Neonatal Exposure to Estradiol Valerate Increases Dopamine Content in Nigrostriatal Pathway During Adulthood in the Rat

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- neonatal
- estradiol
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- dopamine
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- amphetamine

Abstract

Research in programming has focused in the study of stimuli that affect sensitive periods of development such as prenatal and neonatal stage. We previously showed that exposure to estradiol valerate to female rats during the first 12 h of life increased catecholamine content in ventromedial-arcuatus hypothalamus of the adult rat. However, changes in others dopaminergic circuits have not been studied. The purpose of this work was to determine the neurotransmitters changes induced by neonatal estradiol valerate (0.1 mg/50 µl s. c. per rat) administration on nigrostriatal pathway of adult female rats. Sesame oil (50 µl s.c. per rat) was administered in a control parallel group. EV-1 adult rats presented effective markers of long-term estrogenization as decreased serum levels of progesterone and a reduction in the size of estrogen-sensitive organs. In the brain, neonatal estradiol valerate administration led to a significant increase in dopamine content in striatum, substantia nigra and ventral tegmental area. With respect to the contents of dopamine metabolites, only 3-methoxytyramine content increased in substantia nigra and ventral tegmental area. In addition, the content of noradrenaline increased only in striatum. Interestingly, estrogenized rats lacked locomotor activity induced by acute dose of amphetamine (1 mg/kg i.p.). Altogether, these results show that neonatal exposure to estradiol valerate permanently modified the content of monoamine neurotransmitters in nigrostriatal pathway and amphetamine-induced locomotor activity of adult female rats. This might imply that estrogenized rats could have changes in the expression of key proteins in dopaminergic regulation, as tyrosine hydroxylase and dopamine transporter.

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Introduction

The programming concept was defined by Lucas as "the physiological redirection of a tissue or organ by a stimulus, in a sensitive period of development, that produces adverse functional changes in adulthood" [1]. Research in programming has focused in the study of stimuli affecting specific windows of sensitivity such as prenatal and neonatal stages. For example, the exposure to variable stress from day 14 to 21 of gestation causes in the adult rat offspring a significant increase in locomotor activity induced by amphetamine [2]. In addition, the exposure of female rats to estrogens during neonatal stage, elicits increased catecholamine content of adrenal gland [3], reproductive disorders [3,4], sexual differentiation of the brain [5], and increased [4,6] or decreased [7] content of neurotransmitters in some brain areas.

Furthermore, it has been observed in adult animals that sex hormones affect the synthesis of enzymes, transporter proteins, and some types of receptors of the monoaminergic neurotransmitter systems. For example, a significant reduction of dopamine transporter (DAT) levels has been shown in nucleus accumbens (NAcc) 4–5 weeks after ovariectomization and the restoration of normal DAT levels after estradiol replacement [8]. On the other hand, exposure to estrogenic compounds such as *p*-nonylphenol enhances tyrosine hydroxylase (TH) activity producing an increase in catecholamine synthesis in cultured bovine adrenal medullary cells [9]. Other studies have shown that sex hormones such as estrogens increase TH expression in substantia nigra and ventral tegmental area (SN-VTA) [10], whereas androgens decrease TH

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immunoreactivity in the same brain areas [11]. Accordingly, sex hormones act as neuromodulators on dopaminergic system in the brain. However, little evidence is available about the long-lasting effects of neonatal exposure to sex hormones on dopaminergic system involved in reward and movement. The purpose of this work was to determine the long-term changes in catecholaminergic nigrostriatal pathway and the locomotor activity induced by amphetamine of adult rats exposed to neonatal estradiol valerate (EV) administration. The choice of early stimuli with EV was based on its pharmacokinetic properties, because this compound produces both, long lasting plasma concentrations and persistent estrogenization in adult rats with one dose [3,4]. We found that neonatal EV administration produced long-lasting changes in the content of catecholamines in SN-VTA and striatum, notwithstanding serum levels of estradiol had already returned to control values.

Materials and Methods

Animals

Thirty newborn female Sprague Dawley pups from 5 litters were used. All animals were housed in a temperature-controlled room (22 ± 2 °C) under a 12-h light cycle with lights on at 06:00 h with food and water ad libitum. All experimental procedures were approved by Ethics Committee of the Faculty of Science Universidad de Valparaíso and the Institutional Animal Experimentation Ethics Board and the Science Council (FONDECYT) of Chile. Efforts were made to minimize the number of animals used and their suffering.

The female pups were divided randomly into 4 groups of animals. Two groups of animals were each subcutaneously injected during the first 12 h of life with 0.1 mg EV dissolved in 50 µl of sesame oil per pup (EV-1). Others 2 groups were single subcutaneously injected with 50 µl sesame oil (Control). The dose of EV used was as previously published [3,4]. All the pups were raised with a lactating mother until the weaning age at PND21. After weaning animals were housed in a group of 6 per standard cages. Length and frequency of estrous cycles (from PND40 to PND60) and the time of vaginal opening were measured only as markers of the effectiveness of neonatal EV-1 administration [3]. At PND60–62 rats were euthanized in diestrus stage by decapitation and trunk blood was collected to determine serum levels of progesterone and estradiol. The right ovary, uterus, and pituitary gland were removed and weighed on analytical balance (Chyo, model JK-180). At the same time, the brain was removed and SN-VTA and striatum were microdissected at 4 °C as described by Torrens et al. [12] and Abarca et al. [13], respectively. Brain tissues were weighed and stored at −80 °C for further analysis.

Neurotransmitter content in the SN-VTA and striatum

Tissue homogenization was performed according to Chi et al. [14]. Briefly, the tissue was collected in 400 µl of 0.2 N perchloric acid and then homogenized in a glass-glass homogenizer. The homogenate was centrifuged at 12 000 × *g* for 15 min at 4 °C (Hermle LaborTechnik GmbH, model Z233MK-2) and the supernatant was injected into a high-performance liquid chromatograph (HPLC) instrument coupled to electrochemical detection, to measure dopamine (DA), noradrenaline (NA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 3-methoxytyramine (3-MT) content. The pellet was resuspended in 1 N NaOH for protein quantification by the Bio-Rad Protein Assay (Bio-Rad Laboratories, Inc., Richmond, CA, USA) using bovine serum albumin as standard. The contents of DA and NA were expressed as picograms per milligram of total protein. Ten microliters of each supernatant were injected to the HPLC system with the following setting: A isocratic pump, (model PU-2080 Plus, Jasco Co. Ltd., Tokyo, Japan), a UniJet microbore column (MF-8912, BAS, West Lafayette, IN, USA), and an amperometric detector (set at 650 mV, 0.5 nA; model LC-4C, BAS, West Lafayette, IN, USA). The mobile phase, containing 0.05 M NaH_2PO_4, 1.0 mM 1-octanesulfonic acid, 0.27 mM EDTA, 1.0 % (v/v) tetrahydrofuran, and 4.0 % (v/v) acetonitrile (CH_3CN) (pH adjusted to 2.6) was pumped at a flow rate of 100 µl/min. The level of neurotransmitters and metabolites were assessed by comparing the respective peak area and elution time of the sample with a reference standard and the quantification was performed using a calibration curve for each neurotransmitter (Program ChromPass, Jasco Co. Ltd., Tokyo, Japan). Under these experimental conditions, retention times were 3.4 min for NA, 6.1 min for DOPAC, 7.1 min for DA, 12.7 min for HVA, and 14.2 min for 3-MT. Standards, EDTA and 1-octanesulfonic acid were purchased from Sigma-Aldrich, Inc. (St Louis, MO, USA), and all other reagents were of analytical grade.

Determination of serum levels of estradiol and progesterone

Estradiol (E2) levels were determined by enzyme immunoassay (EIA) following the manufacturer's instructions (11-ESTH-430; Alpco Diagnostic, Windham, NH, USA). Intra-assay and interassay variations were less than 5 %; the minimal detectable value of E2 was 10 pg/ml of serum. Progesterone levels were determined by EIA following the manufacturer's instructions (11-PROGH-305; Alpco Diagnostic). Intra-assay and interassay variations were less than 5 %; the minimal detectable value of progesterone was 0.1 ng/ml of serum.

Locomotor activity

Basal and amphetamine-induced locomotor activities were measured in control and EV-1 groups. Each animal was placed in a test cage (44 long × 22 height × 28 wide cm) and for the first 30 min basal locomotor activity was recorded. At 30 min, each animal was injected with a dose of amphetamine (1 mg/kg i. p. dissolved in saline) and its locomotor activity was recorded during 60 min. The locomotor activity was recorded by internet protocol (IP) cameras (Model LX-C202, Lynx Security, China) fixed above the each test cage and connected to a computer in another room. Videos were analyzed with ANY-maze video tracking system (Stoelting Co., IL, USA) under license acquired by Dr. Alexies Dagnino-Subiabre. Test cages were wiped and cleaned with 5 % ethanol solution after each trial.

Statistical analysis

Unpaired one-tailed *t*-test was used to determine significant differences between mean ± sem values of control and EV-treated rats (**Table 1–3** and **Fig. 1**). A 2-way ANOVA was performed to determine differences between groups in locomotor activity experiment (**Fig. 2**). The statistical analyses were carried out with GraphPad Prism v5.0 (GraphPad Software, San Diego, CA, USA).

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Tissue or Hormone	Control			Estrogenized			p-Value
	Mean	SEM	n	Mean	SEM	n	
Ovary weight (mg)	40.23	1.61	7	7.36	0.72	7	<0.0001
Uterus weight (mg)	331.94	16.13	7	136.87	8.40	7	<0.0001
Pituitary weight (mg)	12.45	0.48	7	7.21	0.19	7	<0.0001
Serum progesterone (ng/ml)	6.82	0.92	7	1.09	0.22	7	<0.0001
Serum estradiol (pg/ml)	44.40	3.91	7	63.17	13.28	7	0.1166

All of these tissues are rich in estrogen receptors and are sensitive to a persistent neonatal estrogenization. With respect to sex hormones, the exposure to EV at PND1 decreases progesterone serum levels in adult female rats without affecting serum levels of estradiol

Table 1 Exposure to estradiol valerate (EV) at PND1 significantly decreases ovary, uterus, and pituitary weights in adult female rats.

Striatum Neurotransmitters (pg/mg of protein)	Control			Estrogenized			p-Value
	Mean	SEM	n	Mean	SEM	n	
DA	111 448.4	6 707.6	7	137 070.0	11 053.8	7	0.0355*
DOPAC	29 427.4	3 269.6	7	39 891.6	5 780.1	7	0.0705
HVA	9 379.6	1 004.0	7	12 429.7	3 223.0	7	0.1920
3-MT	5 973.0	759.5	7	6 772.4	1 401.1	7	0.3125
[DOPAC/DA]	0.2619	0.0245	7	0.2890	0.0371	7	0.2763
[HVA/DA]	0.0831	0.0062	7	0.0847	0.0138	7	0.4597
[3-MT/DA]	0.0526	0.0050	7	0.0473	0.0057	7	0.2491
[Metabolites/DA]	0.3974	0.0346	7	0.4211	0.0470	7	0.3457

DA: Dopamine; DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: homovanillic acid; 3-MT: 3-methoxytyramine; DOPAC + HVA + 3-MT: Metabolites

*p < 0.05 compared to the control group

Table 2 Striatal monoamine levels from control and EV-1 adult female rats.

SN-VTA Neurotransmitters (pg/mg of protein)	Control			Estrogenized			p-Value
	Mean	SEM	n	Mean	SEM	n	
DA	11 509.9	1 590.7	7	23 133.9	5 559.5	7	0.0337*
DOPAC	4 993.6	1 267.9	7	8 598.4	2 514.1	7	0.1123
HVA	1 896.4	467.3	7	2 882.1	640.8	7	0.1188
3-MT	2 244.1	259.1	7	3 990.9	378.1	7	0.0448*
[DOPAC/DA]	0.4026	0.0628	7	0.3590	0.0297	7	0.2711
[HVA/DA]	0.1544	0.0256	7	0.1281	0.0129	7	0.1884
[3-MT/DA]	0.2163	0.0413	7	0.1573	0.0236	7	0.1194
[Metabolites/DA]	0.7876	0.0686	7	0.6441	0.0359	7	0.0445*

DA: Dopamine; DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: homovanillic acid; 3-MT: 3-methoxytyramine; DOPAC + HVA + 3-MT: Metabolites

*p < 0.05 compared to the control group

Table 3 Substantial nigra-ventral tegmental area (SN-VTA) monoamine levels from control and EV-1 adult female rats.

Results

Assessment of serum sex hormones levels and the size of estrogen-sensitive organs as a measure of the effectiveness of neonatal EV administration

The administration of EV at PND1 produced a weight decrease in ovary, uterus and pituitary gland at PND60 (**Table 1**). In addition, serum progesterone levels decreased in EV-1 rats compared to controls; however, serum estradiol levels in EV-1 rats was similar to control rats at PND60 (**Table 1**).

Neurotransmitters and metabolites content in SN-VTA and striatum in EV-1 and controls rats

We observed that neonatal EV administration produced a significant increase in DA content in SN-VTA and striatum at PND60 (**Fig. 1a, b**). In addition, EV-1 rats showed an increase in the content of NA in striatum at PND60 compared to control rats (**Fig. 1c**), but no changes in NA content were seen in SN-VTA at PND60 (**Fig. 1d**). Regarding the metabolites in SN-VTA we only found a slight increase in the content of 3-MT in EV-1 rats. Accordingly, the ratio of total content of DA metabolites (DOPAC + HVA + 3-MT) on DA showed a reduced turnover in EV-1 rats (**Table 2**). In striatum the content of DA metabolites and the ratios of metabolites on DA did not change significantly in EV-1 rats (**Table 3**).

Basal and amphetamine-induced locomotor activity in EV-1 and controls rats

We observed that basal locomotor activity does not change between groups during the first 30 min. However, the amphetamine-induced locomotor activity (30–90 min) was higher in control rats than in EV-1 rats. A 2-way repeated measures ANOVA analysis showed a significant effect when comparing control vs. EV-1 rats: treatment [$F_{(1,252)} = 22.06$, $p < 0.0001$), time [$F_{(17,252)} = 4.523$, $p < 0.0001$] and interaction [$F_{(17,252)} = 3.196$, $p < 0.0001$] (**Fig. 2**).

Discussion

Our results show that EV administration to neonatal rats produces changes in catecholamine content in nigrostriatal path-

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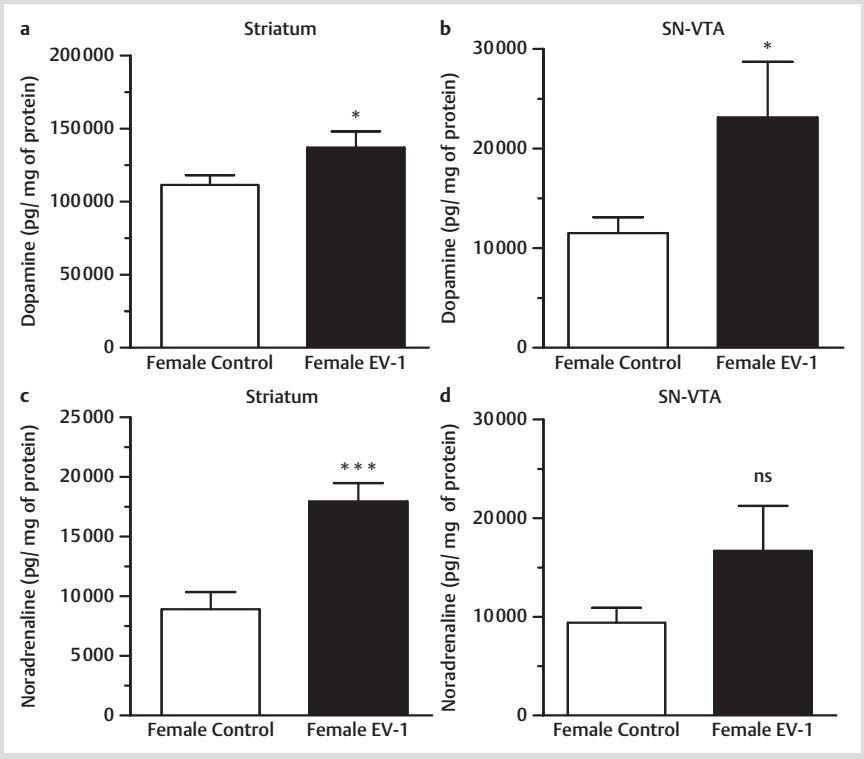

Fig. 1 Effect of neonatal exposure to estradiol valerate (EV) at PND1 on concentration of dopamine and noradrenaline in striatum **a**, **c** and substantia nigra-ventral tegmental area **b**, **d**. Results are expressed as pg/mg of protein and represent the mean ± SEM (n = 7 per group). *p < 0.05, ***p < 0.0001, and ns: not significant.

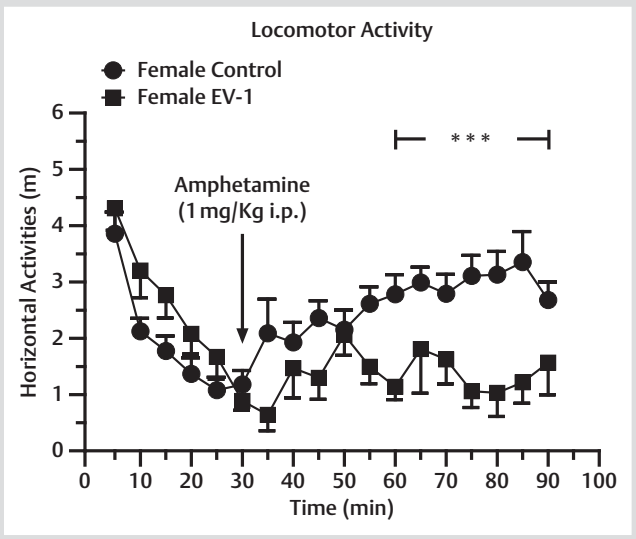

Fig. 2 Effect of neonatal exposure to estradiol valerate (EV) at PND1 on locomotor activity induced by amphetamine administration in female rats. Results are expressed as mean ± SEM (n = 11 per female control, n = 5 per female EV-1). ***p < 0.0001.

way during adulthood. These effects in the brain are associated with a condition of permanent estrogenization that alters rat reproductive function. Previously we demonstrated that neonatal administration of EV produces an increase in catecholamine content (DA and NA) in the ventromedial hypothalamus-arcuatus nucleus, which forms part of tuberoinfundibular dopaminergic system [4]. However, other dopaminergic areas have not been studied with this model.

Early EV exposure produces long term impairments of reproductive function that can be easily noted as atrophy of different sensitive tissues [3, 15]. As a control of our procedure of neonatal estrogenization we show that EV administration at PND1 produces atrophy in the ovaries, pituitary gland, and uterus. In the present work we detected significant changes in the amount of catecholamine neurotransmitters in the nigrostriatal dopaminergic pathway in rats that were exposed to estradiol at PND1. These results could be interpreted in 2 ways. First, the long-term reproductive abnormalities produced by early exposure to estradiol, that is, absence of corpora lutea and lower progesterone levels in EV-1 rats, could affect the nigrostriatal circuitry when rats are adult. Second, the higher estradiol levels during development can produce a disruption of developing nigroestriatal pathway, which persists until the adulthood.

Catecholamine content in nigrostriatal pathway in adult rats which were exposed to estradiol at PND1

We observed that neonatal administration of EV increases tissue DA concentration in areas of the nigrostriatal pathway, while NA concentration only increases at striatal level. It is noteworthy that the estradiol concentration had fallen to control values when the assessments were done at PND60. This indicates that estradiol administration at PND1 may cause permanent changes in the content of catecholaminergic neurotransmitters in the nigrostriatal pathway, which are not dependent of the serum estradiol concentration at PND60. One possibility for this effect on catecholamine neurotransmitters may be due to long-lasting epigenetic changes in catecholamine synthesis enzymes, such as TH. Recently, it has been shown in in vitro studies that the TH gene has estrogen response elements (ERE) in its promoter and that estradiol activates TH transcription through estrogen receptor alpha (ERα) [15]. In this sense, immunohistochemistry studies in adult female rats and mice have shown a relationship between the levels of expression of TH in SN-VTA and serum concentration of estradiol. A decrease in TH-immunoreactive cells has been observed in SN-VTA of rats and mice OVX, and the

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replacement with ERα or ERβ selective agonists induces a recovery of the levels of TH positive cells in this region [10].

Based on this background, our results suggest that the increase in catecholamine content in nigrostriatal pathway might be produced by long-term epigenetic changes mediated by estrogens, facilitating an increase in the TH expression in dopaminergic neurons. Further experiments are necessary to test this hypothesis.

The increased catecholamine content in the nigrostriatal pathway can occur through other proteins susceptible to epigenetic changes induced by estradiol. In this regard, it has been shown that methylation patterns of estrogen receptors change at PND60 in female rats that have been exposed during the first hours of life to estradiol [16]. The percent methylation of ERα in the preoptic area and of ERβ in mediobasal hypothalamus decreases in estrogenized females [16]. In this sense, a decrease in the percentage of methylation of ERs genes could lead to an increased transcription of the ERs mRNA, increased translation to ERs proteins, and to a greater effect of estradiol on its receptors such as those involved in TH transcription.

At neurochemical level, the content of DA in homogenized tissues represents mainly the intracellular levels of the neurotransmitter. To test the DA turnover, we measured the total metabolites of DA to get an estimated value of DA releasability in SN-VTA and striatum. Absence of changes in the turnover of DA in striatum means no alterations in DA basal release in this region (**Table 2**). However, in SN-VTA we observed a slight but significant decrease in DA turnover that represents a lower basal releasability of DA in EV-1 rats (**Table 3**).

Basal and amphetamine-induced locomotor activity in adult rats which were exposed to estradiol at PND1

This study was focused in brain areas involved in the production of movement (nigrostriatal pathway) and reward (mesocorticolimbic pathway) [17]. The reward system is formed mainly by dopaminergic projections from VTA to limbic and cortical areas as NAcc and prefrontal cortex, respectively (for review, see [18]). Although we did not measure tissue concentrations of DA in NAcc, we observed an increase of DA content in cell bodies of the SN-VTA dopaminergic neurons. Perhaps this increase in tissue concentrations of DA in SN-VTA is associated with an increase in DA content in NAcc and may imply changes in the releasable pool of DA against chemical stimuli such as cocaine or amphetamine. To test behavioral changes, we measured the basal locomotor activity and the response to acute dose of amphetamine (1 mg/kg i. p.). Surprisingly, we found that EV-1 lacked of response to amphetamine administration indicating that early estrogen exposure probably have several targets to modulate the activity of nigroestriatal pathway. This finding could be explained by a reduction in the expression of the dopamine transporter (DAT: molecular target of amphetamine action) in striatal dopaminergic terminals. In this context, some studies have demonstrated that neonatal exposure to Bisphenol-A (BPA: an endocrine disrupter with estrogenic activity) in rodents produces a significant reduction in protein [19] and mRNA [20] levels of DAT at 5 weeks old. A specific mechanism for this effect has not been studied; however, at behavioral level it was demonstrated that the administration of a dose of cocaine does not increase locomotor activity in OVX adult rats [21]. In the same way, others behaviors associated with the reinforcing effects of drugs of abuse such as conditioned place preference to amphetamine [22] and cocaine self-administration [23] did not occur in OVX adult rats. These findings are very interesting because the authors demonstrate that ovarian sex hormones positively modulate brain dopaminergic circuits. In this sense, the characterization of long-term reproductive effects in our model showed that progesterone levels at PND60 were significantly lower in EV-1 rats (**Table 1**). This decrease in serum levels of progesterone could be responsible for the absence in amphetamine-induced locomotor activity that we observed in control rats. In vitro studies demonstrate that progesterone modulates striatal DA release in slices of male and female rats [24–26].

Recently it has been shown that the administration of testosterone and progesterone decreases cocaine self-administration in female rhesus monkeys [27]. Finally, if we consider that in our model of neonatal, EV administration produces significant changes in the content of catecholamines in nigroestriatal pathway, in the behavioral response to amphetamine, and in serum progesterone levels in adult female rats, we may assume that the repeated exposure to drugs of abuse might have higher rewarding effects in EV-1 rats and may be a factor of vulnerability to drug addiction.

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Conflict of Interest

The authors of this paper declare that they have no conflicts of interest.

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