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Research report

Neonatal 3,4-methylenedioxymethamphetamine (ecstasy) alters dopamine and serotonin neurochemistry and increases brain-derived neurotrophic factor in the forebrain and brainstem of the rat

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Abstract

Growing concerns surround the risk of fetal exposure to 3,4-methylenedioxymethamphetamine (MDMA; ecstasy). Prior animal studies using neonatal rats administered MDMA from postnatal days (P) 11–20 (a period approximating third trimester brain development in humans) have demonstrated long-lasting decrements in serotonin (5-HT) and learning; however, no studies have examined the acute post-MDMA response of the brain at this early age. Specifically, it is of interest whether MDMA administration to neonatal rats produces the expected depletion of monoamines and whether the brain exhibits any ameliorative response to the pharmacologic insult. In the current study, this model was employed to determine whether forebrain and brainstem dopamine (DA) and 5-HT neurochemistry were altered 24 h after the last injection (P21), and whether brain-derived neurotrophic factor (BDNF) was upregulated in response to MDMA exposure. All forebrain structures examined (frontal cortex, hippocampus, and striatum) showed significant MDMA-induced reductions in 5-HT and its metabolite, 5-HIAA, and significant increases in the DA metabolite, HVA, as well as DA turnover (HVA/DA). In the brainstem, there were significant increases in 5-HIAA, HVA and DA turnover. BDNF was significantly increased (19–38%) in all forebrain structures and in the brainstem in MDMA-exposed neonates versus saline controls. These data suggest that MDMA exposure to the developing rat brain from P11–20 produces similar alterations in serotonin and dopamine neurochemistry to those observed from adult administrations. In addition, a compensatory increase in BDNF was observed and may be the brains ameliorative response to minimize MDMA effects. This is the first report demonstrating that MDMA exposure results in increased levels of BDNF and that such increases are correlated with changes in monoamine levels. Future research is needed to elucidate any deleterious effects MDMA-induced increases in trophic activity might have on the developing brain and to examine earlier gestational exposure periods in order to assess the risk throughout pregnancy.

Theme: Neural basis of behavior

Keywords: MDMA; Ecstasy; Neurotoxicity; Perinatal; BDNF; Dopamine; DOPAC; HVA; 5-HT; 5-HIAA; Frontal cortex; Striatum; Hippocampus; Brainstem; CoulArray detection; HPLC; ELISA

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA) use continues to rise among women of childbearing age, raising serious concerns over the risk of fetal exposure from women who are, or become pregnant [29]. MDMA's most prominent pharmacologic effect is its ability to block the reuptake of serotonin (5-HT) and reverse the flow at the 5-HT transporter (SERT), resulting in cytosolic release of 5-HT. This 5-HT depletion is associated with serotonergic terminal field loss that spares associated cell bodies and axons of passage [22]. Pharmacologically, MDMA has similar actions on dopamine (DA) and noradrenergic transporters although it binds with less affinity. Significant dopamine terminal loss has also been demonstrated under specific MDMA dosing schedules [26].

More recently, studies have demonstrated that MDMA produces serotonergic terminal loss in the developing brain [5,20,21]. One particular model, which has recently received

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attention, exposes neonatal rats to MDMA from postnatal days (P) 11–20 [5,35], a period that the authors contend is analogous to human third trimester hippocampal development. P11–20 exposure produced serotonergic reductions in the frontal cortex and the hippocampus at P105. Such animals also exhibited lasting deficits in sequential learning and spatial memory tasks.

While these studies demonstrate that neonatal MDMA exposure can induce long-lasting reductions in neurochemistry and alterations in learning and memory, no studies have examined the acute post-MDMA administration response of the brain at this early age, specifically, whether MDMA administration to neonatal rats produces the expected depletion of monoamines and whether the brain exhibits any ameliorative response to the pharmacologic insult. For example, brain-derived neurotrophic factor's (BDNF) role in the developing brain is to promote neuronal differentiation [15], neurite outgrowth and elongation [27] synapse formation [34] and survival [9]. It has been shown to be upregulated in response to various types of neuronal injury including electroconvulsive stimuli [2], chronic amphetamine administration [19], neonatal asphyxiation [28], and mild traumatic brain injury [7].

Therefore, the current study sought to examine the consequences of a P11–20 MDMA exposure, 24 h after the final administration on 5-HT and DA neurochemistry and BDNF levels in the frontal cortex, hippocampus, striatum and brainstem. It was hypothesized that MDMA administration would result in profound depletion of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) and that the reductions in the 5-HT system would be associated with a compensatory increase in BDNF levels. In addition, the correlation between any alterations in DA neurochemistry and BDNF was also examined.

2. Materials and methods

2.1. Subjects and drug administration

Timed-pregnant Sprague–Dawley albino rats (Zivic–Miller, $n = 8$) were received at least 96 h prior to parturition. Subjects were placed on a 12-h light/dark cycle schedule in a temperature-controlled room (21 °C). Dams generally delivered late on E21 (also considered P0), and the following full postnatal day was then considered P1. On P1 litters were culled to eight offspring (four males and four females). Offspring remained group-housed with the dam throughout the entire study. Each pup could be identified via tail markings throughout the study. Beginning on P11 through P20, two males and two females from each litter received twice daily injections (s.c.) of 20 mg/kg (±)-3,4,-methylenedioxymethamphetamine hydrochloride (MDMA) (5 ml volume) and the remaining two males and two females received saline (5 ml/kg). Each pup was weighed twice daily for injection purposes and to track weight gain.

On P21, one pair of male/female offspring from each litter and drug condition were used for quantitation of monoamine neurochemistry and BDNF.

The animal facility was accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care and complied with all Federal animal care and use guidelines. Protocols were all approved by the Institutional Animal Care and Use Committee of Rush-Presbyterian-St. Luke's Medical Center.

2.2. Tissue perfusion and dissection

At P21, rats were processed following a modified version of our previously published method [14,16,17] for analysis of brain monoamines. Briefly, rats were anesthetized with an i.p. injection of ketamine/xylazine (285 mg/kg/9.5 mg/kg) and transcardially perfused with ice-cold saline + 0.1% sodium heparin (15 ml/min for 5 min) in order to remove endogenous circulating monoamines and growth factors from blood vessels. The subject was then decapitated, brain quickly removed and placed in a frozen stainless steel brain blocker (Stoelting, Wood Dale, IL). Using razor blades, the brain was sectioned into 1–2 mm slabs with the frontal cortex (FC), striatum (STR), hippocampus (HIPP) and brainstem (BS) dissected out unilaterally in order to correlate within structure neurochemistry with growth factor values. Tissues were placed in vials, frozen on dry ice and stored at −80 °C until analysis.

2.3. Neurochemistry

For high-performance liquid chromatography (HPLC) analysis, an antioxidant solution (0.4 N perchlorate, 1.343 mM ethylenediaminetetraacetic acid (EDTA) and 0.526 mM sodium metabisulfite) was added to the samples followed by homogenization using an ultrasonic tissue homogenizer (Biologics, Gainesville, VA). A small portion of the tissue homogenate was dissolved in 2% sodium dodecyl sulfate (SDS) (w/v) for protein determination (Pierce BCA Protein Reagent Kit, Rockford, IL). The remaining suspension was spun at $14\,000 \times g$ for 20 min in a refrigerated centrifuge. The supernatant was reserved for HPLC.

Samples were separated on a Microsorb MV C-18 column (5 μm, 4.6 × 250 mm, Varian, Walnut Creek, CA) and simultaneously examined for DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-HT and 5-HIAA. Compounds were detected using a 12-channel coulometric array detector (CoulArray 5200, ESA, Chelmsford, MA) attached to a Waters 2695 Solvent Delivery System (Waters, Milford, MA) under the following conditions: flow rate of 1 ml/min; detection potentials: 50, 175, 350, 400 and 525 mV; scrubbing potential: 650 mV. The mobile phase consisted of a 10% methanol solution in distilled H_2O containing 21 g/l (0.1 M) citric acid, 10.65 g/l (0.075 M) Na_2HPO_4, 176 mg/l (0.8 M) heptanesulfonic acid, and 36 mg/l (0.097 mM) EDTA at a pH of 4.1.

Unknown samples were quantified against a six-point standard curve with a minimum r^2 of 0.97. Quality control samples were interspersed with each run to ensure HPLC calibration.

2.4. Brain-derived neurotrophic factor

Dissected brain structures were placed in 250 μl of lysis buffer containing 0.5% Triton-X, 1 mM EDTA and 1:100 of mammalian tissue protease inhibitor cocktail (Sigma-Aldrich, P8340). Samples were then homogenized on ice using an ultrasonic tissue homogenizer, (Biologics) followed by shaking at 4 °C for 1 h. Five microliters of the tissue homogenate was combined with 2% SDS for protein determination using the Pierce BCA Protein Assay Reagent Kit. Samples were then centrifuged at 4 °C for 20 min at $14\,000 \times g$, supernatant collected and stored at − 80 °C until the date of assay. The ELISA reaction was completed using the Immunolon 4 HBX 96-well plate (in duplicate) according to the ELISA manufacturer's instructions (Promega Emax ImmunoAssay Systems Kit (G7610), Madison, WI). The samples were read within 30 min at 450 nm, using a spectrophotometer (Multiskan Spectrum, Thermolab Systems) with unknown values determined through interpolation against the BDNF standard curve (acceptable r^2>0.95). Duplicate optical density values not within 15% of each other were both excluded from further analyses.

2.5. Statistics

All statistical analyses were conducted using the statistical package SPSS 11.0 (Chicago, IL). Data were analyzed using a two-way ANOVA with treatment group (Saline versus MDMA) and gender as factors. Correlations were evaluated on both treatment and control groups combined using a two-tailed bivariate analysis producing a Pearson coefficient value. *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. Neonatal weight gain

Neonatal weight differences were apparent almost immediately between saline- and MDMA-exposed pups (on P12: MDMA, 30.26 g versus saline, 28.72 g; $F_{(1,92)} = 4.955$, $p < 0.01$). The weight disparity between groups continued through to P20. At P20 the differences in total weight gain was significantly different without any influence of gender (41.35% difference) ($F_{(1,91)} = 221.167$, $p < 0.001$).

3.2. Neurochemistry

Two-way ANOVA produced no differences based on gender on any neurochemical measure. For the purpose of separating by gender in the tables, one-way ANOVAs were performed on all neurochemical measures separately for males and females. Serotonin and dopamine neurochemical measures and S.E.M. are expressed in Tables 1 and 2, respectively.

3.2.1. Frontal cortex

Neonatal exposure to MDMA, at P21, produced a 52.31% and a 36.38% reduction in 5-HT and 5-HIAA, respectively, versus saline controls ($F_{(1,28)} = 48.148$, $p < 0.0001$; $F_{(1,28)} = 44.71$, $p < 0.001$). Dopamine was unchanged, although its metabolites were significantly increased: HVA (44.5% increase; ($F_{(1,28)} = 22.137$, $p < 0.0001$) and DOPAC (36.54% increase; $F_{(1,28)} = 12.537$, $p < 0.005$). Dopamine turnover was also significantly elevated: HVA/DA (43.14% increase; $F_{(1,27)} = 11.048$, $p < 0.01$) and DOPAC/DA (30.12% increase; $F_{(1,27)} = 8.583$, $p < 0.01$).

3.2.2. Hippocampus

Neonatal MDMA exposure from P11–20, at P21, also produced significant reductions in 5-HT (by 31.84%; $F_{(1,28)} = 10.748$, $p < 0.005$) and 5-HIAA (by 41.87%; $F_{(1,28)} = 64.538$, $p < 0.001$). The dopamine metabolite HVA

Table 1
Effects of neonatal MDMA versus saline (SAL) exposure on the frontal cortex (FC), striatum (STR), hippocampus (HIPP) and brainstem (BS) serotonin neurochemistry, at postnatal day 21 in males and females

		5-HT		5-HIAA		5-HIAA/5-HT	
		Male	Female	Male	Female	Male	Female
FC	SAL	1.70 ± 0.10	1.78 ± 0.18	3.32 ± 0.16	3.22 ± 0.20	2.02 ± 0.17	2.16 ± 0.44
	MDMA	0.82 ± 0.11†	0.83 ± 0.07†	2.08 ± 0.18†	2.08 ± 0.15†	2.87 ± 0.53	2.58 ± 0.20
STR	SAL	2.81 ± 0.31	3.31 ± 0.23	8.81 ± 0.45	9.00 ± 0.37	3.35 ± 0.35	2.85 ± 0.25
	MDMA	2.06 ± 0.35	2.41 ± 0.24*	6.23 ± 0.56†	6.41 ± 0.36†	3.43 ± 0.41	2.84 ± 0.33
HIPP	SAL	2.14 ± 0.14	2.02 ± 0.95	6.45 ± 0.35	6.11 ± 0.39	3.08 ± 0.26	2.84 ± 0.42
	MDMA	1.42 ± 0.12†	1.41 ± 0.10	3.64 ± 0.25†	3.63 ± 0.27†	2.64 ± 0.22	2.62 ± 0.20
BS	SAL	6.25 ± 0.22	5.78 ± 0.91	11.29 ± 0.64	10.21 ± 1.03	1.93 ± 0.14	1.83 ± 0.15
	MDMA	6.03 ± 0.55	6.40 ± 0.81	12.85 ± 0.71*	12.57 ± 0.65*	2.19 ± 0.13	2.09 ± 0.17

Values represent nanograms of compound per milligram of protein content (mean ± S.E.M.).
* $p < 0.05$ indicates significant differences between treatment and control groups using ANOVA.
† $p < 0.01$ indicates significant differences between treatment and control groups using ANOVA.

Table 2
Effects of neonatal MDMA versus saline (SAL) exposure on the frontal cortex (FC), striatum (STR), hippocampus (HIPP) and brainstem (BS) dopamine neurochemistry, at postnatal day 21 in males and females

		DA		DOPAC		HVA		HVA/DA		DOPAC/DA	
		M	F	M	F	M	F	M	F	M	F
FC	SAL	0.29 ± 0.08	0.20 ± 0.03	0.24 ± 0.17	0.17 ± 0.01	0.58 ± 0.09	0.51 ± 0.07	2.32 ± 0.44	2.85 ± 0.46	0.91 ± 0.13	0.96 ± 0.13
	MDMA	0.30 ± 0.10	0.21 ± 0.02	0.32 ± 0.05	0.25 ± 0.02†	1.07 ± 0.11†	0.89 ± 0.10†	4.48 ± 0.87*	4.60 ± 0.55*	1.17 ± 0.19	1.28 ± 0.12
STR	SAL	62.36 ± 1.74	65.69 ± 2.40	11.94 ± 0.91	11.50 ± 0.43	7.68 ± 0.55	7.55 ± 0.46	0.12 ± 0.01	0.12 ± 0.01	0.19 ± 0.01	0.18 ± 0.01
	MDMA	70.58 ± 3.90	68.41 ± 3.72	16.72 ± 1.30†	16.77 ± 1.20†	13.37 ± 0.90†	12.39 ± 0.91†	0.19 ± 0.01†	0.18 ± 0.01†	0.24 ± 0.02†	0.25 ± 0.02†
HIPP	SAL	0.41 ± 0.04	0.53 ± 0.09	0.16 ± 0.02	0.18 ± 0.02	0.18 ± 0.02	0.18 ± 0.02	0.43 ± 0.03	0.38 ± 0.06	0.38 ± 0.03	0.36 ± 0.04
	MDMA	0.53 ± 0.08	0.53 ± 0.06	0.21 ± 0.04	0.21 ± 0.02	0.27 ± 0.03*	0.24 ± 0.02*	0.52 ± 0.02*	0.49 ± 0.05	0.39 ± 0.04	0.44 ± 0.05
BS	SAL	1.52 ± 0.24	1.29 ± 0.17	0.51 ± 0.07	0.39 ± 0.04	0.35 ± 0.03	0.29 ± 0.03	0.25 ± 0.03	0.23 ± 0.02	0.35 ± 0.03	0.31 ± 0.02
	MDMA	1.68 ± 0.24	1.53 ± 0.26	0.57 ± 0.07	0.51 ± 0.05	0.48 ± 0.04*	0.42 ± 0.03*	0.31 ± 0.03	0.32 ± 0.05	0.36 ± 0.03	0.37 ± 0.04

Values represent nanograms of compound per milligram of protein content (mean ± S.E.M.).
* $p < 0.05$ indicates significant differences between treatment and control groups using ANOVA.
† $p < 0.01$ indicates significant differences between treatment and control groups using ANOVA.

($F_{(1,28)} = 11.698$, $p < 0.005$) and dopamine turnover (HVA/DA: $F_{(1,28)} = 4.332$, $p < 0.05$) were also significantly increased by 31.17% and 30.32%, respectively. No changes in dopamine or DOPAC were seen.

3.2.3. Striatum

Neonatal exposure to MDMA produced a 27.48% and a 29.15% reduction in 5-HT and 5-HIAA, respectively ($F_{(1,27)} = 7.977$, $p < 0.01$; $F_{(1,27)} = 34.192$, $p < 0.001$). Dopamine was unchanged, although its metabolites were significantly increased: HVA (41.01% increase; $F_{(1,27)} = 53.203$, $p < 0.001$) and DOPAC (30.02% increase; $F_{(1,27)} = 25.762$, $p < 0.001$). Dopamine turnover rates were also significantly elevated: HVA/DA (35.93% increase; ($F_{(1,27)} = 60.879$, $p < 0.001$) and DOPAC/DA (24.57% increase; $F_{(1,27)} = 12.884$, $p < 0.001$).

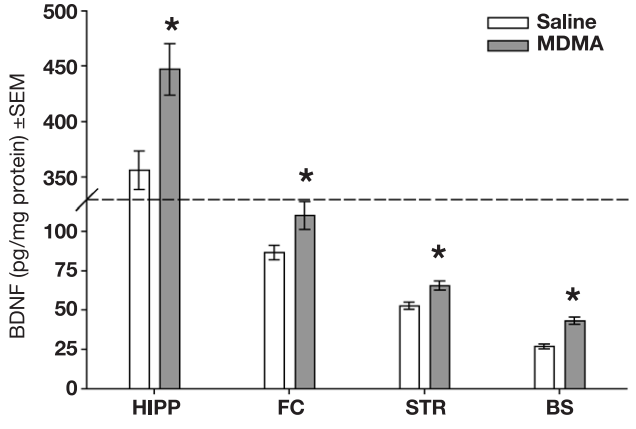

Fig. 1. Neonatal MDMA exposure from postnatal days (P) 11–20 produces significant increases in brain derived neurotrophic factor in the hippocampus (HIPP: MDMA, $n = 16$; SAL, $n = 16$), frontal cortex (FC: MDMA, $n = 16$; SAL, $n = 15$), striatum (STR: MDMA, $n = 14$; SAL, $n = 15$), and brainstem (BS: MDMA, $n = 14$; SAL, $n = 13$), measured at P21. *Significant difference between MDMA- versus saline-treated neonates at $p < 0.05$ using two-way ANOVA with gender and treatment as factors. There was no effect of gender.

3.2.4. Brainstem

Serotonin's metabolite, 5-HIAA, was significantly increased in the MDMA-exposed group by 15.4% ($F_{(1,28)} = 5.915$, $p < 0.05$). P21 HVA and HVA/DA were both significantly increased in MDMA-exposed pups versus controls (HVA by 28.27%; $F_{(1,28)} = 14.633$, $p < 0.001$ and HVA/DA by 22.81%; $F_{(1,28)} = 4.708$, $p < 0.05$).

3.3. Brain-derived neurotrophic factor

All structures revealed a significant increase in BDNF: a 21.36% increase in the FC ($F_{(1,27)} = 4.93$, $p < 0.05$), a 20.35% increase in the HIPP ($F_{(1,28)} = 9.231$, $p < 0.005$), a 19.65% increase in the striatum ($F_{(1,25)} = 13.527$, $p < 0.001$) and a 38.32% increase in the brainstem ($F_{(1,25)} = 39.018$, $p < 0.001$) (Fig. 1). There was no effect of gender.

Correlations between BDNF and neurochemistry yielded the following results. In the FC, there was a significant negative correlation between 5-HT and BDNF ($r_{(31)} = -0.384$, $p < 0.05$). Hippocampus revealed a significant positive correlation between HVA and BDNF ($r_{(31)} = 0.41$, $p < 0.05$). In the striatum, there were correlations between BDNF and: 5-HT ($r_{(31)} = -0.405$, $p < 0.05$), 5-HIAA ($r_{(31)} = -0.41$, $p < 0.05$), DA ($r_{(29)} = 0.418$, $p < 0.05$), DOPAC ($r_{(29)} = 0.543$, $p < 0.01$), HVA ($r_{(29)} = 0.653$, $p < 0.001$) and HVA/DA ($r_{(28)} = 0.583$, $p < 0.001$). Brainstem BDNF correlations revealed a positive relationship with HVA ($r_{(27)} = 0.429$, $p < 0.05$) and dopamine turnover (HVA/DA; $r_{(27)} = 0.429$, $p < 0.05$).

4. Discussion

In all forebrain target structures (FC, STR, and HIPP), measured at P21, neonatal MDMA exposure from P11–20 produced immediate reductions in 5-HT terminal markers, indicated by reductions in 5-HT and 5-HIAA. Dopamine was essentially unchanged, but its metabolites were greatly increased resulting in greater DA turnover. Similar increases

in HVA and dopamine turnover (HVA/DA) were observed in the brainstem, although the 5-HT pattern was quite different than that observed in other structures (no 5-HT changes and increases in 5-HIAA). In addition, all structures examined showed a significant (19–38%) increase in BDNF levels in MDMA-exposed animals versus saline controls. These increases in BDNF levels were significantly correlated with increases in HVA in STR, HIPP and BS and with decreases in 5-HT in the FC and STR.

Profound reductions in both 5-HT and 5-HIAA in the FC, HIPP and STR observed in the current study are consistent with reports of MDMA-induced serotonergic terminal field loss [4,11,13,24,25,32]. While 5-HT and 5-HIAA were measured 24 h following the final administration and traditionally neurotoxicity is assessed following a delay of many days after the final administration, in a previous report employing the same administration model used in the current study, 5-HT was found to be reduced in the hippocampus and frontal cortex at P105 (although to a lesser extent) [5]. Therefore, since the 5-HT reductions observed acutely are also observed long-term, this may indicate early signs of 5-HT terminal field loss. Future investigations are necessary to confirm this assumption by evaluating neurochemistry following a delay after the final administration.

The observed dopaminergic system's response to neonatal MDMA exposure was to maintain normal DA levels through increased DA turnover (produced by increases in DA metabolites, HVA and DOPAC) in all forebrain structures examined. These data suggest that the DA system was able to adapt to MDMA-induced transmitter depletion.

However, it should be noted that when BDNF is infused into the supranigral region, it can significantly increase HVA and dopamine turnover (HVA/DA) in the striatum [1]. This suggests that the increases in HVA and dopamine turnover that we have observed may be secondary to MDMA-induced increases in BDNF and not necessarily the result of MDMA-induced alterations in monoamines.

While increases in BDNF are commonly associated with neuronal repair and neuroprotection, recent reports suggest otherwise. BDNF infused into the nucleus accumbens or ventral tegmental area enhanced the effects of cocaine and appeared to facilitate the development of sensitization to repeated cocaine exposures [10]. This suggests that MDMA may subsequently enhance the reward associated with drugs of abuse, predisposing those exposed to subsequent drug dependence. BDNF can also induce release of the excitotoxin, glutamate, and does so to a greater extent in immature astrocytes than in mature astrocytes [23] contributing to, rather than preventing, neurotoxicity.

MDMA is also an anorectic and results in slower weight gain when administered to neonatal rats. It is important to consider whether MDMA's anorectic properties contribute to the observed neurochemical alterations. Williams et al. [35] found that MDMA-induced learning and memory deficits following the same P11–20 exposure used in the current model were independent of weight differences between groups, suggesting that our results are likely MDMA-specific. It should be noted that dietary restrictions have been shown to induce increases in BDNF in cerebral cortex, hippocampus and striatum of adult rats [6]. Future studies should examine whether the specific reductions in food intake in neonatal rats from P11–20 increases BDNF independent of MDMA exposure.

Drug-induced alterations in growth factors whether direct or indirect during critical periods is likely to produce abnormal developmental outcomes. Increases in BDNF during the neonatal period has been shown to influence the development of the motor system (alterations in Ia/motoneuron functional connectivity) [30], the circuitry of the cortex and cerebellum (alterations in dendritic growth and branching in nonpyramidal neocortical interneurons) [12], and the visual system (survivability of neurons in the superior colliculus) [31,33].

While the current study does demonstrate that neonatal MDMA administration produced profound alterations in the dopaminergic, serotonergic and trophic systems of the brain, the need for future studies involving the current administration paradigm should also be assessed. The P11–20 administration approximates the time during which a portion of hippocampal development takes place in the third trimester of humans [5,35]. While some differentiation does occur during this period (the granule cell layer continues to develop through P14) [3], the vast majority of hippocampal development was completed prior to birth (between embryonic days 14 and 20). In addition, recent epidemiologic studies suggest that MDMA use among pregnant women takes place almost exclusively during the 1st trimester [8,18]. However, recent epidemiologic reports of MDMA use during pregnancy are limited to sampling bias and thus likely underrepresent broad population use patterns.

In conclusion, this is the first report demonstrating that MDMA exposure results in increased levels of BDNF and that such increases are correlated with changes in monoamine levels. We hypothesize that BDNF is involved in a neural compensatory response to MDMA-induced alterations in neurochemistry. Future investigations into earlier exposures and consequences of elevated trophic activity during development are warranted.

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