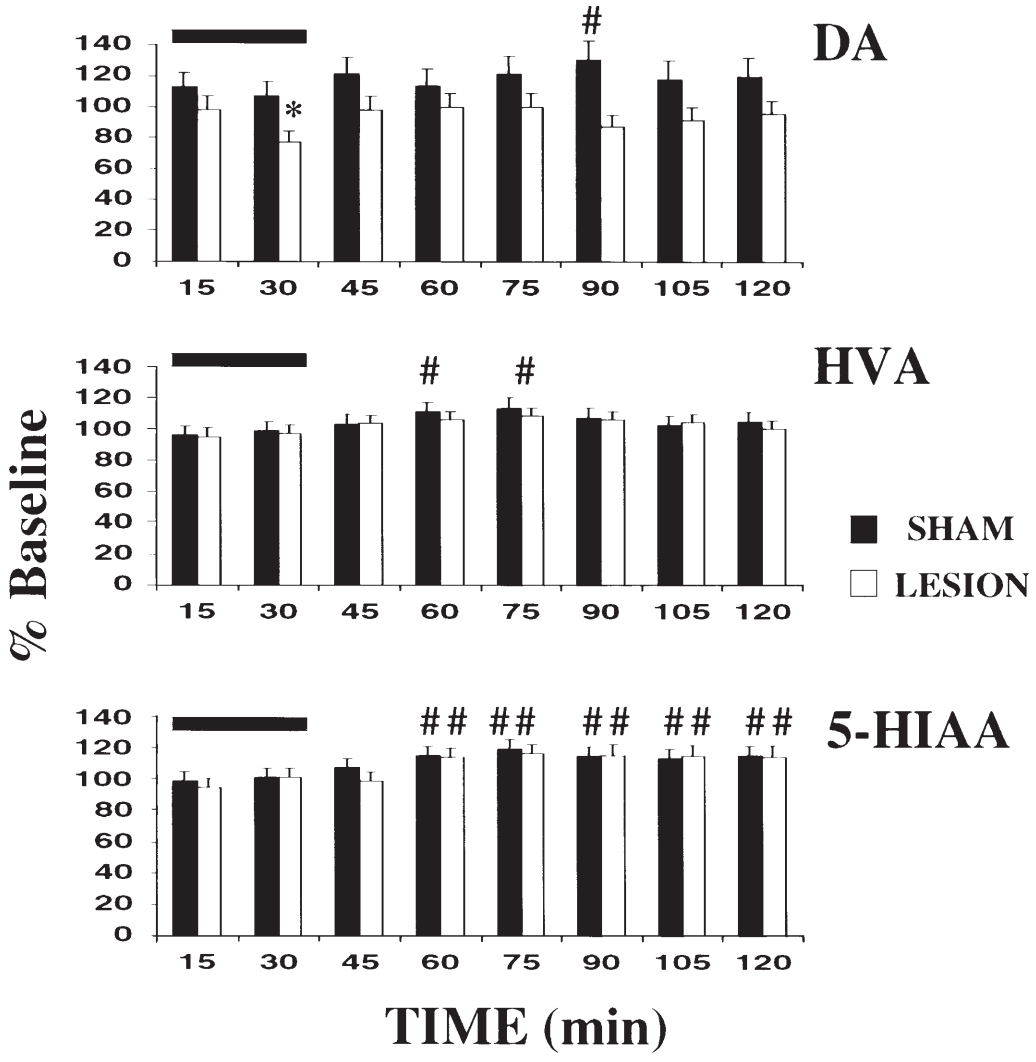

Fig. 3. The effects of restraint on the extracellular levels of DA, HVA and 5-HIAA in the nucleus accumbens in LESION and SHAM rats. The results (mean ± S.E.M) are given in per cent of the mean of two baseline levels before restraint. *LESION group significantly different from SHAM group, $p < 0.05$. #significantly different from a baseline level, $p < 0.05$. A horizontal bar indicates time of restraint. For baseline levels, see Table 1

ANOVA showed a significant effect of time ($F_{(8,64)} = 2.97$, $p < 0.01$), but no lesion effect $F_{(1,8)} = 0.09$, $p = 0.77$). Post hoc analysis revealed an increase of HVA levels above baseline (by 14%, $p < 0.05$) in the sham operated rats 30 and 45 min after release from restraint (i.e., 60 and 75 min from the beginning of the experiment) (Fig. 3). For 5-HIAA, ANOVA showed a significant time effect ($F_{(8,64)} = 5.8$, $p < 0.0001$) but no lesion effect ($F_{(1,8)} = 0.05$, $p = 0.82$). In both lesioned and sham operated rats 5-HIAA levels were elevated after release of the animals from restraint, (by 15–20%), $p < 0.05$, (Fig. 3).

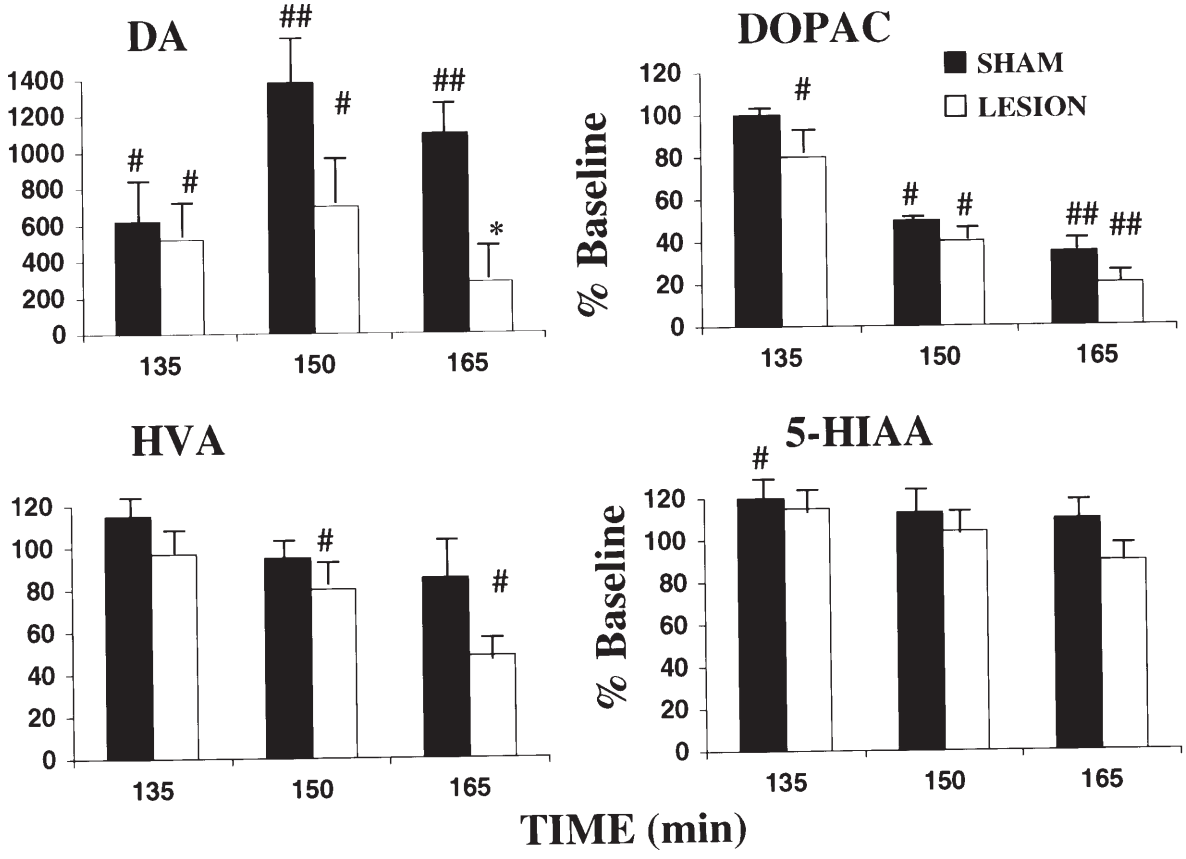

Fig. 4. The effects of amphetamine (5 mg/kg, i.p.) on the extracellular levels of DA, DOPAC HVA and 5-HIAA in the nucleus accumbens of LESION and SHAM rats. The results (mean ± S.E.M) are expressed as per cent of the mean of two baseline levels before restraint. *LESION group significantly different from the SHAM group, $p < 0.05$. #,##significantly different from baseline levels, $p < 0.05$, $p < 0.01$. Amphetamine was injected at 120 min. For baseline levels, see Table 1

Effect of amphetamine

Treatment with AMPH (5 mg/kg, i.p.) significantly increased extracellular DA levels in both controls and the lesioned rats. ANOVA showed a significant effect of lesion and time $F_{(1,8)} = 6.53$, $p < 0.05$, $F_{(3,24)} = 5.91$, $p < 0.01$ respectively) as well as a significant lesion × time interaction ($F_{(3,24)} = 5.91$, $p < 0.01$). Post hoc analysis revealed that DA release was significantly attenuated in the lesioned as compared to the sham operated rats 45 minutes after the injection (i.e., 165 min from the beginning of the experiment), $p < 0.05$, (Fig. 4). DOPAC levels were significantly reduced after AMPH injection (time effect $F_{(3,24)} = 178.06$, $p < 0.0001$). This attenuation in DOPAC tended to be more pronounced in the lesioned as compared to the sham operated rats, but the difference did not reach significance (Fig. 4). HVA levels were also significantly altered after AMPH treatment (lesion $F_{(1,8)} = 16.25$, $p < 0.05$;

time $F_{(3,24)} = 16.25$, $p < 0.0001$) but a post hoc test did not show a significant difference between the lesioned and the sham rats at any time point (Fig. 4). ANOVA for 5-HIAA levels revealed a significant time effect ($F_{(3,24)} = 3.33$, $p < 0.05$, but no lesion effect ($F_{(1,8)} = 0.57$, $p = 0.47$). Post hoc analysis revealed that the sham controls responded to AMPH with increased 5-HIAA ($p < 0.05$ at 135 min), whereas in the lesioned rats this effect did not reach significance. There was no difference in 5-HIAA levels between the lesioned and sham rats at any time point (Fig. 4).

Discussion

The main finding of this study is attenuated DA release in the nucleus accumbens in response to amphetamine and release from stress in adult rats with the neonatal VH lesion. The VH lesion did not alter baseline extracellular levels of 5-HIAA or DA and its metabolites in NA. These findings are consistent with our previous results which showed that the VH lesion diminished tissue concentrations of 3-MT, a DA metabolite thought to be a reliable index of DA release (Lipska et al., 1995), in response to chronic mild stress but not at baseline. These results are particularly intriguing in light of enhanced locomotor activity displayed by the VH lesioned rats in response to stress and AMPH (1.5 mg/kg., i.p.) which has usually been associated with increased rather than diminished NA DA activity.

It should be noted that, in contrast to other studies, we did not find increased DA release in NA during stress. This difference may be attributed to the type and duration of stress. Most stress studies use tail pinch, tail pressure or foot shock (King and Finlay, 1995; Abercrombie et al., 1989) which may more profoundly alter dopaminergic neurotransmission in the NA, as compared to our relatively mild restraint stress. Those few studies that have used restraint as a stressor, applied it for a considerably longer time, i.e. 60 or 120 minutes (Imperato et al., 1991, 1992). Another possibility for our failure to find stress-induced increases in DA may be the cannulae placement. Recent studies have shown that baseline extracellular levels of DA, as measured by in vivo microdialysis, are higher in the NA core than in the shell but the DOPAC/DA ratios are not different between the regions (King et al., 1997). Moreover, Kalivas and Duffy (1995) reported that 20 minutes after discontinuing mild footshock stress, DA release was elevated in the shell but not in the NA core. Although there seem to be some discrepancies between the studies measuring baseline DA levels in different subregions of the NA (Deutch and Cameron, 1992), it is possible that the small changes in DA release expected to be seen during stress might have been missed by placing the cannulae in the NA core. In agreement with other studies, however, we found increased DA after release from stress (Kalivas and Duffy, 1995; Imperato et al., 1992). The physiological significance of this short-term increase of extracellular DA after release from restraint is not fully understood.

Other confounding factors may be the effects of anesthesia (24 hrs prior to microdialysis) and injury due to the probe implantation. Anesthesia has been

shown to acutely elevate DA and DOPAC levels, but the long lasting consequences are not known (Ståhle et al., 1990; Lillrank et al., 1994). Tissue trauma due to implantation of a probe and increasing gliosis after 48 hrs of insertion have been shown to more profoundly affect levels of extracellular neurotransmitters. Our study was designed to limit the problems of direct effects of anesthesia and chronic probe implantation, by implanting the microdialysis probe under Equithesin anesthesia 24 hours prior to the experiment.

As we have previously shown, after puberty, rats with the neonatal VH lesion respond to stress and AMPH stimulation with increased locomotor activity as compared to the sham treated rats (Lipska et al., 1993). These behaviors are generally thought to be linked to excessive dopaminergic action (Pijenburg and Van Rossum, 1973; Kelly et al., 1975; Swerdlow and Koob, 1984; Clarke et al., 1988). In this respect, the finding of attenuated extracellular DA levels in these rats is intriguing. Some, but not all, in vivo microdialysis experiments have shown that hippocampal lesions have marked effects on subcortical DA neurotransmission. For instance, Wilkinson et al. (1993) reported that rats with adult hippocampal lesions display increased locomotor activity and show increased DA release in the NA after AMPH challenge. In contrast, but using a different paradigm, Kolachana et al. (1996) demonstrated that in monkeys with neonatal medial temporal-limbic removals, DA release from the caudate nucleus in response to local K^+-stimulation was significantly attenuated as compared to control monkeys. Wan et al. (1996), on the other hand, using in vivo microdialysis in awake rats, reported that the neonatal hippocampal lesion does not alter DA release in the NA in response to AMPH (1.5 mg/kg). Moreover, no difference in the baseline 5-HIAA levels between lesioned and control rats were reported in this study. It is possible that different experimental designs, i.e., different species, ages at lesion and doses of drugs may explain these inconsistencies.

We have previously speculated that rats with the neonatal VH lesion experience stress as an uncontrollable, aversive situation, to which they are unable to habituate (Lipska et al., 1995). Stress has been shown to activate the dopaminergic system in normal rats by increasing DA release in the MPFC, NA and neostriatum (Keefe et al., 1993; Abercrombie et al., 1989; Imperato et al., 1991). Immobilization, tail pinch, and saline injections are known to activate dopaminergic function in mesolimbic brain regions (King and Finlay, 1995; Keefe et al., 1993; Abercrombie et al., 1989; Hamamura and Fibiger, 1993; Kuczenski and Segal, 1989). Our data implicate, however, that rats with a neonatal VH lesion have an impaired ability to respond to stressful events with increased DA release. Similarly, suppressed dopamine releasing effects in response to stress and to amphetamine have been reported in rats chronically stressed (Imperato et al., 1993) and chronically treated with amphetamine (Imperato et al., 1996; Weiss et al., 1997), despite the enhanced behavioral response in these animals. This reduced responsivity in terms of DA release might be due to downregulated DA synthesis, depleted DA in storage sites, impaired release mechanisms or abnormal transporter system, and may be reflected in the state of DA receptors. Previous studies, however,

using receptor autoradiography for DA D_1 and D_2 receptors, did not find changes in these receptors in these animals (Knable et al., 1994), although reduced striatal D_2 mRNA levels were recently reported in the lesioned animals (Lipska et al., 1997). There is also a possibility that other DA receptor subtypes ($D_{3,4}$ or D_5) are altered in these rats. Flores et al. (1996) have recently found reduced D_3 receptor binding in adult rats with a similar neonatal VH lesion, but we have not confirmed this finding in our binding or in situ hybridization studies (Lipska et al., 1997).

We have previously suggested that intracellular signal transduction mechanisms may be affected by the developmental lesion, and have shown that the neonatal VH lesion results in changes in AMPH-induced gene expression. AMPH is known to induce expression of the immediate early gene c-fos in the striatum and neocortex, probably by activating DA D_1 receptor signalling systems (Graybiel et al., 1990; Merchant et al., 1994) or by stimulating glutamate receptors (Johanson et al., 1994). Our current data are consistent with the previous findings of decreased AMPH-induced expression of c-fos mRNA in the ventromedial striatum in the lesioned rats (Lillrank et al., 1996). Thus, both these studies suggest DA hyporesponsivity in situations when special demands are imposed upon the dopaminergic system of the VH lesioned rats.

DOPAC levels in response to AMPH were somewhat attenuated in the lesioned rats. Extracellular DOPAC is believed to be derived largely from newly synthesized DA that is deaminated into DOPAC intracellularly by monoaminooxidase (MAO) before being released (Soares-Da-Silva et al., 1990; Zetterström et al., 1988). Therefore, DOPAC may provide a measure of DA synthesis. AMPH has been shown to increase extracellular DA but to decrease DOPAC and HVA in normal rats (Zetterstrom et al., 1986). This decrease in DOPAC in response to AMPH may be explained by its action on inhibiting MAO (Jones et al., 1988) or its ability to increase DA release from a newly synthesized pool and thus leaving less DA inside the cell for deamination to DOPAC. Our data might suggest, therefore, that DA production in the soluble pool may be somewhat down regulated in the lesioned rats as reflected in slightly reduced DOPAC levels. Because DA levels in the synaptic cleft are regulated both by vesicularly stored and soluble cytoplasmic pools of DA (McMillen et al., 1980; Hurd and Ungerstedt, 1989), downregulation in one pool may not be detected in baseline levels but becomes more apparent when AMPH induced DA release is measured. Changes may also exist in other systems that can alter DA function and mediate the effects of AMPH, for example serotonergic and glutamatergic systems (Johansson et al., 1994; Kuczenski and Segal, 1989). In this study, however, the baseline levels of 5-HIAA were not significantly altered, although there was a trend for a reduction in the lesioned rats.

We have reported previously that rats with a neonatal VH lesion are hyperresponsive to the stimulatory effects of the NMDA antagonist MK-801 (Lipska and Weinberger, 1996) suggesting alterations of glutamatergic activity. However, receptor autoradiographic and in situ hybridization studies did not reveal any changes in NMDAR1 receptors (Al-Amin et al., 1996),

although this does not preclude changes in other glutamatergic receptor subtypes. Such changes might be expected considering that the lesion destroys intrinsic VH neurons, some of which are glutamatergic projection neurons that innervate NA. Since the nucleus accumbens receives DAergic input from the VTA (Bjorklund and Lindval, 1984) and glutamatergic input from, among other structures, the VH (Groenewegen et al., 1987; Sesack and Pickel, 1990; Swanson and Cowan, 1977; Jay and Witter, 1991), it is possible that due to the VH lesion less glutamate is released in NA and that DA release is attenuated. In addition, previous studies from this laboratory suggested that early hippocampal deefferentation affects the development of other brain regions, such as the MPFC, that is also involved in the regulation of striatal/NA function (Lipska and Weinberger, 1993; Lillrank et al., 1996; Lipska et al., 1998).

We have studied the effects of this neonatal VH lesion as a potential animal model for certain aspects of schizophrenia, a disorder in which postpubertal onset of symptoms and developmental structural pathology in the hippocampal region are implicated (Lillrank et al., 1995; Weinberger and Lipska, 1995). Using this model, we attempted to elucidate mechanisms underlying the behavioral abnormalities that emerge postpuberty by studying extracellular DA release. These results confirm and extend our previous findings from in vitro tissue measurements of attenuated DA release in the VH lesioned animals exposed to environmental or pharmacological stimuli, but also raise a new challenge to the face validity of the model. While the animals are behaviorally hyperresponsive to stress and AMPH and respond to antidopaminergic drugs analogous to patients with schizophrenia, they are hyporesponsive at the level of stimulated DA release. In contrast, patients with schizophrenia manifest decreased radioligand binding in the striatum following systemic AMPH administration, suggesting increased DA release (Laruelle et al., 1996; Breier et al., 1997). While the exact mechanism for this clinical finding is uncertain, the resolution of this apparent discrepancy will require additional experimentation.

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