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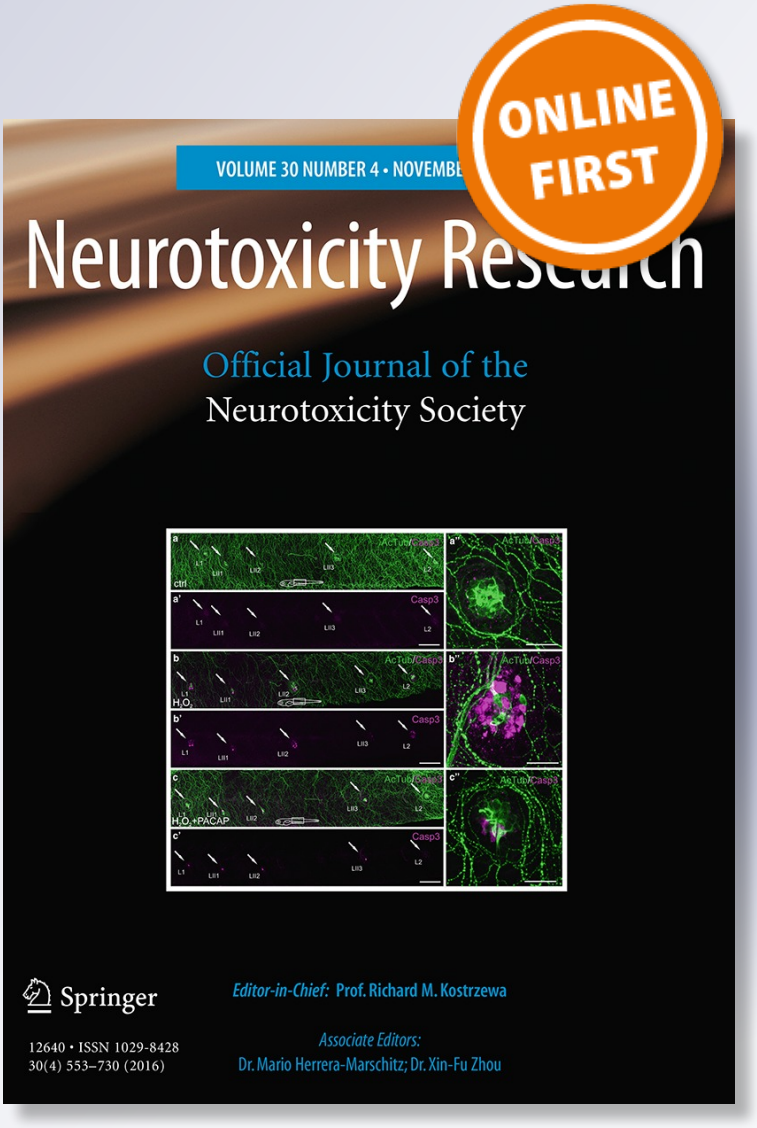

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REVIEW

Unravelling the Link Between Prenatal Stress, Dopamine and Substance Use Disorder

Verónica Pastor[1] · **Marta Cristina Antonelli**[1] · **María Eugenia Pallarés**[1]

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Abstract Substance use disorder (SUD) refers to the detrimental use of psychoactive substances and it is related to a cluster of behavioural, cognitive and physiological dysfunctions indicating that the individual continues using the substance despite significant substance-related problems. Although it is one of the most prevalent neuropsychiatric diseases affecting society worldwide, the mechanism underlying the vulnerability of certain individuals is not well understood yet. It is now widely accepted that, in addition to genetic factors, environmental adversities during critical stages of development of an organism could also be considered as risk factors that contribute to SUD. It has been suggested that prenatal stress (PS) could play an important role in the causal mechanisms of SUD, since it was shown that PS leads individuals to poor stress management and behavioural problems, both of which increase the risk of SUD. It is widely accepted that gestational stress exposure in rats interferes with the correct progeny development. In particular, research in this field points out that the development of the mesocorticolimbic dopaminergic (DA) system is sensitive to disruption by exposure to early stressors. Interestingly, PS induces behavioural abnormalities that are similar to those observed in individuals that present SUD. Since dysfunction of mesocorticolimbic DA pathway has been reported in both prenatally stressed and SUD individuals, in this review we will summarise the current knowledge supporting that PS may serve as a strong candidate to explain the vulnerability of certain individuals to develop SUD following repeated drug exposure. We will also propose a mechanistic hypothesis to explain PS-induced changes on mesocorticolimbic DA system.

Keywords Foetal programming · Prenatal stress · Substance use disorder vulnerability · Mesocorticolimbic dopaminergic system

Abbreviations

COMT	Catechol-*O*-methyltransferase
CPP	Conditioning place preference
D1R	Dopaminergic D1-like receptor
D2R	Dopaminergic D2-like receptor
DA	Dopaminergic
DAT	Dopamine transporter
DOPAC	Dihydroxyphenylacetic acid
MAOB	Monoamine oxidase B
MAP2	Microtubule-associated protein type 2
NAc	Nucleus accumbens
PFC	Prefrontal cortex
PS	Prenatal stress
SA	Self-administration
SUD	Substance use disorder
TH	Tyrosine hydroxylase
VP	Ventral pallidum
VTA	Ventral tegmental area

Introduction

Curiosity, distress, poor stress management, trauma or social rebelliousness, among other causes, could drive people to experiment with psychoactive substances including alcohol, nicotine and illicit drugs (WHO 2010).

✉ María Eugenia Pallarés
mpallares@fmed.uba.ar; pallamaria@gmail.com

[1] Instituto de Biología Celular y Neurociencia "Prof. Eduardo De Robertis", Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

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In some individuals, the regular consumption of those substances potentially leads them to take drugs compulsively despite the fact that they experience negative health problems and social consequences such as cardiovascular or liver dysfunctions, employment loss, legal issues and educational deficits, among others. These individuals develop a substance use disorder (SUD), that as stated on the Diagnostic and Statistical Manual of Mental Disorders-version V (DSM-5), it is described as: "the essential feature of a SUD is a cluster of cognitive, behavioural, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems" (DSM-V 2013). SUD is a major health and social problem worldwide. For instance, the United Nations Office on Drugs and Crime has reported that: "It is estimated that a total of 246 million people, or 1 out of 20 people between the ages of 15 and 64 years, used an illicit drug in 2013. 1 out of 10 drug users is a problem drug user, suffering from SUD or drug dependence" (United Nations Office on Drugs Crime 2015). Moreover, "the annual number of drug-related death (estimated at 187,100 in 2013) has remained relatively unchanged. An unacceptable number of drug users continue to lose their lives prematurely, often as a result of overdose, even though overdose-related deaths are preventable" (United Nations Office on Drugs Crime 2015).

On the other hand, many individuals occasionally consume psychoactive substances without developing dependence to them. For example, lifetime cumulative probability estimates indicated that only 26.6% of alcohol abusers and 9.4% of cannabis abusers would develop SUD on those substances at any time in their life (Florez-Salamanca et al. 2013; Lopez-Quintero et al. 2011). Even for a very addictive drug such as cocaine, only 16% of people develop SUD within 10 years of its first use (Lopez-Quintero et al. 2011; Wagner and Anthony 2002). Therefore, one of the major challenges in the drugs of abuse field is to identify which are the possible mechanisms involved in the transition from an individual with a milder SUD (represented in abuse) to a severe SUD (characterised by compulsive drug use or dependence) (Wise and Koob 2014).

Although some of the risk factors for an increased vulnerability to compulsive drug use are mainly genetic, it was shown that the exposure to environmental adversities during critical stages of development could also increase the risk of SUD (Liang et al. 2013). It has been extensively demonstrated that gestational stress exposure, as well as maternal deprivation during early development, negatively affects the proper development of the progeny by inducing long-term or permanent neurobiological changes. These changes mainly affect the physiology of neuroendocrine, metabolic systems and behavioural patterns resulting in an increased risk of diseases in later life including a higher propensity to develop SUD (Charil et al. 2010; Huizink et al. 2004; Maccari et al. 2014; 2016). In particular, both human and animal research in this field point out that the development of the mesocorticolimbic dopaminergic (DA) system is sensitive to disruption by exposure to early stressors (Baier et al. 2012; Reynaert et al. 2015). Mesocorticolimbic DA system is involved in emotion-based behaviour including motivation and reward (Wise 2004). Repeated exposure to different types of drugs of abuse (i.e. cocaine, amphetamine, cannabis, ecstasy, opiates such as heroin and opium and alcohol among others) is known to increase DA signalling in mesocorticolimbic circuit and it had long been accepted that rewarding effects of drugs are related to dopamine transmission (Ikemoto et al. 2015; Volkow Nora and Morales 2015). In this review, we will summarise our current knowledge about the impact of gestational stress as a risk factor for SUD vulnerability in later life, in both human and animal models. We hypothesise that alterations in mesocorticolimbic DA system induced by prenatal stress (PS) might be one of the main mechanisms involved in such increased vulnerability to SUD. Given the psychosocial and economical load associated with SUD in society, the understanding of the mechanisms underlying its aetiology is of great public health importance.

Prenatal Stress Enhances Rewarding and Reinforcing Effects of Drugs of Abuses Both in Human and Animal Models

Maternal wellbeing during gestation, as well as during the early postnatal period, is very important for her descendants mental and physical health. During this phase of individual development, the brain is particularly sensitive to remodelling by internal and external environmental factors (Harris and Seckl 2011; Maccari et al. 2014; Moisiadis and Matthews 2014; Sandman et al. 2011). During the last years, epidemiological research has demonstrated that maternal stress during pregnancy is related to an increased risk for adverse offspring outcomes including premature birth, behavioural complications during childhood and the development of affective disorders such as depression, post-traumatic stress disorder, increased anxiety, psychotic disorders and SUD, at adulthood (Charil et al. 2010; Charmandari et al. 2003; Laplante et al. 2016; Maccari et al. 2014; Markham and Koenig 2011; Reynaert et al. 2015). In pregnant women, the stress response can be elicited by a variety of endogenous and exogenous challenges such as relational or financial problems, familiar bereavement, psychosocial threats or exposure to war or to a natural disaster (Laplante et al. 2016; Lederbogen et al. 2011; Lucassen et al. 2014). Stress levels are usually

evaluated by measuring cortisol levels in saliva, blood or hair and with stress-related questionnaires (D'Anna-Hernandez et al. 2011; Nast et al. 2013). In animal models, PS can be induced by different protocols, such as restraint or immobilisation, crowding, repeated tail electroshocks, unpredictable stress and noise, variable stress and flashing lights [reviewed by (Huizink et al. 2004)]. In rodents, PS is related with heightened anxiety- and depression-like behaviours during adulthood (Salari et al. 2016), abnormal stress system responses to acute stress (Grundwald and Brunton 2015), impaired neural development and altered social and reproductive behaviours (Brunton 2013; Gerardin et al. 2005). Physiological and behavioural changes, both in humans and experimental animals' offspring, are associated with re-direction of growth and developmental trajectories during sensitive periods of development, increasing the risk for later pathophysiology (Maccari et al. 2014). Therefore, the concept of 'foetal programming' was put forward to explain how normal pattern of foetal maturity could be modulated by stimulus that takes place during critical developmental windows (Barker et al. 1993; Bleker et al. 2016; Carolan-Olah et al. 2015; Seckl 1998).

Despite the well-known maladaptive changes induced by foetal programming during early life, the biological 'purpose' of this phenomenon may also be interpreted as a strategy to confer adaptive advantages allowing the developing organism to cope with the unfavourable conditions outside the womb (Del Giudice 2012; Gluckman and Hanson 2004). For example, an enhanced behavioural response to stressful conditions may increase vigilance state during stress that could promote successful survival to environmental threats (Brunton 2013; McEwen 2008). It has been shown that mild to moderate gestational stress could benefit children mental and motor de velopment (DiPietro et al. 2006). Indeed, evidence has accumulated to indicate that not all individuals develop maladaptive behaviours or psychiatric disorders despite living in extreme conditions that include ethnic and social disparities (Cadet 2014). These studies could be related with the concept of resilience to stress, but it is beyond the scope of this review to fully describe the concept of vulnerability versus resilience to PS [please see (King 2016); (Oken et al. 2015) for a complete revision].

In this section, we will summarise the current knowledge supporting the hypothesis that PS may serve as a strong candidate to explain the vulnerability of certain individuals to develop a SUD following repeated drug exposure.

Early Adversities in Humans and its Effects on Substance Use Disorder Vulnerability

Environmental influences during childhood such as psychoactive substances availability, maltreatment, parental mental health, sexual abuse and rejection strongly influence the own child's mental health. In this sense, it has been demonstrated that children of stressed parents are prone to show harsh parenting, without supportive and nurturing interactions with their child (Kiff et al. 2011). This also contributes to the development of conduct problems, such as antisocial behaviour, which have been related with increased vulnerability to psychoactive SUD (Enoch 2006; Karam et al. 2016; Zucker et al. 2008). For example, boys aged 8 years with conduct problems have been shown to predict frequent drunkenness 10 years later (Enoch 2006). Nevertheless, there are currently few studies performed that directly link SUD vulnerability with early adversities exposure. Almost four decades ago, Huttunen and Niskanen (1978) directed a retrospective epidemiological study where they reported that the incidence of alcoholism and personality disorders was relatively high in people whose fathers had died before their children's births or during the first year of their children's life, attributing those results to maternal distress. In line with that report, Liang et al. (2013) examined the association between prenatal- or early postnatal–maternal bereavement and the risk of hospital visits due to SUD and they found that children who lost their father from pregnancy to the "under 10" years had increased risks of SUD. The "under 10 years" comprise the time of growth and development from conception to preadolescence. This period of life is of huge importance for human's development since brain undergoes growth and changes in organisation, structure and function that shape basic systems that let the individual to adapt to the world (i.e. perceived ways to learn, problems resolution, communication with other people, stress response and emotion and behaviour regulation) (Andersen 2003). As Zucker and collaborators (Zucker et al. 2008) stated: "Children arrive at the transitions and challenges of adolescence with the personality, human and social capital they have accumulated in childhood, as well as with their record of achievements and failures meeting the various developmental tasks of childhood" (Zucker et al. 2008). Therefore, it is not surprising that many of the factors related with SUD vulnerability are shaped during the first decade of life.

On the other hand, the preclinical literature suggests that psychosocial stress is an important factor in the initiation and maintenance of addictive behaviours in adult life (Goeders 2003; Koob and Kreek 2007). As reviewed by Roberts et al. (2016), epidemiological studies show increased rates of individuals with post-traumatic stress disorder among individuals with SUD. Such individuals also meet additional criteria for other psychiatric disorders such as anxiety disorders and personality disorders. As we previously exposed, maternal psychosocial stress during pregnancy and the early postnatal period contributes to

abnormal behaviours, which are linked to a greater propensity toward substance abuse and SUD vulnerability: higher anxiety, impulsivity, depression, delayed social competence, malfunction of the stress systems responses and mood disorders, among other effects (Alegria et al. 2010; Belin et al. 2016; Bizzarri et al. 2007; Rao et al. 1999).

Prenatal Stress Effects on Rodent Models of Substance Use Disorder Vulnerability

Rodent models have been employed in the literature to explore the effects of gestational stress on the development and behaviour of the offspring. Despite the importance of human studies, animal models offer the advantage that genetic differences are easy to control, as well as the timing and intensity of stress, postnatal environment and drug exposure regimens. The use of animal models, together with the development of modern neurobiological techniques, has provided important information regarding the neurobiology of PS (Monk et al. 2012) as much as of the neurobiology of SUD (Volkow and Baler 2014). Direct comparison between animals and humans is a complex issue; but in this review, we will refer to SUD from studies in animal models although we are aware that SUD represents a psychiatric disorder that is related with specific mental and behavioural conditions in humans. Nevertheless, it is important to point out that both in human and in animal models, the vulnerability to rewarding or reinforcing effects of drugs of abuse varies among individuals.

Several animal models have been developed to explore different behavioural effects triggered by drugs of abuse. Some are used to reveal rewarding or reinforcing effects of psychoactive drugs [for a wider discussion of the difference between reward and reinforcement, see Wise (2009)]. Moreover, withdrawal and reinstatement experiments are used to model certain aspects of relapse to addicted behaviour, following a period of abstinence.

The most common animal models used to study psychoactive drugs effects on prenatally stressed rodents are as follows: self-administration (SA) by which the animals are trained to associate a particular behaviour with the effects of the drugs of interest; conditioning place preference (CPP), which is based on a Pavlovian conditioning that trains the animals to associate a specific environment with the drugs effect and locomotor sensitisation, that implies an increase in a specific motor behaviour in the animal, when it is repeatedly exposed to a drug.

Several studies employing rodent models have been focused on the consequences of gestational exposure to drugs of abuse as a risk factor for developing addiction-like behaviours in adulthood [reviewed in (Glantz and Chambers 2006; Malanga and Kosofsky 2003]. Nevertheless, and despite the fact that gestational stress is a current proposed risk factor for SUD vulnerability, there are few published studies on this field at present. In Table 1, we have summarised the current literature in animal research that relate gestational exposure to stress with animal responsiveness to drugs of abuse. Despite the differences among the type of species selected for the research, as well as differences on the type, frequency or duration of the gestational stress protocols, most of the studies share the finding that there is a general increase in prenatally stressed offspring drug responsiveness, including stimulants and depressors of the central nervous system (Table 1).

One of the first studies to assess PS effect on individual predisposition to drug-seeking behaviour was that of Deminière and collaborators (1992). They reported that prenatal restraint stress enhanced amphetamine SA in adult male Wistar rats. This finding was later confirmed by Hausknecht and collaborators (2013), who reported that PS adult male Sprague-Dawley rats showed an enhanced amphetamine SA although this effect was evident only when amphetamine dose was reduced after acquisition.

On the other hand, Kippin and collaborators (2008) assessed the influence of maternal stress during gestation on cocaine SA and they observed that PS rats did not show a higher active lever response during self-administration acquisition of several cocaine doses with respect to control group. In agreement with this, Thomas and collaborators (2009) did not observe PS effects on offspring lever responses at low cocaine dose, nor in the number of nose pokes at active or inactive holes. However, they found that PS increased cocaine SA (rate of acquisition and overall drug intake) in young adult male rats when escalating doses were used (Thomas et al. 2009). Furthermore, it was reported that adult prenatally stressed offspring exhibited increased cocaine-seeking during extinction and increased cocaine-primed reinstatement, supporting the idea of a higher vulnerability to cocaine effects in PS rats (Kippin et al. 2008).

Gestational stress was also reported to increase CPP induced by both types of drugs of abuse: stimulants and depressors of the central nervous system. In adult male rats, it was reported that PS increased CPP associated with the depressor drug diazepam (Lakehayli et al. 2015) and morphine (Yang et al. 2006). On the other hand, an increased CPP associated with cocaine was shown in adult PS C57BL/6 J mice, but this effect was not observed in DBA/2 J mice (Kippin et al. 2015). For nicotine, an increased CPP in prenatally stressed rats with respect to controls was also reported (Said et al. 2015). Therefore, even though stimulant and depressor drugs of abuse act through different mechanisms of action, both types of drugs induce a greater vulnerability to place conditioning on prenatally stressed animals. This could be attributed to

Table 1 Studies examining the relationship between gestational stress and vulnerability to substance use disorders in rodent models

Rodent species (PND)	Stress protocol	SUD model	Results	Reference
Wistar male rats (PND 80)	Daily 80 electric foot shocks (0.5 mA, for 5 s, 1–2 min apart) on a random basis during 100 min sessions, during the last 10 gestational days	Nicotine CPP	PS increased CPP	(Said et al. 2015)
B6 and D2 male and female mice (PND 60-70)	Restraint stress for 60 min, 3 times daily, during the last 7 gestational days	Cocaine CPP	PS increased CPP only in B6 male and female mice	(Kippin et al. 2015)
Wistar male rats (PND 80)	Daily 80 electric foot shocks (0.5 mA, for 5 s, 1–2 min apart) on a random basis during 100 min sessions, during the last 10 gestational days	Diazepam CPP	PS increased CPP	(Lakehayli et al. 2015)
Sprague–Dawley male rats (PND 90-180)	Restraint stress for 45 min, 3 times daily under a bright light (6500 lx), during the last 10 gestational days	Amphetamine SA	PS increased SA of a low dose/ infusion	(Hausknecht et al. 2013)
Sprague–Dawley male rats (PND 63)	Variable stress during the last 8–9 gestational days	Amphetamine LA	PS increased LA	(Wilson and Terry 2013)
Sprague–Dawley male and female rats (PND 62-67)	Restraint stress, for 45 min 3 times daily during the last 7 gestational days	Cocaine SA and locomotor sensitisation	PS increased SA only in males (escalating doses) and increased locomotor sensitisation only in females.	(Thomas et al. 2009)
Sprague–Dawley male rats (PND 70-80)	Restraint stress for 30 min, 3 times daily, during the last 7 gestational days	Cocaine SA, extinction and reinstatement	PS increased LA, cocaine-seeking during extinction and cocaine-induced reinstatement	(Kippin et al. 2008)
Wistar male rats (PND 52)	Ten foot shocks (0.8 mA for 1 s, 2–3 min apart) in 30 min daily during the last 7 gestational days	Morphine CPP	PS increased CPP and it was reversed with enrichment environment	(Yang et al. 2006)
Sprague–Dawley female rats (PND 30)	Restraint stress for 45 min, 3 times daily under a bright light, during the last 10 gestational days	MDMA LA	PS increased LA	(Morley-Fletcher et al. 2004)
Sprague–Dawley male rats (PND 90)	Repeated restraint stress	Nicotine LA	PS increased LA	(Koehl et al. 2000)
Wistar male rats (PND 50-60)	Restraint stress for 45 min, 3 times daily, under a bright light, during the last 7 gestational days	Amphetamine locomotor sensitisation	PS increased locomotor sensitisation	(Henry et al. 1995)
Wistar male rats (PND 90)	Restraint stress for 45 min, 3 times daily under a bright light, during the last 7 gestational days	Amphetamine SA and LA	PS increased LA and SA	(Deminiere et al. 1992)

Comparison among published studies of the species selected and frequency or duration of the gestational stress protocols, on the offspring drug responsiveness. CPP: conditioned place preference; *LA* locomotor activity, *MDMA* 3,4-methylenedioxymethamphetamine, *PND* postnatal day, *PS* prenatal stress, *SA* self-administration, *SUD* substance use disorder

the observation that both classes of drugs induce an increase of dopamine release in mesolimbic circuit (Mansvelder and McGehee 2002; Shippenberg et al. 1993) and this DA pathway has been shown to be altered in PS animals, as we previously mentioned (Kippin et al. 2008; Silvagni et al. 2008).

PS enhanced locomotor activity induced by psychostimulants like amphetamine (Deminiere et al. 1992; Wilson and Terry 2013), nicotine (Koehl et al. 2000) or 3, 4-methylenedioxymethamphetamine (Morley-Fletcher et al. 2004). In the case of amphetamine, the effect was independent on the gestational stress protocol used (i.e. restraint or variable stress), and on the rat strain (i.e. Wistar or Sprague-Dawley rats). Also, PS induced an increased locomotor sensitisation to amphetamine in male rats (Henry et al. 1995) and to cocaine in female rats but not in males (Thomas et al. 2009). PS effects on locomotor response to cocaine are not clear: Kippin et al. (2008) reported that PS male rats exhibited a greater locomotor response to an acute cocaine injection, whereas Thomas et al. (2009) showed that PS increased cocaine sensitisation in

female rats but not in males. However, it is important to point out that both studies were performed using different doses and protocols. While Kippin and collaborators used an open field with a fix dose of cocaine, Thomas and collaborators used a circular plastic tub with a corridor in the centre, with escalated doses of cocaine. These differences might account for the divergent results and care has to be taken to compare both studies without taking into account the protocols. Overall, their results show that PS-induced changes in behavioural programming influence later psychomotor stimulant responses in both male and female rats, depending on the drug assessed and the administration schedule.

As already exposed, despite the selected animal model or the gestational stress regime chosen for the research, these results strongly suggest that individual predisposition to drug-seeking behaviour may be triggered by early life experiences such as PS (Table 1).

Sex and Age Influences on Substance Use Disorder Vulnerability

As is was recently stated by The National Institutes of Health: "sex is a biological variable that is frequently ignored in animal study designs and analyses, leading to an incomplete understanding of potential sex-based differences in basic biological function, disease processes and treatment response" (NIH 2015). Indeed, changes on DA systems induced by drugs of abuse are sex-specific in both human and animal models [see below; (Becker and Hu 2008)]. Although studies in humans are more complex since they are influenced not only by hormonal conditions but also by social and cultural factors, sex influences on SUD vulnerability have been reported in a drug-specific manner. In this sense, women were reported to abuse prescribed drugs more likely than men, while men were reported to be higher abusers of illicit drugs (Carroll and Smethells 2015; Fattore et al. 2014). In animal models, Becker and Koob (2016) have recently broadly reviewed male and female differences considering the different stages of the addiction process described by Koob and Le Moal (1997). In contrast with human studies, preclinical data revealed usually higher vulnerability to drug effects in females than in males. A broader analysis of sex influence on SUD is beyond the scope of this review, but we are aware of its importance on the study of PS-induced vulnerability to SUD.

Currently, there are relatively few studies that have examined sex differences in drug abuse liability induced by PS. In this regard, Thomas and collaborators (2009) were the first to report a between-sex comparison of gestational stress effects on SUD-increased vulnerability. They showed that males were more prone to PS potentiation of drug seeking relative to females when self-administration of cocaine was employed in Sprague-Dawley young adult rats. PS selectively facilitated the rate of acquisition and overall drug intake of male but not of female rats. In this research, however, only prenatally stressed female rats showed greater cocaine-induced psychomotor sensitisation with respect to controls. In contrast, Kippin et al. (2015) recently reported that PS potentiates cocaine-induced CPP in both male and female B6 mice. It is well known that the consequences of stress are dependent on the timing of exposure and this may interact with sex-specific responses. However, in these two studies gestational stress was applied during the last week of gestation with a little difference on duration of the restraint sessions (Table 1). The inconsistency between Kippin and Thomaśs results could be explained considering that SA and CPP explore different effects of drugs of abuse (Bardo and Bevins 2000). Furthermore, sex-specificity of prenatal stress-induced vulnerability to SUD probably depends on the animal species in which it is assessed.

It is well known that the age in which the first contact with a drug of abuse takes place is an important factor to predict the development of SUD (Fairchild 2011). In fact, DA systems in the brain undergo developmental transformations during adolescence that are associated with increased reward sensitivity and risk taking (Spear 2000). Therefore, adolescence represents a window of vulnerability to the initiation of drug consumption (Adriani et al. 2003; Belluzzi et al. 2004; Mathews et al. 2011; Vastola et al. 2002).

Unfortunately, there are no comparative studies in the bibliography assessing age differences on PS-induced vulnerability to SUD. Most studies were conducted in young adult (Henry et al. 1995; Kippin et al. 2015; Thomas et al. 2009; Wilson and Terry 2013; Yang et al. 2006) or adult rodents (Deminiere et al. 1992; Hausknecht et al. 2013; Koehl et al. 2000; Lakehayli et al. 2015; Said et al. 2015). To our knowledge, there is only one research that assessed PS-induced vulnerability to drug effects on pubertal rats (Morley-Fletcher et al. 2004) and it was only performed in females. While these studies have generally reported an increase on behavioural effects of drugs of abuse in PS adult rodents, it would be interesting to further design comparative studies exploring the interaction between age and PS as risk factors for SUD.

The paucity of data regarding age- and sex-specific responses to early adversity and their related increased vulnerability for SUD—in both human and animal models—highlights the need to consider these two factors together with neurobiological specific changes in order to advance our knowledge on the molecular basis of vulnerability to SUD and, hence, the development of effective treatments.

Prenatal Stress-Induced Changes in Mesocorticolimbic Dopaminergic System as a Possible Mechanism of Increased Vulnerability to Substance Use Disorder

In the previous sections, we have described that most of the behavioural effects induced by drugs of abuse are more prone to take place in individuals who have been exposed to early life adversities such as gestational stress. However, the mechanisms underlying the increased vulnerability to SUD in those individuals remain to be established.

Despite the fact that drugs of abuse have different mechanisms of action, all of them have in common that they impact on the mesocorticolimbic DA system function (Di Chiara 2002; Nestler 2005; Wise 2008) and also on its associated pathways (Oliva and Wanat 2016), triggering neural plastic changes (Kauer and Malenka 2007; Kourrich et al. 2015). Given that PS has been reported to affect the DA system—which is in turn, a hallmark of SUD—we propose that PS impairments on DA mesocorticolimbic system are a decisive factor to develop a higher vulnerability to SUD in the offspring.

Mesocorticolimbic Dopaminergic System: a Basic Framework

Dopaminergic Synapses

Dopamine is the major catecholamine neurotransmitter in mammalian's brain. It is synthesised primarily at the neuronal terminal via the hydroxylation of tyrosine by the action of the rate-limiting enzyme, tyrosine hydroxylase (TH) (Shiman et al. 1971). After its synthesis, dopamine is sequestered from the cytosol and stored into synaptic vesicles by vesicular monoamine transporter (Blakely and Edwards 2012; Liu et al. 1992). Following nerve firing, vesicular dopamine is released into the synapse (Trifaro et al. 1992) where it can activate postsynaptic DA receptors, as well as presynaptic dopamine autoreceptors. DA receptors are G-protein-coupled receptors, which are classified as low-affinity D1-like receptors (D1R: D1 and D5) or high-affinity D2-like receptors (D2R: D2, D3 and D4). The first couples to Gαs proteins and stimulates the adenylate cyclase enzyme activity and thus activates the postsynaptic neuron, while the last one couples to Gαi protein inhibiting the enzyme and thus inhibiting the postsynaptic neuron (Kuhar et al. 1999).

After release, extracellular dopamine is recycled back into the terminal by dopamine transporter (DAT). In the synaptic terminal, dopamine is either repackaged into vesicles or is degraded by monoamine oxidase B (MAOB) (Berry et al. 1994) to form hydrogen peroxide and 3,4-dihydroxyphenylaldehyde, which is oxidised by aldehyde dehydrogenase to 3,4-dihydroxyphenylacetic acid (DOPAC). Approximately, 60% of DOPAC is converted to homovanillic acid by catechol-O-methyltransferase (COMT) and 40% is eliminated without further metabolism (Nikodejevic et al. 1970).

The Mesocorticolimbic Brain Areas

Four DA pathways have been described in the mammalian brain: nigrostriatal, mesolimbic, mesocortical and tuberohypophysial. In this review, we will particularly refer to the mesolimbic and mesocortical DA pathways. Mesolimbic circuit comprises projections from the ventral tegmental area (VTA) to the nucleus Accumbens (NAc), as well as to the olfactory tubercle, amygdala, septum and hippocampus. Mesocortical pathway includes VTA projections to the prefrontal cortex (PFC), perirhinal and cingulate cortex (Chinta and Andersen 2005; Kuhar et al. 1999). Due to the overlap in brain areas between both systems, they are often collectively referred to as the mesocorticolimbic DA system (Fig. 1) (Wise 2004). Numerous complex behavioural and cognitive brain functions, such as planning, initiation of motor activity, process of reward information and promotion of goal-directed behaviours, are very important for integrating mammalian responses and adaptations to the environment (Chinta and Andersen 2008). Moreover, it has been broadly demonstrated that the acquisition and expression of many behaviours related with drugs of abuse involve the activity of VTA neurons (Koob and Volkow 2010; Kravitz et al. 2015; Pascoli et al. 2015; Qi et al. 2016; Schultz 2010; van Zessen et al. 2012) and that rewarding effects of drugs of abuse involve an increase of DA release to the NAc [reviewed by (Volkow Nora and Morales 2015)].

Modulatory Pathways of Dopaminergic System

Mesocorticolimbic circuit is broadly modulated by several neurotransmission systems, such as cholinergic (Changeux 2010; de Kloet et al. 2015; Faure et al. 2014; Mark et al. 2011), GABAergic (Kudo et al. 2012), serotoninergic (Alex and Pehek 2007), noradrenergic (Jenner et al. 1983)

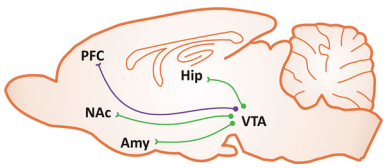

Fig. 1 Schematic representation of the mesolimbic (*green*) and mesocortical (*purple*) dopaminergic pathways in the rat brain. *Amy* amygdala, *Hip* hippocampus, *NAc* nucleus accumbens, *PFC* prefrontal cortex, *VTA* ventral tegmental area

glutamatergic (Carr and Sesack 2000; Lisman and Grace 2005) as well as by neuropeptide systems (Ferraro et al. 2016; Quarta et al. 2011; Rodríguez de Lores Arnaiz and Antonelli 2016). VTA activity and dopamine release to the NAc are influenced by complex connections with several modulatory areas [Fig. 2a; (Juarez and Han 2016; Oliva and Wanat 2016)]. Among excitatory modulation, it is known that PFC sends glutamatergic projections to the VTA neurons (Carr and Sesack 2000; Gabbott et al. 2005). However, glutamatergic inputs from PFC were found to selectively target the VTA-DA neurons that feed back PFC (Carr and Sesack 2000) and the mechanisms by which PFC regulate dopamine release in the NAc are still a matter of debate [see "The Hypo-activity of the Prefrontal Cortex in Prenatally Stressed Rats as a Possible Mechanism 535 for Prenatal Stress-Induced Dopamine Changes" section (Del Arco and Mora 2008; Karreman and Moghaddam 1996; Murase et al. 1993; Taber and Fibiger 1995; Tong et al. 1996; You et al. 1998)]. Furthermore, it is known that PFC receives cholinergic inputs from the basal forebrain and the brainstem (Albuquerque et al. 2009) and it has been recently reported that the activation of alpha7 nicotinic receptors on its layer V pyramidal neurons enhances glutamate release (Poorthuis et al. 2013). Cholinergic modulation is also present in sub-cortical areas, enhancing dopamine release from VTA to NAc (Pidoplichko et al. 2004). In the NAc, there are two populations of medium spiny neurons, which express D1R and D2R, and constitute the direct and indirect GABAergic pathways, respectively. They have overlapping projections to the ventral pallidum (VP), which in turn composes one of the inhibitory inputs to VTA neurons (Kalivas et al. 1993; Kupchik et al. 2015;

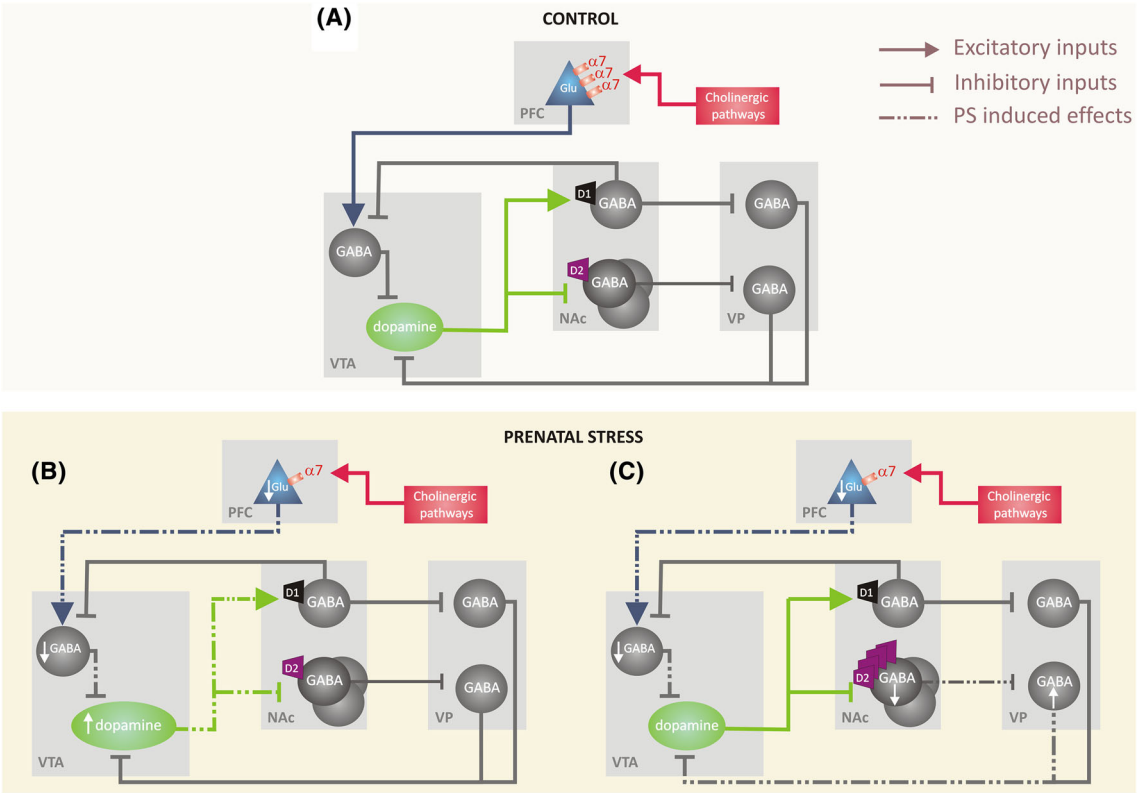

Fig. 2 Prenatal stress-induced hypo-functionality of PFC and dopamine increase in the NAc: a possibly compensatory increase of D2R. **a** In control animals, cholinergic inputs to the PFC allow the cortical activation of VTA-GABAergic neurons, thus modulating VTA-DA neurons and dopamine release into the NAc. Neurons that originate NAc direct pathway sends back inhibitory projections to VTA-GABAergic neurons (short-loop feedback). Most neurons of the VP receive GABAergic innervation from the NAc indirect pathway and send GABAergic projections to the VTA (long-loop feedback). **b** In adolescent–young adult PS rats, the decrease of alpha seven nicotinic receptors in PFC declines cholinergic modulation of its pyramidal neurons, thus impairing cortical activation of VTA-GABAergic neurons and increasing dopamine release into the NAc. **c** In adult PS rats, the increase of D2R in the NAc could be explained as a compensatory mechanism for dopamine increase in those animals. An enhanced inhibition of the indirect pathway in the NAc allows a hyper-activation of the VP, which in turn decreases the abnormally augmented activity of VTA-DA neurons. This figure shows glutamatergic (*blue*), cholinergic (*red*), dopaminergic (*green*) and GABAergic (*grey*) projections. Arrows indicate excitatory and truncated lines indicate inhibitory pathways. *Dot lines* indicate PS effects. *up arrow* increase of neuronal activity; *down arrow* decrease of neuronal activity; α7: alpha 7 nicotinic receptors; D1: dopamine receptors type 1 (these neurons originate the "direct pathway"); D2: dopamine receptors type 2 (these neurons originate the "indirect pathway"); *DA* dopaminergic, *Glu* glutamatergic, *NAc* nucleus accumbens, *PFC* prefrontal cortex, *PS* prenatal stress, *VP* ventral pallidum, *VTA* ventral tegmental area

Root et al. 2015). It is noteworthy that VP is a heterogeneous brain structure and its sub-regions could play different roles on the modulation of VTA activity and drug-seeking behaviour (Mahler et al. 2014; Root et al. 2013). Among inhibitory modulation of mesolimbic DA system, VTA-GABAergic neurons influence VTA-DA activity and it has been shown that the activation of this pathway suppressed dopamine release into the NAc (van Zessen et al. 2012).

Dopaminergic System Changes Underlying Substance Use Disorder Vulnerability

It is widely known that repeated—or even a single—exposure to drugs of abuse can trigger long-lasting changes in mesocorticolimbic DA system that are thought to underlie vulnerability to the development of SUD (Di Chiara 1998; Di Chiara et al. 2004; Robinson and Berridge 2008). Despite the fact that those mechanisms have not been fully elucidated yet, and beyond the importance of other neurotransmitters in reward processing, there is a large consensus that the addictive properties of drugs of abuse are related to their ability to increase dopamine levels, particularly in the NAc (Volkow and Baler 2014). Recent studies using cell-type specific approaches have reported that stimulation of the medium spiny neurons of the NAc direct pathway (i.e. a procedure that is equivalent to stimulate dopamine release from VTA) is necessary for both acquisition and expression of cocaine-induced CPP in mice (Hikida et al. 2013; Lobo et al. 2010). On the contrary, stimulating the indirect pathway (i.e. the equivalent to diminish dopamine release from VTA) reduced cocaine-induced CPP (Lobo et al. 2010). In line with these studies, Kravitz and collaborators (2012) have shown that stimulation of the direct pathway induced persistent reinforcement in the dorsomedial striatum, whereas the activation of the indirect pathway induced transient punishment. These findings support the hypothesis that the direct pathway could mediate reward processes, while the indirect pathway could participate in aversion. Therefore, dopamine can activate the direct pathway by binding to D1R, and thus increasing reward; and it can inhibit indirect pathway by binding to D2R, and thus decreasing aversion. This could explain why the highest reward occurs when dopamine is released excessively to the NAc and reaches significantly high levels that allow it to bind to the low-affinity D1R in addition to the high-affinity D2R (Steinberg et al. 2014).

In human addiction research, imaging studies have long been used to explore D2R expression in striatal areas (Volkow et al. 1990). In this regard, it has been reported that a reduction of D2R binding is associated with the abuse of different drugs both in human and animal models [reviewed by (Trifilieff and Martinez 2014)], whereas high levels of D2R has been proposed as a protective SUD development factor (Volkow et al. 2006). Indeed, a higher expression of postsynaptic D2R in the NAc has been associated with an increased motivation, i.e. a higher effort for a specific reward (Trifilieff et al. 2013), and with a decrease of cocaine (Thanos et al. 2008) and alcohol self-administration (Thanos et al. 2001). Moreover, a pharmacological blockade of D2R has been associated with a preference of less effort and smaller immediate rewards (Salamone et al. 2007), i.e. with a higher vulnerability to develop SUD.

Imaging techniques have also been used to explore the role of the PFC in self-control, and its importance in preventing addictive behaviours was well established (George and Koob 2010; Goldstein and Volkow 2011). In this regard, an impairment of PFC excitability has been shown following cocaine SA with a much more pronounced effect in compulsive rats, which take the drug in spite of receiving an electric shock (Chen et al. 2013). Interestingly, using optogenetic stimulation of PFC neurons, these authors showed that restoring PFC activity decreased cocaine-seeking behaviour. It is noteworthy that cholinergic projections from the basal forebrain to the PFC have been described as excitatory inputs to its pyramidal neurons (Albuquerque et al. 2009; Bloem et al. 2014; Hedrick and Waters 2015). Considering that the effect was reported to be mediated at least in part by alpha 7 nicotinic receptors (Poorthuis et al. 2013), the integrity of the expression levels of those receptors could be important to prevent SUD vulnerability.

Prenatal Stress-Induced Changes in Mesocorticolimbic Dopaminergic Systems

Retrospective studies performed in individuals that were exposed to gestational stress or childhood maltreatment, demonstrated that these early insults increased the propensity to develop psychiatric abnormalities later in life which are also related to mesocorticolimbic DA system or modulatory pathways dysfunction (Kasanova et al. 2016; Pruessner et al. 2004).

In our group, we have employed a prenatal restraint stress model throughout our studies, where the pregnant dam is placed individually in a transparent plastic restrainer fitted closely to body size for 45-min periods three times a day (9:00, 12:00 and 16:00 h), between gestational days 14 and 21. Our results on mesocorticolimbic DA system revealed that in male young adult offspring PS decreased dopamine release in cortical areas after dopamine-release stimulation with amphetamine (Carboni et al. 2010). Moreover, our group found an increased dopamine release in NAc shell both at basal, or stimulated dopamine-release conditions in adolescent and young adult PS rats (Silvagni et al. 2008). In line with our results, Kippin et al. (2008)

reported an increase of basal dopamine in PS offspring of 10–12 weeks of age. In addition, PS changed the expression of specific transcription factors that promote differentiation of DA neurons during development, as well as the immune-expression of the TH enzyme, and DAT (Converse et al. 2013; Katunar et al. 2009, 2010).

DA receptors have also been shown to be affected by PS. In 1995, the group of Henry and collaborators was the first to evaluate receptor levels in PS adult rats and they found an increase in the number of D2R in the NAc, a decrease in D3 receptors and no differences in D1 receptor levels (Henry et al. 1995). In agreement with these results, we also found an increase in D2R levels in PFC and in the core region of the NAc of adult male prenatally stressed rats (Berger et al. 2002). Moreover, the effect was reversed if PS rats were adopted at birth by a non-stressed dam (Barros et al. 2004). It has been suggested that the increase of D2R in NAc may occur at the transcriptional level as it was reported in offspring of dams exposed to electroshock during gestation (Lakehayli et al. 2015; Said et al. 2015), and in an rodent model of prenatal administration of dexamethasone (Rodrigues et al. 2011). However, non-transcriptional mechanisms have been also proposed to explain accumbal changes on D2R expression in a model of neonatal isolation (Lovic et al. 2013).

In addition to mesocorticolimbic DA system modifications, PS has been shown to impact regulatory pathways associated to dopamine neurotransmission. In this sense, the cholinergic system is an interesting target to be explored in order to evaluate vulnerability to psychiatric illnesses in later life because of its strong involvement in neural plasticity, learning and memory (Udakis et al. 2016; Yakel 2013). In concordance with that, our group has recently reported an impairment of cholinergic modulation in the PFC of prenatally stressed offspring (Baier et al. 2015): we found a reduction in gene expression and protein levels of the alpha seven nicotinic receptor in adult male rat, suggesting that PS has long-lasting effects over the cholinergic modulation of cortical areas. Cholinergic modulation in sub-cortical areas, including projections from VTA to NAc, has also been reported to be altered as a consequence of gestational stress [reviewed by (Holgate and Bartlett 2015)], supporting the importance of this neurotransmission system in early programming of DA pathways.

Dopamine, Substance Use Disorder and Early Adversities: Cross-Sensitisation of Neurochemical Responses Between Prenatal Stress and Drugs of Abuse

Dysfunction of mesocorticolimbic DA system has been extensively explored both in studies related to SUD vulnerability [reviewed by (Volkow Nora and Morales 2015)], as well as in studies associated to PS consequences on descendants brain development [reviewed by (Baier et al. 2012)]. Therefore, gestational stress becomes an interesting candidate to explore the aetiology of the vulnerability to develop SUD after repeated drug exposure observed in certain individuals.

Our group has previously investigated the effect of prenatal repeated restraint stress on basal dopamine output in the NAc and in the PFC of freely moving adolescent (30–35 days) and young adult (60–70 days) rats (Carboni et al. 2010; Silvagni et al. 2008). We found that basal extracellular concentrations of dopamine in the NAc shell of both adolescent and young adult PS rats were significantly higher than in relative controls, in agreement with Kippin et al. (2008) who reported an increased DA basal extracellular concentration in the NAc of 10–12 week-old prenatally stressed rats. The mechanism by which PS exerts basal increased levels of extracellular dopamine in the NAc is still unknown. In this section, we will point out possible mechanisms underlying this phenomenon and its influence on SUD vulnerability.

Prenatal Stress Delays Dopamine Removal From the Synaptic Cleft

Considering PS-induced alterations in DA systems, a possible explanation for the increase of dopamine in the NAc could be that PS may alter DAT expression or MAO/COMT activities, thus retarding dopamine removal from the synaptic cleft. In this sense, it was reported that after childhood adversities, patients with a low COMT activity allele showed increased risk for the development of alcohol use disorder (Schellekens et al. 2013). In animal models, it was reported that a lower expression of MAO-A is related with alcohol abuse (Cervera-Juanes et al. 2016), an effect that is enhanced by early life stress (Bendre et al. 2015). Furthermore, reduced levels of DAT protein in VTA have been reported for prenatally stressed mice (Son et al. 2007). More studies are needed to understand the cellular mechanisms underlying the increased levels of extracellular dopamine in the NAc of PS individuals. Beyond the alteration of the neurotransmitter removal from the synaptic cleft, it has been suggested that PS increases the activity of VTA-DA neurons, thus supporting an increase of dopamine release [see below; (Hausknecht et al. 2013; Oosterhof et al. 2016)].

Prenatal Stress Enhances Ventral Tegmental Area-Dopaminergic Neurons Activity

It was reported that PS led to a persistent reduction in VTA-DA neuron population activity (number of spontaneously active neurons) in the offspring during adulthood

(Hausknecht et al. 2013). However, the firing rate in the remaining spontaneously active neurons was not altered and these authors showed that the reduction of DA neurons activity was presumably mediated by over excitation to the degree of depolarisation block. Indeed, the overexcitation of VTA-DA neurons in PS rats was recently confirmed by Oosterhof et al. (2016). These authors reported an increase of baseline firing and bursting activity of VTA-DA neurons in PS rats, evidenced probably because it did not occurr to the extent of depolarisation block. In addition to our microdialysis studies (Silvagni et al. 2008), those findings support a PS-induced presynaptic effect underlying extracellular dopamine increase, which probably involves an increased release of dopamine instead of—or in addition to—a decreased removal from the synaptic cleft.

The Hypo-activity of the Prefrontal Cortex in Prenatally Stressed Rats as a Possible Mechanism for Prenatal Stress-Induced Dopamine Changes

As we have already mentioned VTA-GABAergic neurons inhibit VTA-DA cells, modulating motivation-like behaviours (Tan et al. 2012; van Zessen et al. 2012). Indeed, drugs of abuse and acute stress were shown to impair long-term potentiation at those inhibitory synapses (Niehaus et al. 2010), an effect that was suggested to be mediated by a decrease of glutamate release to the VTA (Guan and Ye 2016; Nugent et al. 2007). Therefore, the increased activity of VTA-DA neurons observed in PS rats could be explained by a reduction in the inhibition exerted by VTA-GABAergic neurons, most likely due to the impairment of its glutamatergic modulation. In support of this hypothesis, it is important to consider the influence of cortical inputs on VTA, although the mechanisms by which PFC regulate dopamine release in the NAc are still unclear. It has been proposed that glutamatergic projections from the PFC activate VTA-DA neurons, and, therefore, increase dopamine release in the NAc (Karreman and Moghaddam 1996; Murase et al. 1993; Taber and Fibiger 1995), although morphological studies do not support this hypothesis; instead theysuggested that VTA-DA neurons that project to the NAc do not receive glutamatergic terminals from the PFC (Carr and Sesack 2000; Juarez and Han 2016), but see Beier et al. (2015). Moreover, Del Arco and collaborators (2008) have shown that the blockade of NMDA receptors on PFC, i.e. the decrease of PFC activity, enhanced dopamine release in the NAc, indicating that PFC has an inhibitory influence on those VTA-DA neurons. It has been suggested that this inhibition occurs by activation of VTA-GABAergic neurons (Carr and Sesack 2000; Jackson et al. 2001; Sesack and Carr 2002). In support of that assumption, it has been recently shown that the blockade of NMDA receptors in PFC increased spontaneous firing and bursting activity of VTA-DA neurons, while decreasing spontaneous activity of VTA-GABAergic neurons (Tan et al. 2014). Interestingly, by using morphine-induced CPP, these authors suggested that mesocortical DA pathway controls mesolimbic DA modulation of opiate reward. Therefore, a deregulation of prefrontal cortical pathways could result in an increase of dopamine release in the NAc as a consequence of a decreased activity of VTA-GABAergic neurons and, ultimately, influence the rewarding effects of drugs of abuse.

Prenatal Stress Alters Prefrontal Cortex Neuronal Morphology and Activity

It was shown that PS induces alterations of PFC at different levels. In our group, we found a reduction in MAP2 (a microtubule-associated protein type 2, present almost exclusively in dendrites) immunoreactive neuronal processes in PFC of prepubertal and adult PS male rats (Barros et al. 2006; Pallarés et al. 2013). Moreover, it was reported that PS reduced dendritic spine densities on the PFC (Muhammad and Kolb 2011; Mychasiuk et al. 2012; Weinstock 2011), suggesting that PS would be reducing dendritic arborisation. Moreover, decreased ERK2 and CREB mRNA levels in PFC were recently reported in PS rats (Zhu et al. 2016). Taking into account that those factors are neuronal activity markers (Ha and Redmond 2008), those findings suggest a hypoactivation of PFC during adulthood in PS rats.

Prenatal Stress Reduces Cholinergic Activation of Prefrontal Cortex

The role of nicotinic acetylcholine receptor in SUD-increased vulnerability following PS still remains relatively unexplored, despite its broadly modulatory influence on mesocorticolimbic circuit (Changeux 2010; Picciotto et al. 2012), including the PFC (Poorthuis et al. 2013). In this sense, an interesting finding performed by our group that supports a hypoactivation of PFC is the decrease of alpha 7 nicotinic receptors in PS rats (Baier et al. 2015), suggesting an impaired cholinergic activation of this brain area. Taking into account the inhibitory influence of PFC over VTA-DA neurons (Carr and Sesack 2000; Del Arco et al. 2008; Jackson et al. 2001; Sesack and Carr 2002; Tan et al. 2014), this impaired cholinergic modulation and the likely consequent decrease in activity of cortical neurons could, at least in part, explain the increase of basal dopamine release in the NAc that has been shown in PS rats (Kippin et al. 2008; Silvagni et al. 2008).

In summary, we propose that an impaired function of PFC, possibly by an altered cholinergic modulation as well as morphological changes, could underlie an enhanced

activity of VTA-DA neurons as a consequence of a decreased activity of VTA-GABAergic neurons and, thus, an increase of basal extracellular dopamine levels is observed in the NAc of PS rats (Fig. 2b).

Prenatal Stress Increases the Expression of Dopaminergic D2-like Receptor in the Nucleus Accumbens: a Compensatory Phenomenon?

As we mentioned before, medium spiny neurons of the NAc inhibit the VP GABAergic neurons, predominantly through the indirect pathway (Kupchik et al. 2015), and due to VP inhibitory inputs to the VTA, the activation of the indirect pathway enhances dopamine release from the VTA to the NAc [see Fig. 2b; (Oliva and Wanat 2016)]. However, VTA-DA release to the NAc can inhibit the indirect pathway by activating D2R, mediating a long-loop negative feedback to the VTA (Rahman and McBride 2001). In PS rats, not only basal dopamine release is higher than in controls, but there is also an overexpression of D2R in the NAc (Berger et al. 2002; Henry et al. 1995). The increase of D2R corresponds to the presynaptic autoreceptors or to the postsynaptic receptors on dopaminoceptive neurons of the NAc- or a combination of both- is still unknown. However, both mechanisms could be interpreted as a compensatory phenomenon occurring during adulthood (Berger et al. 2002; Henry et al. 1995) as a protection mechanism to counteract the increase of dopamine release to the NAc observed in adolescent and young adult PS rats (Silvagni et al. 2008). An increased presynaptic D2R density would modulate negatively the release of dopamine from VTA-DA neurons (Benoit-Marand et al. 2001; Ford 2014). Even though it has been classically described that receptors are downregulated upon an increase of the ligand (Shaw and Scarth 1991), it is well known that postsynaptic forms of long-term plasticity comprise an increase of postsynaptic receptors even following an increased release of the neurotransmitter (Castillo et al. 2011; Jones and Bonci 2005). In this sense, a possible long-term compensatory mechanism, could explain the increase of postsynaptic D2R density following an increase of dopamine release. The imbalance of D1/D2 receptors observed in PS rats could promote a major inhibition of the indirect pathway mediated by dopamine, thus enhancing the activity of the VP and then inhibiting VTA-DA neurons [Fig. 2c; (Anzalone et al. 2012; Rahman and McBride 2001)]. Further studies are needed to explain if D2R increase in adulthood is a compensatory mechanism for the increase in DA release from the VTA in adolescent or young adult PS rats and its importance in preventing SUD development. Interestingly, increasing D2R signalling in the NAc of animals with a history of drug self-administration has been hypothesised to shift their behaviour away from drug use and towards non-drug reward (Trifilieff and Martinez 2014), suggesting that an enhanced expression of accumbal D2R could have a protective factor to revert SUD (Volkow et al. 2006).

Prenatal Stress Enhances Psychostimulant-Induced Increase of Dopamine in the Nucleus Accumbens

Considering that Accumbal dopamine plays a prominent role in the reinforcing effects of drugs of abuse (Di Chiara et al. 2004), the enhanced dopamine input into the NAc observed in PS individuals might be sensitising this circuit increasing vulnerability to SUD after exposure to substances of abuse. In this regard, others and we have conducted microdialysis studies to evaluate psychostimulant-induced dopamine output in PS rats. After an acute injection of nicotine, the increased total dopamine release in the shell region of the NAc was higher than in controls for PS rats (Silvagni et al. 2008). For cocaine, it was also shown that PS increased drug-stimulated dopamine transmission in the NAc (Kippin et al. 2008), a finding that had also been described on a rodent model of neonatal isolation as an early life adversity (Kosten et al. 2003). For amphetamine, our group found that in response to an acute systemic injection of the drug, the dopamine output was higher in adolescent and adult PS rats, than in controls (Silvagni et al. 2008). Interestingly, this finding is in line with a recent clinical study that observed an increased dopamine response to amphetamine in the NAc of individuals with a history of childhood adversity (Oswald et al. 2014).

As we mentioned previously, increased levels of D2R in the NAc were reported in adult PS rats (Berger et al. 2002; Henry et al. 1995; Lakehayli et al. 2015; Said et al. 2015), and we propose that it is a compensatory change for the increased dopamine release in the NAc (Fig. 2c). However, impaired D2R expression in PS rats repeatedly exposed to drugs of abuse has been recently reported (Lakehayli et al. 2015; Said et al. 2015). Considering that reduced levels of D2R are a consistent finding in human individuals with SUD [see (Trifilieff and Martinez 2014)], these results suggest that repeated exposure to drugs of abuse in individuals prenatally exposed to stress is a trigger factor to increase their vulnerability for SUD.

Concluding Remarks

Nowadays, there is a large consensus that SUD can be reframed as a developmental disorder. In a broader vision, it has been suggested that a continuous complex variety of adversities from the intrauterine period through early adolescence might rewire key neural circuits of stress and reward, increasing the risk for serious addictive disorders.

Gestational stress has been consistently associated to impairments of the mesocorticolimbic DA pathway that is closely related to cognition, emotion, reward, reinforcement and decision-making.

In view of the limited progress that has been made to reduce the incidence of addiction by current prevention and treatment programs, understanding the effects of early adverse experiences on the development of SUD, might help to design successful interventions as early as the pregnant mother (or even before, on both future parents) in order to assure quality parental care that is currently known to play a critical role in the socialisation and regulation of emotions and behaviours in children.

We have collected data that clearly show that PS could be considered a risk factor for an increased vulnerability for SUD. However, and of no less importance, it should be taken into account that early life adversities—in both human and animal models—probably increase the risk for the development of a psychopathology (such as SUD) in response to a trigger factor (i.e. drugs of abuse) only among a subpopulation that is susceptible to that adversity. It would be beyond the scope of this review to fully describe the concept of vulnerability versus resilience to PS, but we consider that in future research this topic should be contemplated to avoid missing information of mechanisms underlying the increased risk for SUD in prenatally stressed individuals. In addition, there may be a complex relationship between vulnerability to PS and sex/age influence on brain changes or altered behaviour, so it would be interesting to include those factors in future experimental designs in order to expand and refine our knowledge of vulnerability to psychiatric diseases.

Based on our own studies and those of others, PS produces complex and long-lasting neurobiological changes to DA neurotransmission, enhancing sensitivity to psychostimulants, which have led our group to hypothesise that this might play an important role in prenatal stressed-induced vulnerability to SUD in animal models. We proposed that a hypo-activity of the PFC—possibly by an impairment of cholinergic modulation—could underlie the enhancement of the basal and drug-stimulated DA transmission in the VTA–NAc regions observed in PS offspring, which might make them more vulnerable to rewarding effects of psychostimulants. Above all, the study of early life-induced adversities on the mesocorticolimbic DA circuit will allow an approach to new strategies to prevent the development of SUD in human subjects prenatally exposed to stress, and to achieve more personalised and effective treatments.

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