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Review article

Long-term consequences of prenatal stress and neurotoxicants exposure on neurodevelopment

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ABSTRACT

There is a large consensus that the prenatal environment determines the susceptibility to pathological conditions later in life. The hypothesis most widely accepted is that exposure to insults inducing adverse conditions *in-utero* may have negative effects on the development of target organs, disrupting homeostasis and increasing the risk of diseases at adulthood. Several models have been proposed to investigate the fetal origins of adult diseases, but although these approaches hold true for almost all diseases, particular attention has been focused on disorders related to the central nervous system, since the brain is particularly sensitive to alterations of the microenvironment during early development. Neurobiological disorders can be broadly divided into developmental, neurodegenerative and neuropsychiatric disorders. Even though most of these diseases share genetic risk factors, the onset of the disorders cannot be explained solely by inheritance. Therefore, current understanding presumes that the interactions of environmental input, may lead to different disorders. Among the insults that can play a direct or indirect role in the development of neurobiological disorders are stress, infections, drug abuse, and environmental contaminants. Our laboratories have been involved in the study of the neurobiological impact of gestational stress on the offspring (Dr. Antonelli's lab) and on the effect of gestational exposure to toxicants, mainly methyl mercury (MeHg) and perfluorinated compounds (PFCs) (Dr. Ceccatelli's lab). In this focused review, we will review the specialized literature but we will concentrate mostly on our own work on the long term neurodevelopmental consequences of gestational exposure to stress and neurotoxicants.

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1. Introduction

There is nowadays little doubt that early life exposure to a variety of environmental influences is critical for later susceptibility to diseases. Early life is often referred as both the gestational period, during which the fetus is exposed to different environmental constituents, as much as the postnatal period which is also crucial in rendering a susceptible individual. The hypothesis most widely accepted is that the exposure to different influences during *in-utero* and/or postnatal stages of life affects the development of target organs, disrupting the homeostasis and increasing the risk of adult diseases.

Several models have been proposed but most of them stem in Barker's hypothesis of Fetal Basis of Adult Diseases (FeBAD) based on their studies on adult cardiovascular diseases. Barker's hypothesis fits well with almost all diseases and it suggests that the fetus responds to the maternal health status and shows adaptive responses for survival. Later, Gluckman and Hanson suggested that the fetus predicts the extra-uterine environment according to intrauterine conditions, making changes for its better survival. This model was named PAR for Predictive Adaptive Response. An extension of these models was later introduced as the DOHaD (Developmental Origin of Health and Disease) by Gluckman postulating that the postnatal period of development also plays a role in health. A more elaborate vision of this model have been put forward by Van den Bergh who proposes the "Developmental Origins of Behavior, Health and Disease" (DOBHaD) hypothesis that integrates early brain and behavioral development with new insights from the field of epigenetics. The DOBHaD hypothesis opens new perspectives on the prevention of diseases by detecting them before they start to develop, based on the working hypothesis of Ben-Ari (2008), who proposes that early- and late-onset neurological disorders might be, in part, born at early developmental stages before symptoms appear. The core of this working hypothesis is that imaging or non-invasive recordings might unravel signatures of disorders to come, thereby permitting earlier diagnosis and potential treatment of neurological disorders. Therefore, Van den Bergh observes that rather than treating symptoms, there should be an initial appreciation of the disturbed intrinsic and extrinsic factors of the developmental process that will guide the understanding of the nature of the illness and its future treatment.

Lahiri and collaborators described a model termed LEARn (Latent Early life Associated Regulation) in which each of the environmental exposures are considered "hits" acting through induced latent epigenetic changes (Lahiri et al., 2009). According to this model, disorders develop according to an "n" number of hits. The first hit is the early environmental exposure that leads to epigenetic perturbations, and after a long latency period, a second trigger is necessary for the disease to develop.

The importance of these models is revealed by Hertzman (1999) who broadens the approach suggesting that early child development is also influenced by the socioeconomic and psychosocial environment of childhood that will eventually be linked to adult health status. This process has been termed "biological embedding" and has been more recently up-dated to include the epigenetic changes that occur early in life and affect behavior and physiology (Danese and McEwen, 2012; McEwen, 2015). Although these models hold true for almost all diseases, particular attention has been focused on disorders related to the central nervous system since brain sculpting is related to the conditioning of the host defense system that depends on communication with the developing brain (Hertzman, 1999).

The brain is particularly sensitive to alterations of the perinatal microenvironment during early development, although the consequences of prenatal damage may not necessarily be apparent until a critical age when neurodevelopmental defects may be unmasked or precipitated by a subsequent exposure to other insults.The development of the nervous system is a very complex process characterized by stages reached according to a tightly regulated program. Essential processes like cell proliferation, migration and differentiation occur at well-coordinated time points to ensure the establishment of normal brain structure and functions (Andersen, 2003). This arrangement of developmental processes results in different windows of susceptibility towards insults.

Neurobiological disorders can be broadly divided into:

a) Developmental disorders, such as autism spectrum and attention deficit disorders, usually manifested in childhood.
b) Neuropsychiatric disorders, such as bipolar disorder and schizophrenia, most typically appear in adolescence and early childhood.
c) Neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD) usually appear late in life and are characterized by progressive loss of synaptic markers eventually resulting in dementia.
d) Other disorders including major depressive disorders (MDD), substance abuse disorder and anxiety disorders, which onset present a broad range of age and lifestyle.

Most of these diseases share genetic risk factors but the onset of the disorders cannot be explained solely by inheritance. Therefore, current understanding presumes that the interactions of multiple agents, including environmental input, leads to a disorder.Among the different environmental agents that can play a direct or indirect role in the development of neurobiological disorders are food, metals, pesticides, stress, infections and drugs of abuse. A revision of these different agents and its influence on neurodegenerative disorders can be found in Modgil et al.(2014).

In this review, we will concentrate our efforts in reviewing the existing literature but mostly our own work on the long term neurobiological consequences of gestational exposure to stress and toxicants.

2. Prenatal exposure to stress

2.1. Stress definition and mechanisms

The concept of stress has been thoroughly revised in the literature since it was originally defined by Selye (1950) as the "non-specific response of the body to any noxious stimulus". Later,

the concept was refined by distinguishing between 'stressor' and 'stress response' and the most recent revision by Lucassen et al. (2014) proposes that a stressor is "any environmental demand that exceeds the physiological regulatory capacity of an organism", in particular and, as suggested by Koolhaas et al. (2011), "during situations of unpredictability and uncontrollability".

The mechanisms of the physiological stress response that will depend on the intensity of the stressor and its duration can be divided into a very quick response which involves the rapid activation of the sympatho-adreno-medullary (SAM) axis, including components of the autonomic nervous system (ANS) and a delayed response through the activation of the hypothalamic–pituitary–adrenal (HPA) axis. Briefly, the SAM axis represents a heterogeneous network of neural and endocrine functions, which are interconnected to activate sympathetic processes. The release of corticotropin releasing factor (CRF) as neurotransmitter in the locus coeruleus (LC) leads to the activation of medullary centers, which control the sympathetic nervous system. Sympathetic processes may stimulate a neural pathway *via* ganglia, and an endocrine pathway that elicits the release of catecholamines, epinephrine and norepinephrine, into the circulation by the adrenal glands. Circulating catecholamines stimulate effector organs *via* specific adrenergic receptors (Schulz and Vögele, 2015). The HPA axis activation is triggered by CRF in the paraventricular nucleus (PVN) that induces adrenocorticotropic hormone (ACTH) release from the pituitary, which in turn releases glucocorticoids (GCs) from the adrenal. Regulation occurs through negative feedback after GC binding to high-affinity mineralocorticoid (MR) and lower affinity glucocorticoid receptors (GR) (de Kloet et al., 2005). It is important to point out that in the magnitude and the specificity of the individual response to stress is eventually determined by the limbic and hypothalamic brain structures that will coordinate emotional, cognitive, neuroendocrine and autonomic inputs (Lucassen et al., 2014). However, it has been suggested that the two axes are not fully independent from each other. Circulating CRF may inhibit central noradrenergic processes, while noradrenergic activity inhibits CRF production in the hypothalamus (Chrousos and Gold, 1992).

2.2. The SAM and the HPA axes in pregnancy

The SAM is considerably different in pregnant women compared to the non-pregnant state to hold the developing fetus. Normal ANS function is essential to affect changes in blood volume and circulation that take place during normal pregnancy. However, dramatic hemodynamic changes occur during pregnancy, including increased cardiac output, decreased systemic vascular resistance, together with an expanded blood volume (Cunningham et al., 2001). An impaired adaptation of maternal hemodynamics may affect uteroplacental circulation and subsequent fetal development. For instance, changes in umbilical blood flow velocity are suggested to be determined mainly by maternal hemodynamics, including the vascular pressure changes associated with maternal heart rate (Struijk et al., 2001).

Regarding the HPA axis, it is accepted that maternal unbound cortisol rises during pregnancy, particularly after the 21st week of gestation, and reaches levels that are more than twice those of nonpregnant women. Fetal concentrations of cortisol have been found to be linearly related to maternal cortisol concentrations and although Increased cortisol levels during pregnancy can be harmful to the fetus, high levels of the placental enzyme, 11Beta-hydroxysteroid-dehydrogenase type 2 (11B-HSD2), protect the developing fetus by converting cortisol to the inactive form, cortisone. The activity of 11B-HSD2 isinfluenced by several factors, thereby affecting how much cortisol may pass through to the fetus (Lazinski et al., 2008). Animal studies indicate that inhibition of this enzyme in pregnant rats results in offspring that are lower in body weight, with higher glucocorticoid levels, reduced glucocorticoid receptor levels, and onset of depression and anxiety-like behaviors (Welberg et al., 2000). Correspondingly, the placentas of women who demonstrated intrauterine growth restriction have shown decreased 11B-HSD2 gene expression (McTernan et al., 2001).

2.3. Stress during pregnancy

Pregnant women are not exempted of suffering a stress situation and even though it is known that the HPA axis becomes less responsive towards the end of the gestational period (Glover, 2015), it is well established that stress suffered during pregnancy has long term consequences on the child's outcome. During the gestational period, women like any other subject can be exposed to endogenous and exogenous challenges that may be perceived as unpleasant, aversive or threatening in such a way that the homeostasis, wellbeing, overall health or survival is threatened. An unpleasant surprise, relational or financial problems, the loss of a loved one, bereavement, unpredictability, an acute threat with psychosocial demand or even simply daily hassles or living in a city, can all initiate a stress response (Lederbogen et al., 2011; Lucassen et al., 2014). Since the maternal environment, and the mother's responsivity to stressors are the only environment to which fetus is exposed, the placenta plays a crucial role in moderating fetal exposure to maternal factors, and presumably in preparing the fetus for the environment in which it is going to find itself (Glover, 2015).

Even though monitoring of the SAM and the HPA axes in both the mother while pregnant and the infant postpartum are still much needed, changes in both axes have been reported. Regarding the SAM axis, changes in norepinephrine (NE) and epinephrine (Epi) with respect to psychological distress and negative affect during pregnancy have been reported in several investigations (Lazinski et al., 2008). Moreover, DiPietro and colleagues (DiPietro et al., 2000) reported fetal cardiac (heart rate and variability) and maternal physiologic measures (blood pressure and oxygen saturation) explained most of the variance in heart rate and variability at 1 year of age. Regarding the HPA axis, Seckl and colleagues hypothesize that early life events and stress can program neuroendocrine systems and behavior through prenatal endogenous or exogenous glucocorticoid overexposure, and that this fundamental programming process underpins many common disorders, including cardiovascular and metabolic disorders, as well as behavioral inhibition (Welberg et al., 2005, 2000).

Regarding the enzyme 11B-HSD2 mentioned above, rats exposed to acute stress showed an immediate approx. 2 fold increase in activity, while there was no change following 6 days of chronic stress exposure (Welberg et al., 2005). However, when the chronically-stressed rats were exposed to acute stress, they failed to show an up-regulation of enzyme activity, indicating that chronic stress may be detrimental for healthy pregnancy. Also, increased levels of catecholamines, *i.e.* NE and Epi, which are secreted during stress, can down-regulate 11B-HSD2 gene expression in human placental cells (Sarkar et al., 2001). Nevertheless, even if maternal cortisol does not cross the placenta, increased maternal HPA axis activity may stimulate fetal and placenta CRH, which may lead to increased fetal cortisol levels (Frim et al., 1988).

2.4. Mechanisms of developmental re-programming relevant both to animal and human studies

The mechanisms of the underlying developmental re-programming are well established in animal studies but only beginning to

be understood in humans. As mentioned above, animal studies have shown that developmental exposure to stress re-programmes both the peripheral and central nervous system involved in the two stress-regulating subsystems: the HPA and the ANS (Oitzl et al., 2010; Seckl and Holmes, 2007). Van Craenenbroeck et al. (2005) mention the limbic-hypothalamo-pituitary adrenocorticoid (LHPA) axis as the neuroendocrine system responsible in regulating GC hormone homeostasis. Stress triggers physiological and behavioral responses that will finally reinstall the homeostasis between the central nervous system (CNS) and the endocrine system. Repeated stress can be harmful and will induce changes in neuronal circuits especially of the limbic system (hippocampus and the amygdala) and the prefrontal cortex (PFC) (Van Craenenbroeck et al., 2005; Van den Bergh, 2011). These areas are involved in emotional, cognitive processing and temperamental variation in behaviour whose impairments may underlie behavioral problems and psychopatology triggered by prenatal stress (PS).

Numerous studies have shown that PS affects fetal neurodevelopment even though some reports have pointed out the difficulty in discriminating between the effects of prenatal from postnatal insults, indicating that if a mother is stressed during her pregnancy, she may be stressed during lactation as well, with detrimental consequences on her parenting and caring abilities (Glover, 2015). However, many studies have shown evidences of prenatal effects independent of postnatal exposure such as altered outcomes at birth including reduced birth weight (Wadhwa et al., 1993), reduced scores on a neonatal assessment (Rieger et al., 2004), epigenetic changes in the glucocorticoid receptor in cord blood (Hompes et al., 2013), altered fingerprint patterns (King et al., 2009) and handedness (Glover et al., 2004).

Since the understanding of the mechanism underlying the link between PS and adult psychopathologies still rely on animal studies, we will summarize the existing literature and our own work on animal models of PS that are relevant to neurodevelopmental pathologies observed in human subjects. In addition, some relevant studies performed in pregnant women will also be reviewed.

2.5. Prenatal stress in animal models

2.5.1. General considerations

Animal research on the effects of PS on brain development have been conducted mainly in Sprague-Dawley, Wistar and Long-Evans rat strains, but also in Rhesus macaques, guinea pigs, sheeps and mice. Animal studies offer the possibility to control the type, intensity, duration and timing of the stressor applied to the dam, as well as the interaction of the mother with her offspring in a controlled environment. Furthermore, researchers can investigate the long term behavioral outcomes induced by PS. Nevertheless some discrepancies have been found probably from differences in species, strain, sex or age of animal used, as well as in the duration and intensity of the applied stress in relation to fetal development (Charil et al., 2010; Weinstock, 2008).

Rodents differ from primates (including humans) in the duration of gestation (*i.e.*, rats = 21.5 days; monkeys = 165 days, humans = 270 days) and associated levels of brain maturation at birth (Charil et al., 2010). Several major brain developmental events, such as peak of amygdalar development and the appearance of corpus callosum, occur during the final stages of gestation in rats, whereas in monkeys and humans the same events take place during the first half of gestation. Moreover, a considerable amount of neuroendocrine and neural development occurs in the rat and mouse brain after birth, making it more sensitive to environmental conditions and maternal attention, which can also contribute to the overall effect of PS on offspring behaviour (Weinstock, 2008).

Various PS protocols exist in the literature, which differ in the type of applied stressor, daily frequency, length of application and week of gestation chosen. In this review we focused on rodents models since a more comprehensive behavioural, morphological and histological information is available than in other species. In rodents, PS paradigms range from saline injections, suspension, crowding, hypoxia, electric footshock, placental insufficiency, unpredictable stress and noise, and REM sleep deprivation (Huizink et al., 2004; Mastorci et al., 2009). A frequently used protocol is a modified version of Ward and Weisz model consisting of restraining the mothers during the last week of gestation (Ward and Weisz, 1984). This paradigm has been shown to induce a robust psychoneuroendocrine stress activation in the mothers that interferes with the development of neural networks and neuroendocrine systems in the offspring, which in turn modulate behavioral and physiological stress responses in adulthood (Mastorci et al., 2009).

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 inducing anomalies in neuronal development and brain morphology that directly affect offspring behavior (Charil et al., 2010; Mastorci et al., 2009; Ward et al., 2000; Weinstock, 2001). PS induces low birth weight, learning and attention deficits, impaired adaptation to stressful conditions, vulnerability to anxiety and depressive-like behaviors, reduced social interaction and some of the characteristic neuronal changes of schizophrenia (Alonso et al., 1991; Huizink et al., 2004; Lee et al., 2007; Weinstock, 2008, 2001) (Darnaudéry and Maccari, 2008; Koenig et al., 2005; Lee et al., 2007; Yaka et al., 2007; Yang et al., 2006). Furthermore enhanced propensity to self-administer drugs such as amphetamine (Deminière et al., 1992; Fride and Weinstock, 1989; Henry et al., 1995; Wakshlak and Weinstock, 1990)and nicotine (Koehl et al., 2000) were also observed in PS rats. Gestational stress also induced delays in motor development and alterations in locomotor and exploratory activities that depended on the age and the sex of the offspring when those parameters were evaluated (Diaz et al., 1997; Henry et al., 1995; Pallarés et al., 2007). Inappropriate sexual behaviour of adult offspring and gonadal dysfunction have also been reported: PS reduced the number of adult male copulations, decreased the number of ejaculations, enhanced lordotic-like behaviors and increased male partner preference over receptive females (Gerardin et al., 2005; Kapoor and Matthews, 2011; Shono and Suita, 2003). Additionally, a lack of tonic gonadotropin secretion and altered testosterone secretion profiles were also shown, even during adulthood, in prenatally stressed animals (Gerardin et al., 2005; Rodríguez et al., 2007; Shono and Suita, 2003). Alterations on sexual morphological parameters, such as the anogenital distance length and the timing of testicular descent, were also found to be altered (Barros et al., 2006).

It is interesting to mention that most of the alterations described in PS animals are related to changes in midbrain dopaminergic activity, suggesting that the development of the dopamine (DA) is sensitive to disruption by exposure to early stressors. It is well known that midbrain DA system regulates diverse behavioral and cognitive functions which 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, 1995), which have been traditionally related to DA mesolimbic and mesocortical pathways.

The mesolimbic dopaminergic system comprises cells of the Ventral Tegmental Area (VTA) that projects most prominently to the nucleus accumbens (Nac), olfactory tubercle as well as to the septum, amygdala and hippocampus. The mesocortical dopaminergic system includes another group of cells in the medial VTA that project to the prefrontal, cingulate and perirhinal cortex (Chinta and Andersen, 2008; Kuhar et al., 1999). Due to the overlap between the mesocortical and the mesolimbic dopaminergic neurons the two systems are collectively referred to as the mesocorticolimbic system (Wise, 2004). These DA system are involved in emotion-based behavior including motivation and reward (Chinta and Andersen, 2008) and these neurons are critical for the action of antipsychotic, antihyperactivity and psychostimulant drugs (Kuhar et al., 1999).

2.5.2. Results from our laboratory

2.5.2.1. PS effects on the dopaminergic system. Our laboratory has a long standing interest in the effects of PS on the rodent brain development, especially on the mesocorticolimbic dopaminergic pathway (Baier et al., 2012) triggered by the hypothesis that, in human subjects, stressful situations suffered prenatally are related to increase the propensity to develop psychiatric abnormalities in later life. We investigated the effects of PS on the expression of DA and glutamatergic (Glu) receptors in offspring of dams subjected to restrain stress during the last week of gestation and we found that while DA receptors increase almost exclusively in limbic areas, Glu receptors increase both in limbic and motor areas (Berger et al., 2002). Cross-fostering studies confirmed the high vulnerability of DA and Glu systems to variations both in prenatal and in postnatal environment (Barros et al., 2004). PS offspring show high anxiety levels that show direct correlation with benzodiazepine receptors exhibiting a decrease in the number of benzodiazepine receptors binding sites in amygdala and hippocampus (Barros et al., 2006). Moreover PS induces a long-lasting astroglial reaction and a reduced dendritic arborisation with synaptic loss in the brain of adult offspring (Barros et al., 2006). Specific DA transcriptions factors, such as Nurr1 and PiTX3, were found to be altered in PS offspring along with the expression of tyrosine hydroxylase (TH) enzyme (Katunar et al., 2010, 2009). Amphetamine or nicotine stimulation produces an increase in DA levels in NAc shell of adult PS male rats (Silvagni et al., 2008) and a decreased DA release after amphetamine stimulation in prefrontal cortex of adult offspring (Carboni et al., 2010), suggesting that this cortical DA deficit might be triggering a NAchyperfunction and an overall DA imbalance in the prenatally stressed offspring brain.

Based on our own studies, PS increases DA D2 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 transcription factors along development as well as the expression of TH and transporters. In a recent review (Baier et al., 2012) we illustrated the complex relationship between PS and dopaminergic system development with a schematic representation of a typical neuron belonging to the VTA–PFC pathway (Fig. 1.). 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 D2 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 VMAT2, which

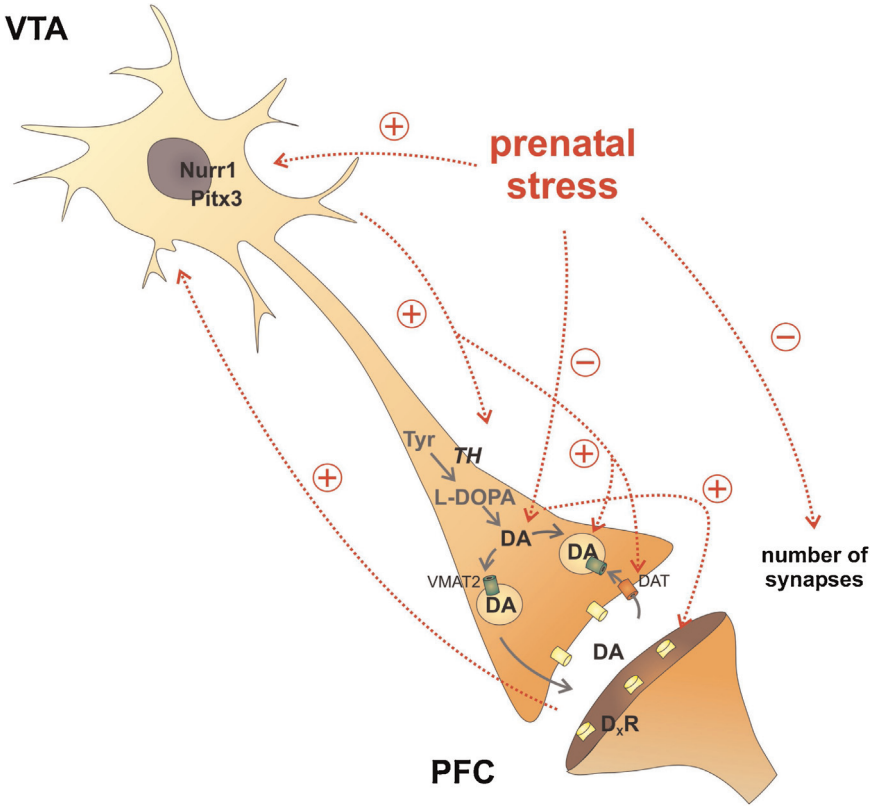

Fig. 1. Schematic representation of the effects exerted by PS on the dopaminergic function. The data correspond to the VTA–PFC pathway of an offspring that was prenatally stressed employing a chronic restraint stress protocol to the dam, during the last week of pregnancy. The effects described occur 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 D2receptors, which in turn activates Nurr1; high levels of this transcription factor could upregulate TH expression, and eventually DAT and VMAT2, 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. (From Baier et al., 2012).

will increase DA levels in an attempt to compensate for the misbalance produced by PS. In addition to the neurochemical alterations described above, PS produces synaptic loss in the brain of adult offspring (Barros et al., 2006).

In light of the interplay of GC and GR with the dopaminergic system outlined in the paragraph above, it might be inferred that the up-regulation of TH expression might be regulated through the specific motifs in the TH promoter and controlled by GR receptors. Recently Virdee et al. (2014) investigated the consequences of the antenatal glucocorticoid treatment (AGT, gestational days 16–19) showing that it induces cytoarchitectural disturbances on indices of DA function in adult rats. These authors show that in adulthood, enrichment of striatal DA fiber density paralleled AGT-induced increases in the numbers of midbrain DA neurons, which retained normal basal electrophysiological properties. This was co-incident with changes in striatal D2-type receptor levels; D1-type receptor levels; DA transporter levels in striatal regions; amphetamine-induced mesolimbic DA release. Besides observing profound, sexually dimorphic changes in markers of DA neurotransmission, they observed a modest or no effect on a range of appetitive behaviors known to depend on mesolimbic DA activity. The authors conclude that their findings provide empirical evidence for enduring AGT-induced adaptive mechanisms within the midbrain DA circuitry, which preserve some, but not all, functions, thereby casting further light on the vulnerability of these systems to environmental perturbations. Furthermore, they demonstrate that these effects are achieved by different, often opponent, adaptive mechanisms in males and females, with translational implications for sex biases commonly found in midbrain DA-associated disorders.

The interplay between GCs and the dopaminergic system is not yet completely unraveled but many studies have focused on the influence of GC on DA synthesis, DA receptors and DA transporters. For example, AP-1 and CREB, specific motifs for transcription factors have been described as target for negatively transcriptional regulation by GR in cytokines promoters (De Bosscher et al., 2003). Interestingly, the promoter regions of genes encoding dopamine synthesizing enzymes, dopamine receptors and the dopamine transporter has also shown specific motifs such as AP-1 and CREB (Van Craenenbroeck et al., 2005). In the adrenal gland, increases in catecholamine biosynthesis, as a response to repeated or chronic stress is associated with an increases TH-gene expression and is controlled by both neurotransmitter and GC hormone receptors (Kvetnansky and Sabban, 1998; Otten and Thoenen, 1975). The TH promoter also contains AP-1 and CRE elements. It has been demonstrated that immobilization stress induces activation of CREB and c-Jun-containing AP-1 complex, which represents *de novo* synthesis in response to stressors of intermediate duration (Sabban and Kvetnanský, 2001). These are just few of many examples of how GC and GR interact with the adult dopaminergic system. If this holds true for the adult system, the developing dopaminergic pathways might result more vulnerable to increases of GC as a consequence of a stress situation.

2.5.2.2. PS impairments on the critical pubertal period. Adolescence and puberty are commonly used as similar concepts but they refer to different events of life. Although the timing of these periods overlaps, adolescence is defined as the gradual period of transition from childhood to adulthood whereas puberty refers as the precise moment where an individual physiologically matures to its reproductive stage. Therefore, adolescence is a longer period of life even though its precise onset and offset are difficult to determine with precision (Spear, 2000). The physiological changes that take place during the adolescence are directed by the sexual hormones that regulate several neuroendocrine systems, modulate behaviors and stimulate (or suppresses) the differentiation, as well as the plasticity of several neural populations. Hence, on peripheral tissues, they induce the appearance of secondary sexual characteristics which are necessary to achieve the reproductive maturation (Nussey and Whitehead, 2001; Sato et al., 2008). On the other hand, their effects on the brain orchestrate several morphological and neurochemical modifications which are necessary for the adolescent brain to mature to an adult form (Andersen, 2003; MacLusky et al., 2006; Paus et al., 2008; Sato et al., 2008; Spear, 2000). During this phase the brain awakens to pleasure, risk and other behavioral features that are common among adolescents of a variety of mammal species in order to provide to the individual, experience and information from the external environment which are necessary for its conception of the "adult world" (Andersen, 2003; Paus et al., 2008; Sato et al., 2008; Spear, 2000). Hormonal actions on several neurotransmitters pathways are very important for the expression of such behaviors. Sexual hormones were shown to regulate the synthesis and the release of neurotransmitters, as well as they also direct the remodelling of several synaptic circuits (Alonso-Solis et al., 1996; Kuppers et al., 2000). Specially, it was observed that they are directly implicated with the development of cognitive, motor and motivational processes related to dopaminergic neurotransmission, probably by inducing modifications at transcriptional and maturational levels (Purves-Tyson et al., 2012). In this respect, it was demonstrated in rats that the densities of both type 1 and 2 DA receptors in PFC of adult males increase from birth until PND 40, when a maximum is achieved. Thereafter the pruning process takes place, during which the number of receptors is diminished (58–75%) to reach adult levels (Teicher et al., 1995). In humans a similar phenomenon was reported (Huttunen and Niskanen, 1978; Seeman et al., 1987). The changes in the number of DA receptors during adolescence parallel the increase and the decrease in the symptoms of ADHD and Tourette syndrome (TS). In addition, they also parallel with the adolescent androgen surges.

Impairments observed in offspring subjected to PS are evident all along the postnatal development of the offspring but the period of adolescence seems to be a pivotal stage after which some impairment become evident or reversed. In agreement, it has been reported that several behavioral and biochemical alterations exerted by PS were seen only after puberty (Diaz et al., 1997; Henry et al., 1995). Being the hormonal changes the hallmark of the adolescent period, sexual hormones become the first suspects of the differential effects of PS. In fact, the 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 dopaminergic system during the pubertal period. When evaluating Nurr1 expression in the VTA of prenatally stressed rats at PND 28, we found a decline that was recovered after puberty, probably indicating an altered vulnerability to gonadal hormones (Katunar et al., 2010). In agreement with other authors, our hypothesis is that the perinatal events might render the cathecolaminergic circuitries more vulnerable to puberty variation of the hormonal circulating levels. In turn, PS might exert a misbalanced hormonal milieu by altering the hypothalamic-pituitary-gonadal axis of the offspring. Catecholaminergic pathways are programmed during fetal stages, but we suggest that PS can modify this program that is further altered under the influence of the hormonal pattern in turn modified by the prenatal insult (Pallarés and Antonelli, 2015). We found that some plastic morphological processes might be programmed prenatally but are relatively insensitive to the increase of sexual hormones during puberty. In our hands, we have shown that PS induced long-term imbalance of pituitary and testicular male sexual hormones concentrations in serum, advanced the spermatogenesis development and exerted an age-dependent misbalance on oestrogen

alpha receptor expression on prefrontal cortex and hippocampal brain areas (Pallares et al., 2013a, 2013b). Since our results on MAP2 immuno-expression on mesocorticolimbic DA brain areas show coincidence with those results obtained when prenatally administering the androgen receptor antagonist flutamide, we suggested that the mechanism of action of PS might be related to the impairment of the organisational role of androgens on brain development.

Therefore, adolescence is a dynamic period of neural development when behavioral circuits are refined and many of the developmental processes that occur during perinatal brain development are repeated during this phase of life: processes such as neurogenesis, programmed cell death, pruning of dendritic arborizations and synapses, myelination and sexual differentiation, take place (Sato et al., 2008). Perturbations in the timing of pubertal hormone influences on the adolescent brain would be predicted to have long-lasting consequences for adult behavior, since adolescence is also a pivotal time on the aetiology of certain psychopathologies (Pallarés and Antonelli, 2015).

2.5.3. PS and gender differences

Even though we have restrained our studies to the male offspring other authors have observed that susceptibility of the relevant circuitry to environmental challenge is sexually dimorphic in a psychopathological context (Bale, 2006). Elucidation of the mechanisms promoting these dimorphisms is an important future challenge. Epigenetic changes in the nervous system are emerging as a critical component of enduring effects induced by perinatal experience, among other effectors. Sex differences in the brain are largely determines by steroid hormone exposure during the perinatal sensitive period that alters subsequent hormonal and non-hormonal responses throughout the life span. Epigenetic programming is out of the scope of this review but is emerging as a critical factor in brain sexual differentiation, which is driven, to a large extent, by a surge in testosterone production by the testes, occurring between GDs 17 and postnatal day 10 in the male rat (McCarthy et al., 2009), the same surge that we suggested might be related to the hormonal changes observed in PS offspring (Pallares et al., 2013a, 2013b). Prenatal synthetic glucocorticoid treatment can also permanently modify the epigenome (Crudo et al., 2013) and produce endocrine and behavioral effects, which may be qualitatively and quantitatively different in males and females (Brummelte et al., 2016; Kapoor et al., 2008; Seckl and Holmes, 2007). Differential interactions of glucocorticoids with the sex-specific gonadal steroid environment at the level of epigenetic markers in the developing male and female midbrain DA systems therefore offers a compelling explanation that might account for their sexually dimorphic programming by antenatal glucocorticoid treatment.

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 might have a correlation in human subjects, thus providing a neurochemical and morphological basis to the observed human psychopathologies associated to gestational stress.

2.6. Some considerations on human studies on prenatal stress

Assessment of the effect of stress during pregnancy on the neurodevelopment of the offspring in humans is difficult, since well controlled prospective or longitudinal studies usually posed ethical dilemmas. However, different strategies have been developed to circumvent this problem and hundreds of studies have been published in the last forty years that have been accurately summarized in several excellent reviews and book chapters (Beijers et al., 2014; Glover, 2015; Graignic-Philippe et al., 2014; King and Laplante, 2015; Markham and Koenig, 2011; Mulder et al., 2002; Silveira and Manfro, 2015; Van den Bergh et al., 2015, 2005; Weinstock, 2005; Welberg and Seckl, 2001).

Even though a recent exhaustive review, concluded that the only most robust, consistent and well replicated results is the association between PS and preterm delivery and low birth weight, (Graignic-Philippe et al., 2014) a meta-analytic study (Tarabulsy et al., 2014) confirmed that there seems to be a low but significant inverse association between indices of maternal PS or anxiety and early child cognitive development.

When an analysis of the existing literature is performed it is observed that, in spite of the differences in the type of stressor, age of outcome assessment and statistical analysis, the most commonly found neurodevelopmental outcome in children are mainly ADHD, higher anxiety, behavioral disorders and cognitive dysfunctions. Depending of the severity of the stressor some studies report a higher incidence of schizophrenia, autism, major depressions, affective disorders and emotional imbalances (Glover, 2011; King and Laplante, 2015; Kofman, 2002; Van den Bergh et al., 2005) This means that from all possible neurological pathologies, PS has been predominantly associated with diverse psycho-and psychiatric pathologies.

It is interesting to point out that most of these psychopathologies have been related to some form of impairments of the dopaminergic pathway. This observation is surprisingly similar to the conclusion arrived after analyzing the results obtained in animal models. As exposed above, exposure to adverse events during gestation in animal models alter neurochemical indicators of midbrain DA activity. Although this observation has not been assessed directly in human studies, the pathophysiology of idiopathic psychiatric disorders including psychosis and mania, as well as schizophrenia and ADHD is generally attributed to dopaminergic mesolimbic and mesocortical pathways.

As mentioned above, and 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 mesocorticolimbic pathways and its relation to cognition, emotion, positive reinforcement, food intake, and decision making, it is tempting to hypothesize that the alterations observed in prenatally stressed animals models might 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.

2.7. Summary

In summary the vast majority of the studies in the literature, including our own research in this field, reported changes on the neurodevelopmental outcome of the offspring that suffered PS. Those effects are mainly on the limbic rather that in the motor system with alterations of neurochemical indicators of midbrain

DA activity. This hypothesis suggests that PS animals will be less prone to develop diseases that involved motor areas. In agreement with the above, recent results from our laboratory indicate that prenatally restraint stressed rats show the same susceptibility than undisturbed animals to an injury caused by an intrastriatal injection of 6-OHDA (Baier et al., 2014). 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. (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 experiment will be necessary in order to determine if PS animals are, or not, 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).

3. Prenatal exposure to toxicants

Human activities have been leading to the release of a variety of chemicals into the environment. As a result, numerous organic and inorganic pollutants are found in blood, hair or body tissues of living organisms, including humans (Damstra et al., 2002). The presence of chemicals in the environment has been linked to adverse health effects pointing to the reproductive, endocrine, nervous, and immune systems as most sensitive targets. Even if over the last 50 years a large number of chemicals are subject to strict regulations and controlled production (Stockholm convention; http://chm.pops.int/), use and disposal, people and animals are constantly exposed to mixtures of chemicals present in the environment. Blood and breast milk contamination are important and reliable indicators of the type of chemical exposures that people are subjected to. Food contamination appears in most cases to be the major factor that influences the concentration of pollutants in body fluids.

Exposure to chemicals have been proposed as possible causes of learning and emotional disorders at young age, and neurodegenerative diseases in later life (Landrigan et al., 2005). In particular, developmental neurotoxicity has been recognized worldwide as a serious threat to human health (Goldman and Koduru, 2000), and experimental and epidemiological studies have shown that neurodevelopmental disorders can be caused by exposure to environmental pollutants, such as lead or methylmercury (MeHg). In addition, the possibility that developmental exposure to neurotoxicants may lead to earlier onset of or accelerated progression of age-related functional decline is a major concern (Landrigan et al., 2005; Rice and Barone, 2000).

A wide range of chemicals have been shown to affect the developing nervous system (reviewed in (Grandjean and Landrigan, 2006, 2014)). The growing awareness on the threat posed by exposure to environmental toxicants has contributed to reducing the burden on public health. However, there is an increasing concern for chemical contaminants that undergo bio-accumulation and bio-magnification.

A major concern is for the contaminants that may have detrimental effects on the developing nervous system, which may be exposed in the prenatal period or in postnatal life *via* maternal milk during the breastfeeding period. Among the chemical contaminants of concern are methylmercury and the perfluorinated chemical PFOS, which are widespread despite the strict regulation of production and disposal.

We used rodent primary neural stem cells (NSCs) as *in vitro* model of developmental neurotoxicity, while *in vivo* analyses were performed in mice prenatally exposed to the environmentally relevant levels of neurotoxicants. Here we review our recent *in vitro* and *in vivo* studies aimed at investigating the mechanisms behind the neurotoxic effects of MeHg and PFOS as well as the long-term consequences on behavior.

3.1. Methylmercury (MeHg)

MeHg is produced by microbial activity that converts inorganic mercury released in the environment by natural as well as anthropogenic sources. It has very high affinity for sulfur-containing anions, particularly the thiol (-SH) groups on the amino acid cysteine. After ingestion, MeHg is absorbed from the gastrointestinal tract to a very large extent and enters the blood stream, where it binds to hemoglobin. It has a half-life of about 50 days in human blood (IPCS, 1990). In mammalians it is mostly found complexed with free cysteine, as well as with cysteine-containing peptides and proteins. The methylmercuric-cysteinyl complex is recognized as methionine by amino acid transporters (Kerper et al., 1992), and is transported freely throughout the body including across the BBB and the placenta.

MeHg became a prototypical example of dietary environmental contaminant after the disaster in Minamata and Niigata in Japan in 1950's and 1960's that resulted in poisoning of subjects who ingested fish and shellfish contaminated by MeHg discharged in waste water from a chemical plant. The pollution at both locations was massive and lasted for several years before it was recognized officially. The symptoms of the affected children in most cases were associated with large and frequent consumption of fish from the contaminated waters: fish and shellfish from Minamata and Niigata had up to 40 ppm of MeHg (Harada, 1995), well above the average MeHg concentration found in fish from most western countries (*i.e.* less than 0.5 ppm, (IPCS, 1990)). There have been reports of MeHg poisoning in the years to follow from different exposure sources. These include MeHg treated grains in Iraq (Amin-Zaki et al., 1976) and consumption of MeHg contaminated pork in New Mexico (Davis et al., 1994). It immediately became clear that the developing nervous system is more vulnerable to MeHg than the adult nervous system as during the outbreaks some mothers with no obvious symptoms of nervous system damage gave birth to infants with severe disabilities (Harada, 1995). MeHg poses therefore a risk to public health as it can affect the development of the brain of infants at concentrations that do not cause overt symptoms in adults.

Most of the information we have about the effects of developmental exposure to low-dose MeHg originate in prospective studies conducted in New Zealand, Seychelles, and the Faroe Islands. The main source of exposure to MeHg is dietary consumption of deep sea and reef fish and shellfish in the first two studies, while in the cohorts from the Faroe Islands, the source of MeHg exposure was the customary consumption of pilot whale blubber. Taken together, these studies show that developmental exposure to MeHg leads to neurodevelopmental delays at the age of 7 years corresponding to approximately 2 months, or 1.5 IQ points, for each doubling of prenatal exposure estimation based on combined retrospective analysis of data from Faroe Islands, Seychelles and New Zealand cohorts (see Grandjean and Herz, 2011). The deficits are manifest in attention, visuospatial function, language, and verbal memory. An extended follow-up to the age of 22 years has identified persistent deficits in motor, attention and verbal tests, as well as delayed brainstem auditory-evoked potentials and alterations of cardiac autonomic activity (Debes et al., 2015, 2006; Grandjean et al., 2004; Murata et al., 2004). We explored the hypothesis that changes in circulating brain derived neurotrophic factor (BDNF) concentration reflects the neurodevelopmental deficits induced by exposure to MeHg *in utero*, and measured the concentration of BDNF in umbilical cord blood samples collected from the newborn children enrolled in the Faroe

Islands cohort (Spulber et al., 2010). Using a supervised non-linear regression model with BDNF serum concentration as continuous outcome variable we found an inverse correlation with prenatal MeHg exposure. In addition, maternal smoking enhanced the negative effect of MeHg on serum BDNF. Altogether, these data suggest that exposure to MeHg blunted the presumably compensatory increase in serum BDNF in response to maternal smoking. The latter is particularly relevant given that the failure to increase serum BDNF in response to perinatal hypoxia has been shown to be associated with adult onset of psychotic disorders (Cannon et al., 2008; Chouthai et al., 2003).

While the evidence on higher susceptibility of the developing nervous system to MeHg neurotoxicity is indisputable, the limited knowledge on the effects of exposure tolowconcentrations of MeHg calls for studies to clarify the mechanisms of developmental neurotoxicty and the long-term consequences of prenatal/perinatal exposure. Particularly relevant is the persistence of neurodevelopmental effects of MeHg, albeit to a lesser extent,untilyoung adultage (see (Debes et al., 2015)).

3.2. Effects of MeHg on neural cells

MeHg induces neurotoxicity by perturbation of intracellular calcium levels, induction of oxidative stress by producing more reactive oxygen species (ROS) or by reducing the cellular oxidative defense and also by interaction with sulfhydryl groups. In the brain MeHg is deposited preferentially in astrocytes and microglia, and to a lesser extent in neurons (reviewed in Ni et al., 2012). However, neurons appear to be the major target of toxicity in the central nervous system (Eto et al., 1992). MeHg induces oxidative stress and activates antioxidant enzymatic systems in both microglia and astrocytes, but the timing of the response is different between the two cell types: microglia become activated and start secreting proinflammatory cytokines within minutes after MeHg exposure, while astrocytes react in a matter of hours after exposure. In astrocytes, MeHg depletes the stores of glutathione (GSH) and inhibits the uptake of cystine. This in turn contributes to oxidative neuronal damage, since astrocytes play an essential role by supplying GSH to neurons. The main mechanism of toxicity in glial cells appears to be induction of oxidative stress, which induces a neuroprotective response in astrocytes by increasing the secretion of neurotrophic factors, such as BDNF and NGF (Takemoto et al., 2015). However, the impact on neuronal function is multimodal and includes alterations in synaptic transmission by reduced astroglial neurotransmitter reuptake and inhibition of LTP by proinflammatory cytokines released by activated microglia (reviewed in Aschner et al., 2007).

We have implemented the use of NSCs culture as a model for mechanistic studies of developmental neurotoxicity. NSCs prepared from the developing nervous system maintain the capability of self-renewal and can differentiate in neurons and glial cells. NSCs prepared from rat embryos are highly susceptible to MeHg toxicity even at concentrations that have no effects in mature neurons or glia cells. MeHg affects proliferation and migration (Burke et al., 2006; Sass et al., 2001; Tamm et al., 2006) and inhibitsneuronal differentiation without altering glial differentiation (Tamm et al., 2006). By using a reporter system we have demonstrated that Notch activity is consistently increased in NSCs exposed to MeHg upon growth factor removal (Tamm et al., 2008). Earlier reports indicate that mercurial compounds bind to and activate metalloproteases that control the cleavage and activation of Notch (Bland and Rand, 2006). In fact, by pretreating NSCs with GM6001 (a potent metalloprotease inhibitor) we could reverse the decrease in neuronal differentiation induced by MeHg providing a possible mechanism for the adverse effects induced by developmental exposure to MeHg (Tamm et al., 2008). We then wanted to investigate the long-lasting effects of exposure to MeHg in the NSC system model (Bose et al., 2012). To this end, we used a model that would allow the identification of long-lasting, heritable effects from the acute effects from direct exposure. Thus, rat NSCs were maintained in a proliferative state by constantly supplying growth factors. The acute effects were investigated after 48 h exposure to MeHg in passage 1 (parent cells, P1). The cells were then passaged to obtain daughter cells (D2 and D3, obtained from passages 2 and 3, respectively). The levels of Hg measured in D2 cells were about 5 times lower than in P1, and in D3 cells Hg concentration was below detection limit. We can therefore assume that D3 NSCs were not directly exposed to MeHg, and all alterations that were similar to P1 cells could be considered heritable, presumably mediated by epigenetic mechanisms. Exposure to nanomolar concentration of MeHg induces a persistent reduction in the proliferation rate, which is not accompanied by cell death. The effect is associated with an up-regulation of cyclin-dependent kinase inhibitors that restrict the G1/S-phase transition (p16 and p21). In addition, exposure to MeHg induces the expression of senescence markers (such as Hmga1 and HP1 gamma). These alterations are consistently found both in NSCs directly exposed to MeHg (P1 parent cells), and in cells that were never directly exposed (D2 and D3 daughter cells). The persistence of alterations induced by MeHg exposure suggested that epigenetic mechanisms might be involved, and in fact MeHg induces global DNA demethylation associated with down-regulation of Dnmt3b, a *de novo* DNA methyl transferase that is enriched in developing tissues (Bose et al., 2012).

NSCs have an essential role not only in the developing nervous system, but also in specific areas of the adult brain where neurogenesis may be important for normal functions of the CNS. NSCs present in the postnatal brain are established during development. To investigate whether the persistent decrease in proliferation induced by MeHg in NSCs is also occurringinvivowelooked at the proliferation rate of NSCs located in one of the two established neurogenic niches that are preserved in the adult brain, namely the subgranular layer of the hippocampal dentate gyrus (DG). This brain region is particularly relevant in relation to MeHg exposure *in vivo* because alterations in hippocampal neurogenesis have been associated to severe behavioral outcomes such as learning impairment and depression, which occur in mice exposed to MeHg during development (Onishchenko et al., 2007). Interestingly, in DG of the adult mice exposed to MeHg there was a reduced density of Ki67 positive cells (a marker expressed by dividing cells). We next investigated whether the reduced proliferation rate would results in a decrease in the number of cells in the dentate gyrus using a stereological approach. The mice exposed to MeHg displayed a consistent reduction in the number of neurons in the granule cell layer (Bose et al., 2012). The relevance of these *in vivo* findings is supported by the fact that treatment with fluoxetine (a commonly prescribed antidepressant drug) both restored the progenitor proliferation rate, and reversed the depression-like behavior in MeHg exposed mice (Bose et al., 2012), in accordance to the neurogenesis hypothesis of depression.

3.3. Developmental exposure to MeHg and long-term behavioral alterations

We have investigated the predisposition to depression-like behavior in mice exposed to low doses of MeHg during prenatal and early postnatal period. Exposure to 0.5 mg MeHg/kg/day *via* drinking water from gestational day (GD) 7 until postnatal day 7 resulted in impaired learning and depression-like behavior in male mice (Onishchenko et al., 2007). For this purpose, we used forced

swimming (FST) and tail suspension tests (TST), which are based on the evaluation of an escape-oriented behavioral response to a stressful situation (Porsolt et al., 1977; Steru et al., 1985). We found that adult male mice exposed to MeHg during early developmental period had a longer immobility time both in FST and TST (Onishchenko and Ceccatelli, 2010). In addition, we detected a decreased expression of BDNF mRNA in the hippocampal dentate gyrus. MeHg-exposure induces long-lasting repressive state of chromatin structure at the BDNF promoter region, with DNA hypermethylation, increased histone H3-K27 tri-methylation and decreased H3 acetylation at the promoter IV (Onishchenko et al., 2008). We further found that chronic treatment with the antidepressant fluoxetine (0.08 mg/kg in the drinking water for 21 days) reversed the depression-like behavior, and restored both the expression of BDNF, and hippocampal neurogenesis in MeHg-exposed mice (Onishchenko and Ceccatelli, 2010).

Taken together, our results provide novel evidence to support the idea that developmental exposure to low levels of MeHg may result in long term consequences predisposing to neurodevelopmental disorder and/or neurodegeneration.

3.4. Perfluorinated chemicals (PFCs)

PFCs are a family of substances that are very stable due to the replacement of carbon-bound hydrogen by fluorine atoms (see (Fromme et al., 2009)). They have been used in a wide range of industrial applications based on their lipid- and water-repellent properties. PFCs are key components of firefighting foams, and a source of contamination relevant for human exposure is represented by test ground areas. They are extremely persistent and have substantial bio-accumulating and bio-magnifying properties. The presence of PFCs in a wide variety of arctic biota, far from anthropogenic sources, shows the capacity of PFCs to undergo long-range transport (Butt et al., 2010). The voluntary phase-out of PFCs production by the major producer in the U.S. between 2000 and 2002 has led to a significant reduction in the use of PFCs-related substances. However, they are still produced in some countries and there is evidence that they continue to be used.The main route of exposure to PFCs is believed to be through consumption of contaminated food, such as fish, aquatic invertebrates, marine mammals (Quinete et al., 2009), and other composite food (Zhang et al., 2010), as well as by contaminated drinking water (Quinete et al., 2009). PFCs elimination half-life is estimated to approximately 4–5 years in humans and persistence of these compounds have raised concerns about the potential adverse impact on human health (Olsen et al., 2007). Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are two most common PFCs found in human subjects as well as in various biota and environmental samples.

The developing nervous system gets exposed to PFOS from maternal blood (Apelberg et al., 2007; Jensen and Leffers, 2008) andfrombreast milk (Sundström et al., 2011). In exposed mammals PFOS leaves the bloodstream and enters most tissues in a dose-dependent manner, especially liver, bone marrow, skin and muscle, with the highest levels detected in liver (Bogdanska et al., 2011). Particularly relevant for the purpose of this review are the recent reports on the effects of PFCs on GC signaling system. PFOS and PFOA have been reported to inhibit 11B-HSD1 (the microsomal enzyme responsible for local generation of active glucocorticoids, particularly relevant for fetal lung maturation) with IC50 in the low micromolar range (Ye et al., 2012). In addition, PFOS and PFOA inhibit human 11B-HSD2 with an IC50 in the nanomolar range (Zhao et al., 2011), and PFOS also enhances the transcriptionalactivity of GR upon cortisol binding (Wilson et al., 2016). Therefore, prenatal exposure to PFOS in paticular potentially results in excess GR signaling in the fetus. The mechanisms behind the neurobehavioral effects of PFOS are not fully understood to date, but endocrine disruption may play a critical role.

Developmental toxicity studies on the effects of PFOS in rodents have revealed a reduction of fetal weight, reduced neonatal survival and also impairments in behavioral tests (Johansson et al., 2008; Lau et al., 2004). Neonatal exposure to PFOS or PFOA in mice induces changes in proteins involved in neuronal growth and synaptogenesis in the developing brain (Johansson et al., 2008). PFOS inhibits neurite growth and dramatically suppresses synaptogenesis due to abnormal regulation of calcium in the hippocampus (Liao et al., 2008). PFOS was also found to disturb calcium signaling transduction in the rat CNS after gestational and lactational exposure (Liu et al., 2010a,b).

3.5. Effects of PFOS on neural cells

There are a number of *in vitro* studies on PFOS toxicity. Slotkin and colleagues have reported that PFOS influences differentiation of PC12 cells by promoting differentiation towards acetylcholine phenotype rather than the dopamine phenotype (Slotkin et al., 2008). A recent study has shown that PFOS exposure of human microvascular endothelial cells, which are the major components of the BBB, can trigger the “opening” of tight junctions through the PI3K signaling pathway (Wang et al., 2011). Exposure of Syrian Hamster Embryo cells has revealed the transforming potential of PFOS in parallel with an increased expression of peroxisome proliferator-activated receptor (PPARs) genes (Jacquet et al., 2012).

We have used rat NSCs to investigate the effects of PFOS (Wan Ibrahim et al., 2013) at concentrations similar to those found in human populations (nanomolar range) (Björnberg et al., 2005; Ehresman et al., 2007; Fromme et al., 2007; Guvenius et al., 2003). We assessed the effects of PFOS on the fate of NSCs during spontaneous differentiation by immunocytochemical stainings-for stem cell status (*e.g.* Nestin), as well as markers for early neuronal differentiation (*e.g.* Tuj1), and astroglial and oligodendrocytic lineage differentiation (*e.g.* GFAP and CNPase, respectively). The results show that PFOS promotes NSC neuronal differentiation at both 25 and 50 nM as demonstrated by the increased number of Tuj1-positive cells. Exposure to 50 nM PFOS not only increased the number of differentiated neurons, but also the number of oligodendrocytes (CNPase-positive). Considering the sequential differentiation of NSCs, where neurogenesis precedes gliogenesis (Qian et al., 2000), the increase differentiation in NSCs towards both neuronal and oligodendrocytic cells after exposure to 50 nM PFOS is intriguing. In Tuj1-positive cells, we found that exposure to 50 nM PFOS increased neurite outgrowth by increasing not only the number, but also the maximum distance reached by the neurites of differentiating cells. Similarly, the maximum distance reached by the arborization of CNPase-positive cells was significantly increased by PFOS. Altogether, these data suggest that PFOS promotes the differentiation and maturation of NSCs. To explore this hypothesis we investigated the functional aspects of NSC differentiation by measuring Ca^{2+} oscillations. Spontaneous Ca^{2+} oscillations have been implicated in different vital cell processes such as progression of the cell cycle, regulation of migration and neuronal differentiation (Gomez et al., 1995; Gu and Spitzer, 1995; Komuro and Rakic, 1996; Resende et al., 2010) Spontaneous Ca^{2+} signals have been shown to occur more frequently at early stages of neural precursor differentiation, and become less frequent as the stem cells differentiate into mature neurons (Ciccolini et al., 2003). When we measured spontaneous Ca^{2+} oscillations after 7 days of spontaneous differentiation we found that PFOS decreased the number of cells showing spontaneous Ca2+ activity in agreement with the morphological analysis.

3.6. Developmental exposure to PFOS and long-term behavioral alterations

We investigated the long-lasting effects of developmental exposure to PFOS (0.3 mg/kg/day *via* food throughout pregnancy) in a battery of behavioral tests to evaluate motor function, circadian activity, and emotion-related behaviors (Onishchenko et al., 2011). We found significant effects of PFOS on locomotor activity predominantly in maleoffspring and further investigated the effects of PFOS on circadian activity of mice housed in social groups. All groups of animals displayed higher levels of activity during the dark phase and early morning hours, followed by lower activity levels during the light phase, with no significant difference in total activity counts over light or dark periods between control and PFOS-exposed groups, either in males or females. However, when we analysed the resting time, we found a significant difference in the number of long inactive periods (typically associated with sleeping) in both males and females exposed to PFOS. The increased number of inactive periods and the ensuing fragmentation of spontaneous activity allows for several interpretations. One possibility is that the PFOS-exposed mice develop fatigue faster than controls, and this is partially supported by the modest decrease in performance in the rotarod test. Another possible interpretation is suggested by the similarity with the fragmentation of spontaneous activity described in a mouse model of ADHD (Lange et al., 2012). The latter is supported by findings in zebrafish larvae exposed to PFCs during development (Ulhaq et al., 2013). We addressed this hypothesis and investigated the possible mechanisms by comparing the neurodevelopmental effects of PFOS in zebrafish larvae with the established effects in rodent models. Similar to the rodent model, spontaneous activity appeared fragmented in zebrafish larvae exposed to PFOS, and the effect magnitude increased in a dose-dependent fashion. Interestingly, the larvae exposed to the lower dose (1 mg/L, equivalent to 0.19 μM) did not display alterations in spontaneous activity in baseline conditions, but only during sustained hyperactivity periods induced by short dark periods occurring during the active (light) phase of the dark-light cycle (Visual Motor Response, VMR). Thus, the PFOS-exposed zebrafish larvae did increase the activity during the dark pulse similar to the control larvae, but the activity decayed faster than in controls. This was similar to the behavioral findings in mice exposed to PFOS *in utero*. In contrast, the larvae exposed to the higher dose (10 mg/L, equivalent to 1.86 μM) displayed severe alterations in spontaneous activity, which were characterized by clusters of very intense activity that were separated by prolonged periods of inactivity. Moreover, the acoustic startle response triggered episodes of sustained hyperactivity that typically lasted for about 5 s after stimulation (for comparison, a normal startle response consists of a single bout of activity that is about twice as intense as spontaneous bouts generated without external stimulation, and typically lasts less than 0.1 s). The hyperactive phenotype we observed in zebrafish larvae exposed to the 10 mg/L PFOS – both spontaneous and acoustic startle-induced hyperactivity – was reversed by acute administration of dexamfetamine (Spulber et al., 2014) in a monotonic dose-dependent fashion. Our findings provide evidence for impaired dopaminergic signaling induced by developmental exposure to PFOS and support the association of impulsivity and ADHD with PFOS exposure in children.

Epidemiological studies have suggested an association between PFC exposure in children and ADHD, but the results are controversial. Cross-sectional studies have shown an association between the level of PFCs and ADHD and impulsivity in children aged 9–15 (Gump et al., 2011; Hoffman et al., 2010), but the findings were not confirmed by recent studies with longitudinal design (Liew et al., 2014; Ode et al., 2014; Strøm et al., 2014). However, there are relevant methodological differences among the studies, and the correlations were made with either the levels of PFCs at the time of testing (in the cross-sectional studies), or with the estimated prenatal exposure from maternal blood, or umbilical cord blood at the time of birth (in the longitudinal studies). It is relevant to mention that from all PFCs measured, only PFOS was found to be associated with negative effects on the nervous system.

In summary, our *in vitro* neurodevelopmental studies on PFOS show that exposure to concentrations similar to those found in humans alters the differentiation potential of NSCs resulting in an increased number of neuronal cells as well as oligodendrocytes. Similar changes occurring in the developing brain may lead to impaired plasticity, which has been associated with neurodevelopmental disorders, such as ADHD (see Luoni et al., 2015; Muller et al., 2014). Although experimental data support the epidemiological association between developmental exposure to PFOS and ADHD, more studies are needed for elucidating the mechanisms of neurotoxicity.

4. Conclusions

In summary, a vast literature from animal and human studies supports the knowledge that adverse conditions in uterus,such as stress or toxicants, during sensitive periods of development influences the development of an individual, possibly through permanent alterations in different brain areas. Nevertheless, the understanding of the effects of PS or environmental neurotoxic contaminants on the developing fetus is woefully incomplete yet. It can be speculated that prenatal environmental factors, acting on the mother and/or the foetus alter the different functions of an organ or tissue system to prepare the unborn animal optimally for the environmental conditions *ex-utero* (Del Giudice, 2012). However, in adverse conditions like those induced by gestational stress or by neurotoxicants acting as endocrine disruptors and/or interfering with neurogenesis and differentiation, offspring may display short and long-term consequences that may lead to alterations at different levels resulting in behavioraland molecular abnormalities with increased risk of disease.

Further studies will be needed to determine whether adverse intrauterine events of different nature and origin alone or in combination might pose a serious risk for the development of neurological and psychiatric disorders. The identification of the mechanisms and the initial latent disturbances preceding the later onset of neurodegenerative/neuropsychiatricdisorders is of critical importance to recognize subjects at risk and to develop preventive and early therapeutic strategies.

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