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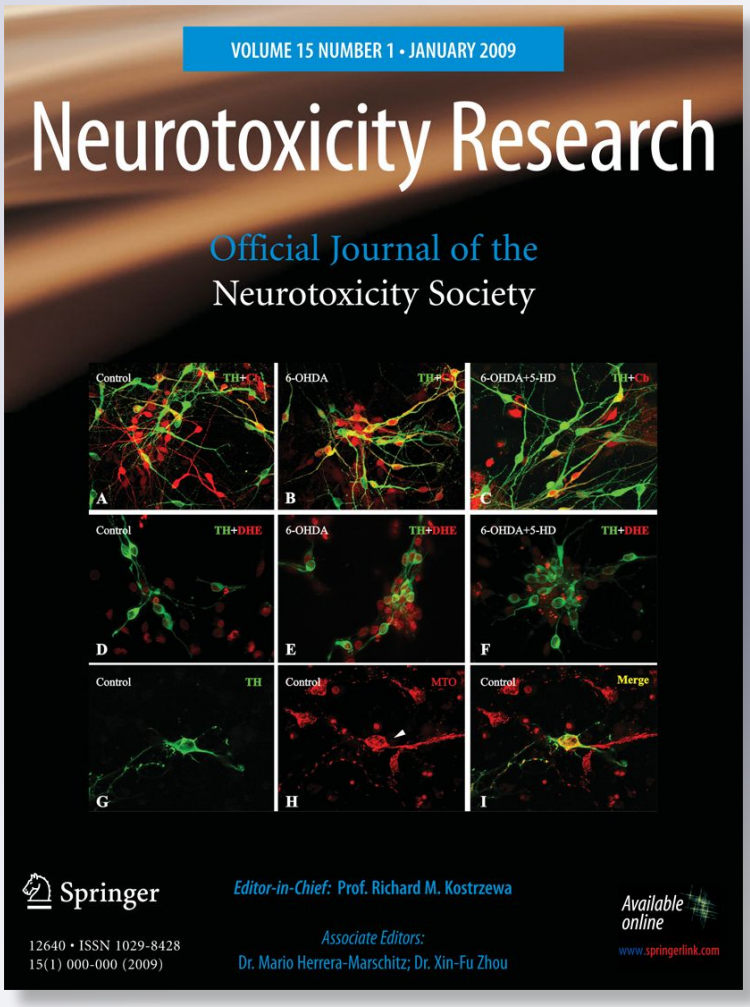
Neurotoxicity Research
Neurodegeneration, Neuroregeneration, Neurotrophic Action, and Neuroprotection

ISSN 1029-8428

Neurotox Res
DOI 10.1007/s12640-011-9305-4



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DOI 10.1007/s12640-011-9305-4

REVIEW ARTICLE

Gestational Restraint Stress and the Developing Dopaminergic System: An Overview

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Received: 20 July 2011 / Revised: 15 December 2011 / Accepted: 20 December 2011
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Abstract Prenatal stress exerts a strong impact on fetal brain development in rats impairing adaptation to stressful conditions, subsequent vulnerability to anxiety, altered sexual function, and enhanced propensity to self-administer drugs. Most of these alterations have been attributed to changes in the neurotransmitter dopamine (DA). In humans; dysfunction of dopaminergic system is associated with development of several neurological disorders, such as Parkinson disease, schizophrenia, attention-deficit hyperactivity disorder, and depression. Evidences provided by animal research, as well as retrospective studies in humans, pointed out that exposure to adverse events in early life can alter adult behaviors and neurochemical indicators of midbrain DA activity, suggesting that the development of the DA system is sensitive to disruption by exposure to early stressors. The purpose of this article is to provide a general overview of published studies and our own study related to the effect of prenatal insults on the development of DA metabolism and biology, focusing mainly in articles involving prenatal-restraint stress protocols in rats. We will also attempt to make a correlation between theses alterations and DA-related pathological processes in humans.

Keywords Prenatal stress · Restraint · Rat brain · Limbic system · Dopamine

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Abbreviations

6-OHDA	6-Hydroxydopamine
AADC	L-Amino acid decarboxylase
AAS	Androgenic-anabolic esteroids
ACTH	Adrenocorticotropic hormone
ADHD	Attention-deficit hyperactivity disorder
AMG	Amygdala
COMT	Catechol-*O*-methyltransferase
CPu	Caudate putamen
CPu-L	Caudate putamen lateral
CPu-M	Caudate putamen medial
CRH	Corticotropin-releasing hormone
DA	Dopamine
DAT	DA transporter
DFC	Dorsal frontal cortex
DOPAC	3,4-Dihydroxyphenylacetic acid
E	Embryonic day
EAAT	Excitatory amino acid transporter
GLT	Glutamate transporter
HPA	Hypothalamic–pituitary–adrenal
HPG	Hypothalamic–pituitary–gonadal
HVA	Homovanillic acid
L-DOPA	L-3,4-Dihydroxyphenylalanine
MAOB	Monoamine oxidase B
mdDA	Mesodiencephalic dopaminergic
mGluR	Metabotropic glutamate receptor
MPC	Medial prefrontal cortex
NAc	Nucleus accumbens
NAc-C	Nucleus accumbens core
NAc-S	Nucleus accumbens shell
NMDA	*N*-methyl-D-aspartic acid
PD	Parkinson's disease
PFC	Prefrontal cortex
PND	Postnatal days
POA	Preoptic area

Published online: 04 January 2012

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PS	Prenatal stress
SN	Substantia nigra
SNc	Substantia nigra pars compacta
TH	Tyrosine hydroxylase
TF	Transcription factors
VGluT2	Vesicular transporter of glutamate
VMAT2	Vesicular monoamine transporter 2
VTA	Ventral tegmental area

Introduction

It is well known that midbrain dopamine (DA) system regulates diverse behavioral and cognitive functions that are critical for integrating mammalian responses and adaptations to the environment. The corticolimbic system is considered to be of particular interest for the pathophysiology of idiopathic psychiatric disorders including psychoses and mania, as well as in schizophrenia and attention-deficit hyperactivity disorder (ADHD) (Biederman 2005), which have been traditionally related to dopaminergic mesolimbic and mesocortical pathways. The hypothesis that schizophrenia and ADHD have a neurodevelopmental origin is now the most widely accepted explanation for the pathophysiology of these diseases (Koenig et al. 2002; Lewis and Levitt 2002). At present, most models that explain the cause of schizophrenia propose interactive effects between multiple susceptibility genes and environmental factors. In this regard, Lewis and Levitt (2002) pointed out that many environmental events occur during the prenatal or perinatal period. It has been demonstrated that prenatal stress (PS) exerts a strong impact on fetal brain development in experimental animal models (Weinstock 2001). In the last years, increasing evidences demonstrate that exposure to different stressful events during the last week of pregnancy in rats interferes with the correct progeny development showing delays in motor development, impaired adaptation to stressful conditions, altered sexual behavior, and learning deficits (Weinstock 2001, 2008; Huizink et al. 2004; Darnaudery and Maccari 2008). In addition, the offspring display anomalies in neuronal development and brain morphology, as well as changes in cerebral asymmetry that persist into adulthood (Fride and Weinstock 1989). Evidences provided by animal research, as well as retrospective studies in humans, pointed out that exposure to adverse events in early life can alter adult behaviors and neurochemical indicators of midbrain DA activity, suggesting that the development of the DA system is sensitive to disruption by exposure to early stressors.

The main aim of the present article is to summarize and discuss the information available about the relationship between PS and dopaminergic neurotransmission, focusing primarily on how prenatal insults could affect DA metabolism and biology, as well as how these alterations are reflected in DA-related pathological processes in humans.

Prenatal Stress Protocols

Several PS protocols exist in the literature, which vary in type of stressor, daily frequency, length of application, and week of gestation chosen. The types of stressors employed in the literature have been summarized by Huizink et al. (2004) and in rodents, which range from suspension, crowding, repeated tail shocks, restraint, immobilization, saline injections, unpredictable stress and noise, and flashing lights. They make a detailed analysis of the different types of protocols in terms of the stressor, timing, physiology, and species since they argue that the difference in methodology has made the comparability across studies very difficult and may explain discrepant findings.

Since we have focused this review in the effect of PS on DA metabolism, we have summarized the existing literature in Table 1 in relation to the stress protocols. It can be observed that the protocols employed can be reduced to restraint, restraint and bright light, flashing lights/sounds, and a variable stress protocol. These stressors might not be comparable to each other and might give different physiologic stress responses in the gestant mother. However, there are several common aspects among these protocols. None of them involves the infliction of pain and, in the majority, the exposure to stress was applied in the third week of gestation. The species employed are mainly rats, either Wistar or Sprague Dawley, except in one case where they employed ICR mice. The frequency and duration of the stress application differ among protocols, and this might produce a different intensity in the physiological response of the mother. According to Archer and Blackman (1971), the intensity of the response of the mother is more important than the intensity of the stimulus.

In the prenatal restraint model that we have employed throughout our studies, the pregnant dams are placed individually in a transparent plastic restrainer fitted closely to body size for 45-min periods three times a day (09:00 h, 12:00 h, and 17:00 h) between days 14 and 21 of pregnancy (E 14–21). Control pregnant females were left undisturbed in their home cages. Buynitsky and Mostofsky (2009) have reviewed the literature on restraint protocols and state that restraint is a preferred means of stressing animals mainly because it is painless, straightforward, does not involve bodily harm, and is inexpensive. The physiological changes associated with restraint seem to result from the distress and aversive nature of having to remain immobile, and these changes manifest as mainly

Table 1 Prenatal stress models (A) and prenatal glucocorticoid exposure models (B) described in the review

Reference	Species (strain)	Stressor	Timing of		Results
			Stressor	Assessment	
A. Prenatal stress models described in the review					
Adrover et al. (2007)	Rats (W)	Restraint (3 × 45 min/day)	E 14–21	P 90	Loss of left–right asymmetry of D2-R in NAc
Alonso et al. (1997)	Rats (SD)	Suspension stress, 3 h/day	E 15–21	P 90	↑ DA, ↓ DOPAC, ↓ HVA in right NAc
Barros et al. (2004)	Rats (W)	Restraint (3 × 45 min/day)	E 14–21	P 90	Partial reversion of PS effect in D2-R and NMDA-R by adoption
Barros et al. (2006a, b)	Rats (W)	Restraint (3 × 45 min/day)	E 14–21	P 90	↓ Dendritic arborization in FC and HPC CA1. Synaptic loss in FC and HPC CA1
Berger et al. (2002)	Rats (W)	Restraint (3 × 45 min/day)	E 14–21	P 90	↑ D2-R in MPC, DFC, CA1, and NAc; ↑ NMDA-R in MPC, DFC, CA1, CA3, CPu-L, CPu-M, NAc-C, and NAc-S ↑ Group III mGluR in MPC and DFC
Carboni et al. (2010)	Rats (W)	Restraint (3 × 45 min/day)	E 14–21	P 90	↓ DA release (amphetamine stimulated) at P 60
Fride and Weinstock (1989)	Rats (Albino)	Flashing lights and sound from a bell (5 min random during 4 h. 3 days per week)	E 1–21	P 120	♂: ↓ directional preference and ↓ DA turnover rates in CPu. ♀: reversal direct preference and ↓ DA turnover rates in CPu
Fumagalli et al. (2009)	Rats (SD)	Restraint and bright light (3 × 45 min/day) Forced swim stress	E 14–21	P 80	Acute swim stress enhanced phosphorylation of NMDA-R and CAMKII in ctrl. PS attenuated such activation
Gerardin et al. 2005	Rats (W)	Restraint stress (1 h/day)	E 18–22	P 22 and 75	↓ T levels, delayed latency to the first mount and first intromission, and ↓ ejaculations ↑ of DA and serotonin levels in striatum
Henry et al. (1995)	Rats (W)	Restraint/Bright light (3 × 45 min/day)	E 14–21	P 90	= D1-R, ↑ D2-R, and ↓ D3-R in NAc
Katunar et al. (2009)	Rats (W)	Restraint (3 × 45 min/day)	E 14–21	P 60	IHC identification of Ptx3+ and Nurr1+ cells in different brain areas
Katunar et al. (2010)	Rats (W)	Restraint (3 × 45 min/day)	E 14–21	P 7, 28, and 60	In VTA↑ Nurr1+ cells at P 7, 28, and 60; ↓ Pitx3+ cells at P 7 and ↑ Pitx3+ cells at P 28
Kippin et al. (2008)	Rats (SD)	Restraint (3 × 45 min/day)	E 14–21	P 70–84	Cocaine naive: ↑ locomotor activity; ↑ DA-R (NAc) ↓ Glu, and 5-HT. Cocaine-experienced: ↑ cocaine seeking; ↓ Glu (NAc) and ↑ DA (PFC)
Lemaire et al. (2000)	Rats (SD)	Restraint (3 × 45 min/day)	E 14–21	P 28; 3, 10, and 12 months	PS ↓ cell proliferation in the in the dentate gyrus. PS ↓ granule neurons from P 90. PS impaired HPC-related spatial tasks and blocked the↑ of learning-induced neurogenesis
Mabandla et al. (2009)	Rats (SD)	Variable stress protocol	E 14–21	P 75	PS ↓ number of TH+ cells in midbrain of 6-OHDA-lesioned rats

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Table 1 continued

Reference	Species (strain)	Stressor	Timing of		Results
			Stressor	Assessment	
Pereira et al. (2006)	Rats (W)	Restraint stress (1 h/day) Restraint stress + testosterone	E 18–22	P 22 and 75	Neonatal T replacement prevented the reduction in anogenital distance, prevented the ↓ in T levels during the adulthood and improved sexual performance
Rodriguez et al. (2007)	Rats (W)	Restraint stress (3 × 30 min/week)	E 5–21	P 30, 45, and 70	LNL offspring: ↓ in testicle weight and T levels. HNL offspring: ↓ in LH levels
Shono and Suita (2003)	Rats (W)	Reverse light dark cycles Restraint stress (3 × 60 min/day)	E 14–18	P 21 and 30	↓ of T and LH in testes. ↓ the number of animals with complete testicular descent
Silvagni et al. (2008)	Rats (W)	Restraint (3 × 45 min/day)	E 14–21	P 90	DA release (basal and amphetamine stimulated) at P 28 and 60
Son et al. (2006)	ICR mice	Restraint (6 h/day)	E 8–19	P 42	In HPC: impaired spatial learning, ↓ NMDA mediated LTP, ↓ NR1, and NR2B subunits
Song et al. (2009)	Rats (SD)	Restraint (3 × 45 min/day)	E 14–21	P 30	PS produce mitochondrial DNA oxidative damage in ♀ and ♂
Ward and Weisz (1984)	Rats (SD)	Restraint (3 × 45 min/day)	E 14–21	E 17, 18, 19, and 21	PS ↓T plasma levels in ♂
Ward et al. 2003	Rats (SD)	Restraint (3 × 45 min/day) 36% ethanol provided ad libitum on liquid diets Restraint stress and ethanol diet	E 14–20; tarting at E 10	E 16–20, P 17–20	PS: ↓ PN T. Ethanol: ↑ T on E 18 and 19 PS + ethanol: blocked the normal ↑ in T between E 17–19
Zhu et al. (2004)	Rats (SD)	Restraint (3 × 45 min/day)	E 7–13 and E 14–20	P 30	PS ↓cell number in ♀ and ↑ nNOS + cells in ♀ and ♂. PS in E 14–20 ↑ intracellular Ca^{2+} and ROS in HPC CA3 in ♀
Zuena et al. (2008)	Rat (SD)	Restraint and bright light (3 × 45 min/day)	E 11–21	P 90	In ♂ ↑ anxiety-like behavior, ↓survival of newborn cells in the dentate gyrus, ↓ activity of mGlu1/5, ↑ levels of BDNF. In ♀ ↓ anxiety, ↑ activity of mGlu1/5, = BDNF levels
B. Prenatal glucocorticoid exposure models described in the review					
Diaz et al. (1997)	Rats (SD)	Implantation of corticosterone pellet	E 16–delivery	P 21, 90, and 120	In prepuberal ♂↑ spontaneous locomotion. In ♀ ↑ in spontaneous rearing. In adult ♂ ↑ exploratory activity. In adult ♀↓ spontaneous locomotion and ↓ apomorphine-induced motility and locomotion
Fukumoto et al. (2009)	Rats (W)	DEX was injected subcutaneously in pregnant rats	E 14.5–20.5	E 16.5, 17.5, 18.5, 19.5, 21.5, P 3 and 7	PN DEX caused retardation of radial migration of post-mitotic neurons during the development of CTX. Identification of caldesmon as the GC main target

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Table 1 continued

Reference	Species (strain)	Stressor	Timing of		Results
			Stressor	Assessment	
McArthur et al. (2005)	Rats (SD)	DEX addition to the drinking water of pregnant or nursing dams	E 16–19	P 1–7 and 70	PN DEX ↑ TH + cells in SNc and VTA of ♀ and ♂. PtN DEX ↑ TH + cells in SNc in ♀; in VTA ↑ TH + cells number in ♀and ♂. PN DEX ↑DA in striatum in ♂ and ↑ DOPAC in NAc from ♀
McArthur et al. (2007)	Rats (SD)	DEX addition to the drinking water of pregnant or nursing dams	E 16–19	P 1–7 and 70	SNc volume is ↑ in ♀ compared with ♂ in ctrl. PN DEX ↑ SNc volume in ♂ and ↓ SNc volume in ♀. PtN DEX ↓ SNc volume in ♀. VTA volume was ↑ in ♀ compared with ♂ in ctrl. PN DEX ↑VTA volume in ♀and ♂
Owen and Matthews (2007)	Guinea pigs	Injection of BET at three gestational days.	E 40/41, 50/51, and 60/61	P 10	PN BET ↑ locomotor activity and ↓ NR1 mRNA in CA1/2 and CA3 areas from HPC only in ♀

SD Sprague-Dawley, *W* Wistar, *BET* betamethasone, *CTX* cortex, *ctrl* control, *DEX* dexamethasone, *GC* glucocorticoid, *HPC* hippocampus, *HNL* high number of offspring per litter, *LNL* low number of offspring per litter, *PN* prenatal, *PtN* postnatal, *R* receptor, *T* testosterone; ↑, increase; ↓, decrease; ♀, females; ♂, males

increases in adrenocorticotropic hormone (ACTH) and corticosterone.

In our model, the intensity and duration of the stress seem to be sufficient since we have assessed a variety of parameters including behavioral and biophysiological (beside the dopaminergic ones) in the offspring showing long-term effects of the maternal stress reflecting lack of habituation. We have observed that the offspring show delayed testicular descent, increased anxiety, and decrease benzodiazepine receptors in hippocampal and amygdala (AMG) areas, as well as morphological alterations in cortical and striatal areas (Barros et al. 2004, 2006a, b).

Increased levels of stress hormones during pregnancy could affect the fetal nervous system with long-term consequences in the offspring. The mechanism by which the pregnant mother transduces stress to the fetus is still a matter of debate. However, Huizink et al. (2004) propose three possibilities which may act in concert and that are related to (i) the transplacental transport of maternal stress hormones to the fetus, (ii) placental hormones that enter the fetal circulation, and (iii) maternal stress-induced effects on the blood flow to the placenta. Most of the studies agree in pointing out that corticosterone, the main glucocorticoid in rodents, can easily cross the placenta and blood–brain barrier. On the other hand, placental cells can produce corticotropin-releasing hormone (CRH) and related stress hormones under the influence of maternal stress, which can readily enter the fetal circulation. A recent review by Sandman et al. (2011) indicates that, in humans, the increase of placental CRH (pCRH) plays a fundamental role in the organization of the fetal nervous system and that the increase in maternal circulating cortisol stimulates the expression of the genes for the major stress hormones (hCRHmRNA) in the placenta, establishing a positive feedback loop that allows the increase of pCRH, ACTH, beta-endorphin, and cortisol over the course of gestation.

The Dopaminergic System

Development and Localization

DA is the predominant catecholamine neurotransmitter in the mammalian brain, where it controls a variety of functions including locomotor activity, cognition, emotion, positive reinforcement, food intake, and endocrine regulation (Missale et al. 1998). The estimated number of neurons in the adult bilateral mesodiencephalic DA system (A8–A10) ranges from 45,000 in rat to 400,000–600,000 in human. These neurons rise to prominent forebrain projections and receive inputs from various other brain regions.

The development of midbrain dopaminergic neurons is a complex, multi-step process (Van den Heuvel and Pasterkamp

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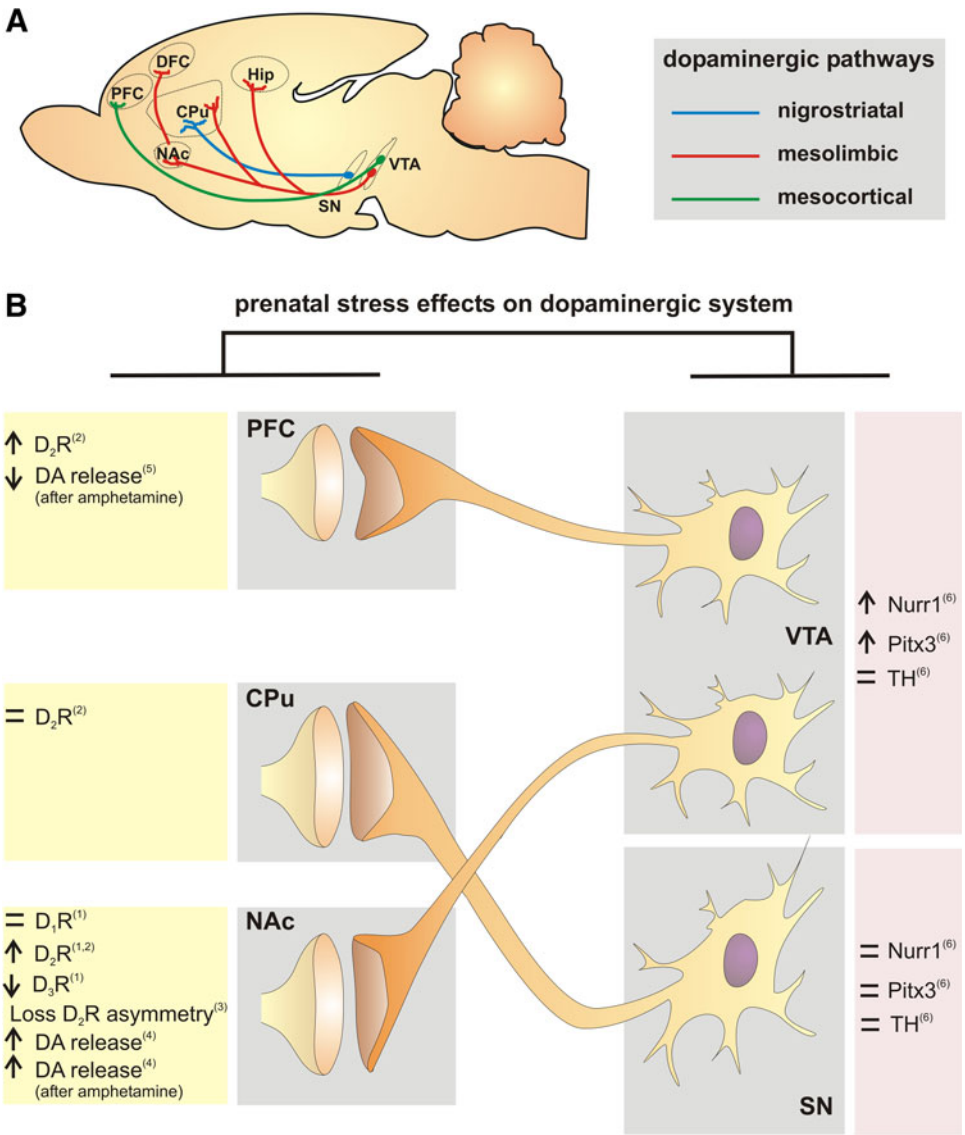

Fig. 1 **a** Schematic representation of the dopaminergic pathways in the rat brain. Dopaminergic neurons can be divided into four groups: nigrostriatal, mesolimbic, mesocortical, and tuberohypophyseal systems (see text for details). **b** Schematic representation of the alterations in the dopaminergic system in the adult rat brain of prenatally restrained stressed rat males. Note that impairments of the dopaminergic system are observed mainly in limbic areas of prenatally stressed rats. *Notes*. (1) Henry et al. (1995); (2) Berger et al. (2002); (3) Adrover et al. (2007); (4) Silvagni et al. (2008); (5) Carboni et al. (2010); (6) Katunar et al. (2010)

2008). Most of the DA-containing cells develop from a common embryological cell group that originates at the mesencephalic–diencephalic junction and project to various forebrain targets (Chinta and Andersen 2005). Several transcription factors (TF) are involved in midbrain dopaminergic neurons differentiation, such as Nurr-1, Pitx3, Lmx1a, and the engrailed TF En-1 and En-2. Nurr1 (also known as NR4A2), is a TF of the orphan nuclear receptor family and is essential to induce final differentiation of ventral mesodiencephalic dopaminergic (mdDA) precursor neurons into dopaminergic phenotype (Zetterstrom et al. 1997; Saucedo-Cardenas et al. 1998). Pitx3 is expressed in all midbrain dopaminergic neurons, and it is specifically involved in the terminal differentiation and maintenance of neurons in the substantia nigra pars compacta (SNc) (Chinta and Andersen 2005; Smidt and Burbach 2007). Lmx1a, which induces the expression of Msx1, and both, through Ngn2, are required to trigger DA cell differentiation (Andersson et al. 2006). The engrailed TF, En-1, and En-2 are essential for the maintenance and generation/differentiation of DA neurons (Simon et al. 2001).

Dopaminergic neurons can be divided into four groups: nigrostriatal, mesolimbic, mesocortical, and tuberohypophyseal systems (Fig. 1a). The first is a major dopaminergic tract in brain that originates in the SNc and sends axons that provide a dense innervation to the caudate nucleus and putamen of the corpus striatum (CPu); nearly 80% of all DA in the brain are found in the corpus striatum. The nigrostriatal pathway plays an essential role in the control of voluntary motor movement. This tract degenerates in PD, a syndrome characterized for a profound depletion of DA in the striatum, responsible for the motor alterations observed (Kuhar et al. 1999). DA-containing cell bodies localized medial to the substantia nigra (SN) in the ventral tegmental area (VTA) provide a diffuse and

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modest innervation to the forebrain. The cells of the VTA project most prominently to the nucleus accumbens (NAc), olfactory tubercle as well as to the septum, AMG, and hippocampus. This subset of projections is known as the mesolimbic dopaminergic system. Another group of cells in the medial VTA project to the prefrontal, cingulate, and perirhinal cortex, forming the pathway known as the mesocortical dopaminergic system (Kuhar et al. 1999; Chinta and Andersen 2005). Owing to the overlap between the mesocortical and mesolimbic dopaminergic neurons, the two systems are often collectively referred to as the mesocorticolimbic system (Wise 2004). These dopaminergic systems are involved in emotion-based behavior including motivation and reward (Chinta and Andersen 2008), and it has been hypothesized that these neurons are critical for the action of antipsychotic, antihyperactivity, and psychostimulant drugs, respectively (Kuhar et al. 1999). In the tuberohypophyseal system, DA-containing cell bodies in the arcuate and periventricular nuclei of the hypothalamus send axons that innervate the intermediate lobe of the pituitary and the median eminence. These neurons play an important role in regulating the release of pituitary hormones, especially prolactin. In addition to these major pathways, DA-containing interneurons have been found in the olfactory bulb and the neural retina (Kuhar et al. 1999).

Biochemistry of Dopaminergic Synapses

DA synthesis primarily occurs at the neuronal terminal (Fig. 2) via the hydroxylation of tyrosine by the rate-limiting enzyme for the DA biosynthesis, tyrosine hydroxylase (TH), to form L-3,4-dihydroxyphenylalanine (L-DOPA). Then, L-DOPA is decarboxylated by aromatic L-amino acid decarboxylase (AADC) to form DA (Shiman et al. 1971). After its synthesis, DA is sequestered from the cytosol and packaged into synaptic storage vesicles by vesicular transporter of glutamate (VMAT2) (Liu et al. 1992). Following nerve firing, vesicular DA is released into the synapse (Trifaro et al. 1992) where it can activate postsynaptic DA receptors (types 1–5), as well as presynaptic DA autoreceptors (see below). Extracellular DA is recycled back into the terminal by DA transporter (DAT). In the synaptic terminal, DA is either repackaged into vesicles by VMAT2 or is degraded by monoamine oxidase B (MAOB) (Berry et al. 1994) to form hydrogen peroxide and 3,4-dihydroxyphenylaldehyde, which is rapidly oxidized by aldehyde dehydrogenase to 3,4-dihydroxyphenylacetic acid (DOPAC). Approximately 40% of DOPAC is eliminated without further metabolism, and 60% is converted to homovanillic acid (HVA) by catechol-*O*-methyltransferase (COMT) (Nikodejevic et al. 1970).

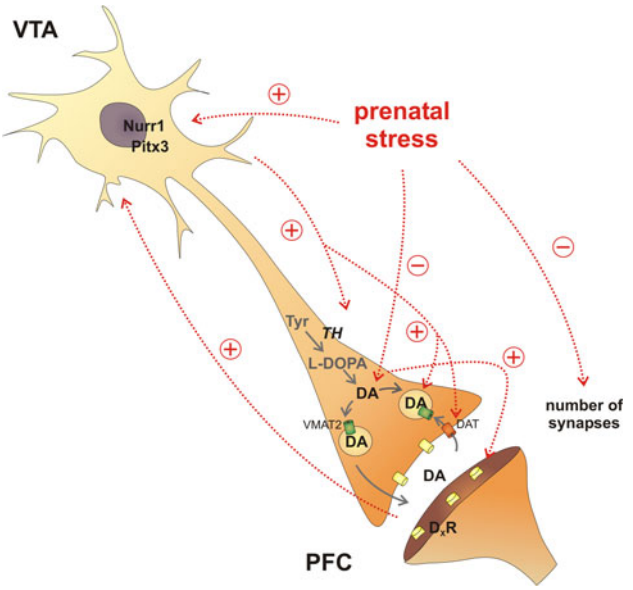

Fig. 2 Schematic representation of the effects exerted by PS on the dopaminergic function. The data correspond to the VTA–PFC pathway of an offspring that was prenatally stressed employing a restraint protocol. The effects described occur at different stages of development. PS exerts an inhibitory effect (indicate by [−]) on DA levels at some unknown stage of DA biosynthesis. Low levels of DA produce an up-regulation (indicate by [+]) of DA D_2 receptors, which in turn activates Nurr1. High levels this transcription factor could up-regulate TH expression, and eventually DAT and $VMAT_2$, which will increase DA levels in an attempt to compensate for the disbalance produced by PS. In addition, PS produces synaptic loss in the brain of adult offspring

DA receptors are G-protein-coupled receptors (GPCRs) with seven hydrophobic domains, an extracellular N terminus and an intracellular C terminus segment. The D_1 receptor is the most widespread DA receptor and is expressed at higher levels than any other DA receptor. It was found in the NAc, AMG, CPu, and prefrontal cortex (PFC). On the other hand, D_5 receptor is poorly expressed in rat brain in comparison with the D_1 subtype. D_5 is mostly expressed in the frontal cortex, hippocampus, and CPu. The three D_2 type receptors D_2, D_3, and D_4 are primarily expressed in the NAc, and olfactory tubercle. In addition, D_2 is also expressed in CPu, D_3 in Island of Calleja, and VTA, and D_4 in hippocampus, CPu, and frontal cortex (Missale et al. 1998; Xu and Zhang 2004).

D_1-like receptors (D_1 and D_5) and D_2-like receptors (D_2, D_3, and D_4) increase or inhibit, respectively, the adenylyl cyclase activity (Kuhar et al. 1999; Kreek et al. 2002). The intracellular signal transduction of DA receptors implies that D_1 and D_2-like receptors work antagonistically to modulate synthesis of cAMP in its targets (Missale et al. 1998; Bibb 2005) and modulate differentially intracellular pathways through phospholipase C, calcium channels, potassium channels, arachidonic acid, Na^+/H^+ exchange, and Na^+–K^+-ATPase (Missale et al. 1998; Bibb 2005).

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On the other hand, DA autoreceptors contribute to the regulation of the synthesis and release of the neurotransmitter itself. Stimulation of these autoreceptors by DA agonists decreases dopaminergic activity (Meltzer 1980; Pothos et al. 1998). Moreover, they have been reported to play an important role in PD, schizophrenia, and drug addiction (Feuerstein 2008).

Prenatal Stress and the Dopaminergic System

PS, DA Receptors, and Levels of DA

Relatively few studies have examined the effect of PS on the expression of the DA receptor's family. Henry et al. (1995) were the first to evaluate the levels of DA receptors in the adult offspring after restraint PS, and found that it increases the number of D_2-like receptors, while D_3 receptors decreases in Nac (Fig. 1b). In our laboratory, we found that prenatal restraint stress enhance D_2-like receptors in different forebrain areas. such as dorsal frontal cortex (DFC), medial prefrontal cortex (MPC), NAc core (NAc-C), and hippocampal CA_1 region in the adult offspring (Fig. 1b). No differences were found in D_2-like receptors levels at medial CPu (CPu-M), lateral CPu (CPu-L), and NAc shell (NAc-S) areas (Berger et al. 2002) (Fig. 1b). However, the changes in D_2 limbic receptors produced by PS that persist until adulthood can be reverted when the progeny is manipulated early in life. We have shown that adoption of a prenatally stressed offspring by a control mother during the first postnatal days can reverse the increase of DA receptors (Barros et al. 2004).

Kippin et al. (2008) showed that upon stimulation with a noncontingent injection of cocaine, NAc levels of extracellular DA were increased both in cocaine naïve and cocaine-experienced PS male rats. In our hands, amphetamine or nicotine stimulation produces an increase in DA levels in NAc-S of adult PS male rats (Silvagni et al. 2008) (Fig. 1b). Several reports have supported the notion that DA neurotransmission in the PFC controls subcortical DA. Moreover, there is now a large body of evidence showing that mesocortical DA exerts a tonic inhibitory influence on subcortical DA function. Brake et al. (2000) have shown that perinatal stress induces a mesocortical DA deficit and a subcortical DA hyperfunction. In line with these observations, we have reported that PS produces a decreased DA release after amphetamine stimulation in PFC of adult offspring (Carboni et al. 2010) (Fig. 1b), suggesting that this cortical dopaminergic deficit might be triggering a NAc hyperfunction and an overall dopaminergic imbalance in the prenatally stressed brain.

Since asymmetrical levels of DA has been reported in several rat brain areas (Rosen et al. 1984) and a right dominance is lost in prenatally stressed animals (Weinstock 2001), we analyzed D_2 receptors in left and right brain hemispheres of adult male rats exposed to PS. We found an increase on D_2 receptors in both sides of Nac-C, despite the fact that the left–right asymmetry observed in the control group was selectively lost in prenatally stressed offspring (Fig. 1b). CPu-M showed an increase of D_2 receptors after PS in both hemispheres and asymmetries in both control and stressed groups, whereas CPu-L showed D_2 receptor asymmetries in both stress and control groups without increases after PS (Adrover et al. 2007). The asymmetrical and higher distribution of D_2 receptors in right versus left sides of Nac-C might reflect a constitutive left biased difference in DA content between sides generating different levels of DA D_2 receptors.

Although scarce in number, all studies found in the literature have shown that levels of DA or its turnover are impaired in prenatally stressed offspring. Loss of asymmetries due to PS induces a higher rate of DA turnover in the right PFC and reduced DA activity in the right NAc and left caudate, which were related to a reduced directional preference in prenatally stressed adult rats in response to amphetamine (Fride and Weinstock 1988). Hemispheric asymmetries are found throughout the brain, but their correlation with function and behavior are not well defined (LeMay 1999). Emotional behaviors in rats are mediated mainly in the right cerebral cortex (Denenberg 1981), and shock avoidance learning is preferentially mediated by the right AMG (Coleman-Mesches and McGaugh 1995). DA has been particularly observed to be lateralized mostly in PFC, since its metabolism in the right hemisphere has been linked to successful escape performance following repeated stress (Carlson et al. 1993). Alonso et al. (1991) reported that maternal daily restraint stress produced a reduction in right-sided preferences in a T-maze of male offspring. The same group, showed later that in female offspring of prenatally stressed rats, DA levels increased whereas DOPAC and HVA levels decrease in the NAc of the right side of the brain (Alonso et al. 1997). Moreover, prenatal distress leads to a lateralized suppression of stress induced activation of prefrontal cortical DA transmission during adulthood (Brake et al. 2000). Such changes may contribute to the decreased ability of prenatally stress offspring to cope with stressful situations (Fride and Weinstock 1989; Huizink et al. 2004; Weinstock 2001).

NAc is an area strongly linked to the rewarding properties of ethanol and other drugs (Nielsen et al. 1999), and damage to the Nac-C causes rats to exhibit impulsive behavior (Cardinal et al. 2004). Since DA system is implicated in impulsivity, long lasting, and selective loss of asymmetries of the D_2 receptors in Nac-C might suggest a novel mechanism by which PS can lead to long-term behavioral and cognitive impairments and may contribute

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to the development of neuropsychiatric disorders including ADHD, depression, and schizophrenia (Weinstock 2001; Huizink et al. 2004).

PS, DA, and Transcription Factors

As we mentioned above, mdDA neurons located in the ventral midbrain are essential for the control of cognitive and motor behaviors and are associated with multiple psychiatric and neurodegenerative disorders. The precise anatomical localization and functional differentiation of DA neurons in the mammalian brain is a complex and multi-step process. It includes early developmental events, such as fate specification, differentiation, and migration, and later events including neurite growth, guidance and pruning, and synapse formation. Significant progress has been made trying to identify some transcriptional determinants which are regulating the regional specification and cellular differentiation, such as Nurr 1, Pitx3, engrailed 1 and 2 (En-1 and En-2), and Lmx1b (Smidt and Burbach 2007). Among these, Nurr1 and Pitx3 have been the most extensively studied TFs. In this section, we describe the most relevant characteristics of these factors and its relation with PS.

Nurr1 expression is detected as early as embryonic day (E) 10.5 in the ventral midbrain in developing DA neurons (Zetterstrom et al. 1997; Castro et al. 2001) just preceding TH expression, in the subventricular population (Wallen and Perlmann 2003). At this stage of the development, Nurr1 expression is restricted to the midbrain, but its expression extends later to other regions of the central nervous system including the cortex and the hippocampus. Moreover it regulates proteins required for DA synthesis and transport, such as TH, VMAT2, and DAT (Zetterstrom et al. 1997; Saucedo-Cardenas et al. 1998; Baffi et al. 1999; Le et al. 1999; Wallen et al. 1999; Smits et al. 2003; Smidt and Burbach 2007; Weidong et al. 2009).

The expression of Pitx3 in the brain, starts at E 11.5 and is maintained throughout adult life in both rodents and humans (Smidt et al. 1997). The mechanism by which Pitx3 influences the development of this specific mdDA subpopulation is still unknown. Extra neural expression of Pitx3 was shown in the developing lens of the eye (Semina et al. 1997). It has been observed that Pitx3 serves a unique function in mdDA neurons, highlighted by the dramatic loss of neurons of the SN in Pitx3-deficient mice (Hwang et al. 2003; Nunes et al. 2003; van den Munckhof et al. 2003; Smidt et al. 2004) which is preceded by deficient TH expression during embryonic development. In fact, Pitx3 seems to regulate the expression of TH, since there is an active high-affinity binding site for the TF in the promoter (Smidt et al. 2004; Maxwell et al. 2005; Jacobs et al. 2009). Although Pitx3 is expressed in all mdDA neurons, only mdDA neurons of the SN are affected by the loss of Pitx3, emphasizing the complex role of Pitx3 in mdDA neurons and the diverse properties of subsets within the mdDA neuronal population.

Employing an immunocytochemistry approach, we have recently shown that the expression of Nurr1 presents a ubiquitous distribution in cerebral cortex, hippocampus, thalamus, AMG, and midbrain, whereas Pitx3 remains restricted to the mdDA neurons such as SN and VTA. The expression of both Nurr1 and Pitx3 increased in prenatally stressed adult offspring in the VTA area, whereas no changes were observed in SN areas (Katunar et al. 2009). We have also extended this study to different postnatal days (PND) where we have analyzed the immunocytochemical expression of Nurr1 and Pitx3 in SN and VTA at PND 7, 28, and 60 of prenatally stressed rats. We found an increase in Nurr1 expression at PND 7, 28, and 60 whereas Pitx3 showed a decrease at PND 28 and an increase at PND 60 in prenatally stressed offspring. It is important to note that Pitx3 expression in the control group of rats show a significant decrease with age whereas Nurr1 shows an increase that is significant between PND 28 and 60. The different expression levels described for Pitx3 and Nurr1 in this study might be supporting the notion that Pitx3 has a prominent role at early stages in the postnatal development of the mdDA system, whereas Nurr1 plays a crucial role in adulthood probably in the maintenance of dopaminergic metabolism through the regulation of the expression of its key enzymes and transporters (Katunar et al. 2010). Growing evidence has been lately showing that Pitx3 and Nurr1 pathways are interconnected at a functional level (Jacobs et al. 2009).

In prenatally stressed rats, Pitx3 expression shows a decrease at PND 28 in VTA to further increase at PND 60 when compared to control. This Pitx3 expression profile in prenatally stressed rats could be interpreted as a consequence of the gonadal hormones surge that might be exerting important challenges to the DA system during the pubertal period. It has been reported that several behavioral and biochemical alterations exerted by PS were seen only after puberty (Henry et al. 1995; Diaz et al. 1997). When evaluating Nurr1 expression in prenatally stressed rats at PND28, we found a decline that was recovered after puberty, probably indicating an altered vulnerability to gonadal hormones. Altogether these results allow us to confirm that the changes observed in key TF as Nurr1 and Pitx3 are selectivity found in the VTA area of the mesencephalon, indicating a major vulnerability of this limbic region to PS. It is interesting to point out that previous results from our laboratory showed that D_2 receptors increased in prenatally stressed offspring only in limbic areas such as cortical areas and NAc, rather than motor areas such as CPu (Berger et al. 2002).

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PS and Gonadal Hormones

Adolescence, defined as the gradual period of transition from childhood to adulthood (Spear 2000), is a phase when the brain awakens to pleasure, risk, and other behavioral features that are common among adolescents of a variety of species. During this period, the gonadal hormones act on peripheral tissues where they induce the appearance of secondary sex characteristics, but they also act centrally to influence both the remodeling of the adolescent brain, orchestrating brain plasticity, and behavioral maturation. In addition, adolescence is a pivotal time on the etiology of certain psychopathologies traditionally linked to dopaminergic pathways. For example, some disorders that have a childhood onset, such as ADHD and Tourette's syndrome, not only deteriorate during puberty but also wane while reaching to adulthood. Others like schizophrenia, substance abuse disorder, and depression typically emerges during late adolescence or early adulthood (Andersen 2003). The modulation of DA pathways by gonadal hormones has long been demonstrated, and in this regard, Yang and Shieh (2007) postulate that the nigrostriatal and mesolimbic systems are modulated by circulating gonadal steroids, estradiol (E 2), and testosterone. Moreover, according to Creutz and Kritzer (2004) the soma projections of midbrain DA systems contain high number of estrogens and androgen receptors.

One of the most important sexual dimorphic brain nucleus is the preoptic area of the hypothalamus (POA) where the distribution of DA nerve cells and fibers is also sex dependent (Beyer et al. 1991). Kawashima and Takagi (1994) reported the effects of testosterone and estradiol 17β on survival, process growth, and dopaminergic function on cultured cells derived from neonatal rat POA. These authors found that steroids administration stimulated basal level of DA synthesis and release in the hypothalamic culture cells. Moreover, neuronal survival was enhanced in the group treated with testosterone, as well as the total processes length and the number of branching (Kawashima and Takagi 1994).

Several studies have investigated the regulation exerted by sex hormones on biosynthetic enzymes gene expression related to DA systems. Regulation of TH gene expression is an important mechanism underlying modulation of catecholamine biosynthesis and homeostasis. The action of steroid hormones on its expression is not well elucidated yet, and there is some discrepancy on its effects, but it was demonstrated that both, androgen and estrogen receptors, control TH gene expression by acting at the promoter level in a ligand-dependent manner or indirectly by changing levels of trophic factors (Maharjan et al. 2005; Jeong et al. 2006). Interestingly, other physiological signals, such as cold stress or glucocorticoids, also regulate its expression (Adler et al. 1999).

As mentioned in a previous sections, mesolimbic DA pathways originated in the VTA are involved in the reinforcing actions of some drugs of abuse (e.g., cocaine), and natural rewarding states, such as feeding, procreating, and drinking. It was shown that during food consumption and mating, mesolimbic DA neurons show characteristic burst firing activity (Dackis and O'Brien 2001). Testosterone was shown to increase the release of DA in this neural pathway both during sexual behavior as well as when it is used as an anabolic effector.

The effect of gonadal hormones on the brain maturation takes place at two different periods of life: (a) during critical periods of development, sex steroids promote cellular and molecular events which will determine sexual differentiation of the brain; and (b) during the onset of puberty, oscillations in their circulating levels affect a wide variety of neuronal phenomena, ranging from cyclic remodeling of synaptic circuitry to transynaptic modulation of neurotransmission (Alonso and Lopez-Coviella 1998). As mentioned above, behavioral and biochemical alterations of DA system exerted by prenatal insults were only seen after puberty (Henry et al. 1995; Diaz et al. 1997) suggesting that perinatal events might render the DA circuitry more vulnerable to puberty variation in the hormonal circulating levels. In the rat, two perinatal testosterone surges were observed: the first over E-18 (Weisz and Ward 1980), and the second, during the first 4 h after birth (Ward et al. 2002, 2003). It is well known that PS induces long-term effects on the hypothalamic–pituitary–gonadal (HPG) axis in males offspring, probably by interfering with those testosterone surges; i.e.,: PS interferes with androgens synthesis during critical stages of the brain sexual differentiation (Ward and Weisz 1984; Ward et al. 2003), inducing abnormal testosterone and luteinizing hormone (LH) levels during the progeny lifespan (Shono and Suita 2003; Gerardin et al. 2005; Pereira et al. 2006; Rodriguez et al. 2007) and feminizing the male sexual behavior, among other effects. In our hands, prenatally stressed offspring showed a delayed testicular descent (Barros et al. 2004). More recent results from our laboratory show a decrease in the ano-genital distance in male progeny; decreased level of LH at PND 28 and diminished levels of both LH and testosterone at 75 PND. In addition, we recently found altered histological testicular morphometric parameters in prenatal stressed animals (*unpublished results*). Although preliminary, these results show that our PS model has long-term effects both, on male progeny HPG axis and in the testicular morphology.

Considering that PS interferes with the normal development of dopaminergic system and that manipulation of the perinatal environment results in long-term changes at the hormonal levels, present challenge is to determine the mechanism by which PS renders a vulnerable DA system to the gonadal hormones surge in early adolescent, and

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therefore, explaining why several psychopathologies are turned on during adolescence in subjects with a PS history.

PS, DA, and Glutamate Metabolism

Glutamate is the principal excitatory neurotransmitter in the mammalian central nervous system. It is an element of integrative brain function, synaptic plasticity, memory, and learning processes (Obrenovitch and Urenjak 1997; Defagot et al. 2002). Glutamatergic neurotransmission is achieved through ionotropic (ligand-gated ion channel) and metabotropic (coupled to cellular effectors) receptors. The *N*-methyl-D-aspartic acid (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors are all glutamate gated ion channels (conducting only Na^+ or both Na^+ and Ca^{2+}). Metabotropic glutamate receptors (mGluR) are subdivided into groups I (mGluR1 and mGluR5), II (mGluR2 and mGluR3), and III (mGluR4, mGluR6, mGluR7, and mGluR8). Group I receptors are coupled to phospholipase C, whereas groups II and III are negatively coupled to adenylate cyclase (Danbolt 2001). Glutamate concentrations are maintained, below toxic levels, in the synaptic cleft by means of neuronal and glial uptake which is performed by the plasma membrane excitatory amino acid transporter (EAAT) family: glutamate transporter-1 (GLT1 or EAAT2), expressed in high levels in astrocytes; glutamate–aspartate transporters (GLAST), also expressed by glia and in some non-neuronal cells; EAAC1 and EAAT4, expressed in neurons and EAAT5, found in both neurons and glial cells (Tanaka et al. 1997; Danbolt 2001; Suchak et al. 2003). In astrocytes, glutamate may be converted to glutamine which is released to the extracellular fluid, taken up by neurons and reconverted to glutamate inside neurons. Glutamatergic neurons sustain release of glutamate, independently of glutamine cycle, through the synthesis of the amino acid by the tricarboxylic acid cycle (McKenna et al. 2006).

Although prenatal brain development is based on a genetic blueprint, the fetal environment can also have a profound influence on brain development that may persist into and be manifested in adulthood. Published studies have reported various effects of PS over glutamatergic system: Zuena et al. (2008) found a reduction in mGlu2/3 receptor proteins in the hippocampus of prenatally stressed rats, and Son et al. (2006) demonstrated that maternal stress impairs the function of postsynaptic NMDA receptors reducing hippocampus long-term potentiation (LTP). They show molecular and electrophysiological evidence consistent with impaired spatial learning and memory in the adult offspring of stressed dams. On the other hand, Fumagalli et al. (2009) reported no basal change in glutamatergic receptor expression in the hippocampus, but they found regionally selective changes in modulatory responses of glutamatergic transmission in the hippocampus and the PFC in prenatal stressed animals.

Studies from our laboratory have shown that adult offspring of stressed rats exhibits high levels of NMDA glutamate receptor in frontal cortex, striatum, CA1 region of the hippocampus, and NAc-C and NAc-S, whereas Group III mGlutR showed a pronounced increase only in medial PFC and DFC (Berger et al. 2002). Concomitantly with the receptor changes, we also found astroglial reaction and a reduced dendritic arborization, with synaptic loss in frontal cortex, striatal matrix, and CA1 regions of the hippocampus of adult prenatally stress rats (Barros et al. 2006a). Since glutamate is intimately linked via a cycle between neurons and surrounding astroglia (Danbolt 2001), these structural and morphological changes suggest that glutamate metabolism might be impaired in the brain of prenatally stressed rats. Preliminary results from our laboratory have shown that although glutamate metabolism evaluated by mass spectrometry was not altered, glutamate uptake in adult prenatally rats were significantly higher than in undisturbed rats (*unpublished results).*

As mentioned above, there is now considerable evidence that PFC regulates the release of DA in the NAc. The mechanism by which cortical inputs regulate NAc DA release is still a matter of debate, but Del Arco and Mora (2008) have thoroughly investigated PFC–NAc interactions and concluded that glutamate plays a crucial role in the DA PFC-NAc regulation. They propose the existence of PFC specific circuits of pyramidal neurons–GABA interneurons network that regulate specific DA and glutamate receptors, and their corresponding direct and indirect outputs. Since we and others (Carboni et al. 2010; Brake et al. 2000; Silvagni et al. 2008) have observed that PS exerts a cortical DA deficit and a subcortical DA hyperfunction, it is tempting to hypothesize that glutamate metabolism might be equally impaired in the prenatally stressed rat brain and might be participating in the impaired cortico-accumbens regulation. In addition, it has been shown that the mesencephalic afferents to the NAc present a dual DA–glutamate phenotype. Recent study has demonstrated that the vesicular transporter of glutamate (VGluT2) is co-expressed with TH in VTA neurons (Dal Bo et al. 2004) as well as the colocalization of these proteins in axon terminals of the NAc in immature PND 15 rats. In both cases, they find an induction or de-repression of the glutamatergic phenotype of DA neurons following a neonatal injury (Dal Bo et al. 2008). Considering that the dual phenotype was found to be present as early as in E 14 and E 15, (Dal Bo et al. 2008), it is tempting to hypothesize that the expression of glutamatergic phenotype in DA neurons is a regulated phenomenon that might be re-programmed by prenatal insult such as gestational stress.

Much study is still needed to unravel the mechanism of DA–glutamate interaction and its long-term vulnerability

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to gestational insults. However, our own research as well as others point out to a disbalanced function of both neurotransmitter pathways as a consequence of PS that might be inter-regulated in a regional basis.

PS and Neurodegenerative Diseases

Barker (1990) proposed that the classical model for adult degenerative disease, which includes the interaction between genes and the environment in adult life, needs to consider the influence of the environment in prenatal and infant lives. Miller and O'Callaghan (2008) suggested that intrauterine environment could program the fetus with developmental plasticity. The human brain develops from a single cell and grows fast reaching an approximate weight of 1,000 g during the first year of life. Many factors may affect this process including pre and postnatal experiences, genes, diet, drugs, stress, trauma, and hormones (Guerrini et al. 2007). Unfavorable developmental conditions may cause adaptations that allow fetal survival; but this long-lasting programming may have adverse consequences in adult (Miller and O'Callaghan 2008). Moderate disturbances, such as prenatal maternal psychosocial stress, have the potential to negatively affect the fetus development and the individual through the entire life-span (Wadhwa et al. 2001). In consideration of the above, it is possible to imagine the existence of a link between PS and the development of neurodegenerative diseases in adulthood. There is a broad consensus that the accelerated age-related cognitive decline is related to an impaired response of the hypothalamic–pituitary–adrenal (HPA) axis (Pardon and Rattray 2008), and that prenatally stressed rats had increased responsiveness of the HPA axis to ulterior stress events (Henry et al. 1994; Darnaudery and Maccari 2008). More importantly, and in agreement with the results obtained in animal models, recent human studies have shown that PS or glucocorticoids treatment is associated with long-term impact on the HPA axis of the human offspring (O'Connor et al. 2005; Van den Bergh et al. 2008; Entringer et al. 2009; Davis et al. 2011).

Deregulation of the HPA axis was related to neurodegenerative disease such as Alzheimer's disease (Green et al. 2006). Even though there is no direct evidence relative to PS, it has been reported that stress increases the susceptibility to develop Alzheimer's disease (Pardon and Rattray 2008; Buynitsky and Mostofsky 2009). Similarly, reports from clinical research demonstrated that stress could influence the onset or the progression of PD (Smith et al. 2002; Metz 2007; Kibel and Drenjancevic-Peric 2008). Employing an animal model of PD, Smith et al. (2008) observed that midbrain neurons of chronic stressed animals, as well as corticosterone-treated animals, were more sensible to a neurodegenerative processes after a neurochemical insult.

Evidences from studies performed in different species, from rats to primates (Lemaire et al. 2000; Coe et al. 2003), demonstrated that PS affects the hippocampal neurogenesis depending on the stress intensity (Fujioka et al. 2006). Maternal glucocorticoid treatment influences the hippocampal physiology of NMDA receptor in postnatal life in a sex-specific manner (Owen and Matthews 2007). Recently, Fukumoto et al. (2009) described that an excess of glucocorticoid affect migration of post-mitotic neurons during the development of the cerebral cortex. In addition, Lemaire et al. (2000) show that aging is accompanied by a progressive decline in hippocampal cell proliferation and that PS accelerates even more these processes.

PD involves a progressive degeneration of the dopaminergic system, which is basically a disorder caused by deficit of DA. The pathological hallmark of PD is the relatively selective loss of DA neurons in the SNc in the ventral midbrain with posterior loss of DA in the nigrostriatal system, and the presence of cell bodies enriched in α-synuclein aggregates. Although traditionally PD has been seen as an age-related disorder, recently it has been proposed that PD could have an early beginning, even prenatal, resulting from the disruption of the normal pathways of neuronal development, making the nigrostriatal system vulnerable to subsequent insults (Barlow et al. 2007; Pardon and Rattray 2008; Weidong et al. 2009). Strong evidence suggests a role for aberrant mitochondrial form and function, as well as increased oxidative stress, in the pathogenesis of PD (Henchcliffe and Beal 2008). Although a relationship, among PS, oxidative stress, and mitochondrial alterations, has been described in the literature, the alterations were found principally in hippocampus (Zhu et al. 2004; Song et al. 2009).

In relation to the DA system, McArthur et al. (2005, 2007) demonstrated that prenatal and postnatal exposures to dexamethasone, a synthetic glucocorticoid, cause population-specific effects on the DA cells of the VTA and SNc in the rat, increasing the number of TH positive cells in both areas, without affecting the DA levels, and its metabolite, DOPAC. Moreover, the alterations in the arrangement of the DA neurons presented sexual dimorphism showing a notable feminization of the spatial cytoarchitecture in males (McArthur et al. 2007). As we mentioned above, Nurr1 and Pitx3 are critical genetic factors regulating the development and maintenance of midbrain dopaminergic neurons. The expression of these transcriptional factors was affected in prenatally stressed adult offspring (Katunar et al. 2009, 2010). It is interesting to note that Katunar et al. (2009) reported that the expression of both Nurr1 and Pitx3 increased in prenatally stressed adult offspring in the VTA, but no changes were observed in the SN. Otherwise, even with higher levels of Nurr1 and Pitx3 from PND7 to PND 60, Katunar et al.

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(2010) do not report an increase in the amount of TH-positive cells in VTA or SN in adult rat.

In the sections described above, we discussed that biochemical alterations in the brain of prenatally stressed animals were mainly observed in limbic rather than in motor areas, suggesting that PS animals will be less prone to develop diseases that involved motor areas. In agreement with the above, preliminary results from our laboratory indicate that prenatally restraint stressed rats show the same susceptibility as the undisturbed animals to an injury caused by 6-OHDA. However, using a perinatal stress model, Pienaar et al. (2008) showed that rats subjected to maternal separation were more susceptible to subsequent insults with 6-OHDA. Later, Mabandla et al. (2009), employing a variable stress protocol, found that prenatally stressed rats were more vulnerable to the toxic effects of 6-OHDA later in life, than non-stressed rats. More experiments will be necessary to determine if prenatally stressed animals are, more susceptible to develop a neurodegenerative processes in motor areas considering that, as mentioned in the introduction section, several factors, including the type of stressor, may contribute to differences in the effects of PS in animal studies (Charil et al. 2010).

In summary, a vast literature supports the knowledge that adverse conditions in uterus influence the development of an individual, possibly through permanent alterations in different brain areas. Further studies will be needed to determine whether adverse intrauterine events in conjunction with environmental factors might be risk factors for the development of neurodegenerative diseases, and in this case, which of the initial latent disturbances and which mechanisms could facilitate neurodegenerative processes in adulthood of prenatally stressed subjects.

Extrapolation of Experimental PS Studies in Animals to Gestational Disturbances in Humans

Awareness of the long-lasting sequelae of gestational stress on the infant development and behavior dates back to the 1940s (Sontag 1941). However, in the last two or three decades, an increasing number of both prospective and retrospective studies in humans have convincingly reported that gestational stress is associated with behavioral, cognitive, and physical alterations in the child (Van den Bergh et al. 2005; Glover et al. 2010). Even though retrospective studies have many limitations (Charil et al. 2010) and prospective studies during the human lifespan are scarce and present ethical dilemmas, the wealth of human studies and the relative coincidence in their results help us draw some important conclusions.

After analyzing the existing literature, it is interesting to observe that, in spite of the differences in the type of stressor, age of outcome assessment, and statistical analysis, the most commonly found outcomes in children are mainly ADHD, higher anxiety, conduct disorders, and cognitive dysfunctions. Depending of the severity of the stressor some studies report a higher incidence of schizophrenia, affective disorders, and emotional imbalances (Kofman 2002; Van den Bergh et al. 2005; Glover 2011). This means that from all possible pathologies, PS has been predominantly associated with diverse psycho-and psychiatric pathologies.

As mentioned in the "Introduction", most of these pathologies have been associated to limbic brain structures and impairments in the dopaminergic pathways. Although we are aware that direct comparison between experimental animals and humans is a complex issue, the understanding of brain mechanism underlying the link between PS and adult psychopathologies still rely on animal studies. In this context, it can be speculated that the impairments, observed in the dopaminergic metabolism of limbic areas in animal studies after PS, might have a correlation in human subjects, thus providing a neurochemical and morphological basis to the observed human psychopathologies associated to gestational stress.

Conclusions

There is a large consensus that restraint stress exerted onto the pregnant dam will have long lasting effects on the dopaminergic development of the offspring. Based on our own studies, PS increases DA D_2 receptors in limbic areas, decreases DA-stimulated release in cortical areas, whereas it increases in NAc, disrupts the DA-glutamate balance, and impairs the expression of specific TFs along development as well as the expression of TH and transporters. An example of the complex relationship between PS and dopaminergic system development is illustrated in Fig. 2. This cartoon is a schematic representation of a typical neuron belonging to the VTA–PFC pathway. PS exerts an inhibitory effect on general levels of DA at some unknown stage of DA biosynthesis. Low levels of DA produces an up regulation of DA D_2 receptors (Berger et al. 2002), which in turn activates Nurr1 (Chung et al. 2005). High levels of Nurr1 might up-regulate TH expression (Smidt and Burbach 2007), and eventually DAT and $VMAT_2$, which will increase DA levels in an attempt to compensate for the disbalance produced by PS. In addition to the neurochemical alterations described above, PS produces synaptic loss in the brain of adult offspring (Fig. 2; Barros et al. 2006). In spite of evaluating both limbic and motor areas, we have observed a repetitive pattern showing that limbic areas seems to be more vulnerable than motor areas to the deleterious effects of a prenatal insult. Considering the importance of DA neurotransmission in the

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mesocorticolimbic pathways and its relation to cognition, emotion, positive reinforcement, food intake, and decision-making, it is tempting to hypothesize that if the alterations observed in prenatally stressed animals models could be extrapolated to the effects of PS in humans. Vulnerable limbic areas in conjunction with genetic or environmental factors might facilitate the development of schizophrenia, ADHD, or drug abuse later in life. It is also important to underline that many of the alterations of the DA metabolism observed by our group and others are only visible after puberty, suggesting that the changes might be related to possible activation of gonadal hormones during this period. It has been suggested that PS might modify the sensitivity of key steps in the DA metabolism to the modulation by sex steroids during puberty. The age of onset of many of the DA-related cognitive pathologies (pre puberty for ADHD and young adult for schizophrenia) might be supporting the notion that prenatal programming of a vulnerable limbic dopaminergic system might be incapable of managing the hormonal variations during puberty.

Acknowledgments The authors wish to thank Mrs. Susana Buglione for the excellent bibliographic management.

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