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Individual differences in the effects of prenatal stress exposure in rodents

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ABSTRACT

Exposure to prenatal stress alters the phenotype of the offspring in adulthood. When the prenatal and adult environments do not match, these alterations may induce pathology risk. There are, however, large individual differences in the effects of prenatal stress. While some individuals seem vulnerable, others appear to be relatively resistant to its effects. In this review we discuss potential mechanisms underlying these individual differences with a focus on animal models. Differences between rodent models selected for stress coping traits are discussed. In addition, the role of circulating factors, like glucocorticoids and cytokines, factors involved in brain development and influences of epigenetic and genetic factors in prenatal stress induced phenotype are covered.

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1. Introduction

The acute stress response, characterized by activation of the sympathetic nervous system, the hypothalamus-pituitary-adrenal axis and the immune system, is a physiologically adaptive response that enables the organism to deal with environmental threats. However, when the stress exposure is chronic, prolonged activation of the stress response may become maladaptive and have adverse consequences for the individual. In addition to disorders directly linked to stress exposure, like post traumatic stress disorder, risk of the development of several other disorders such as affective disorders, type 2 diabetes and cardiovascular disease have been associated with stress (reviewed in (de Kloet et al., 2005)).

Chronic stress during adulthood may have adverse consequences, but the effects of stress exposure during gestation or early childhood may have more severe consequences as it may alter brain development and thereby have long-term consequences on adult phenotype. The idea that the early life environment may alter adult phenotype is described in the Developmental Origins of Health and Disease (DOHaD) hypothesis. This hypothesis states that adverse conditions during the early life period may result in persistent changes in physiology and metabolism that in turn alter risk for disease development in adulthood and was first proposed by David Barker (Barker, 1988). Therefore, this hypothesis was initially referred to as the "Barker Hypothesis". This hypothesis was based on the observation that low birth weight was associated with increased risk for coronary heart disease in adulthood (Barker and Osmond, 1986). Over the last decades more data supporting this hypothesis have become available from studies in both humans as well as in animal models.

2. Human evidence

Evidence that this hypothesis may hold true comes from epidemiological studies in individuals who were exposed to adverse environmental conditions, like natural disasters or war, showing increased risk for metabolic, immune and stress-related disorders later in life. For example, children born during or right after the Dutch Hunger Winter were found to be at increased risk for development of psychiatric and metabolic disorders (Brown et al., 1995; Franzek et al., 2008; Hoek et al., 1998). Similar observations were reported in offspring of women pregnant during Chinese famine in 1959–1961 as higher incidence of schizophrenia was reported in these offspring (St Clair et al., 2005). Interestingly, a study in Russia of individuals exposed to a famine during the same period as the Dutch Hunger Winter, found no adverse effects on metabolic disease susceptibility (Stanner et al., 1997). In contrast to the Netherlands where the famine was followed by a period of growth and abundance, the standard of living in Russia remained

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poor throughout adulthood, suggesting that disorders associated with the prenatal environment may occur when the prenatal and postnatal environment do not match. This concept of a mismatch between the early life and adult phenotype resulting in pathology development has been elegantly described by Nederhoff and Schmidt (Nederhof and Schmidt, 2012).

3. Individual differences – susceptibility and resilience

3.1. The animal model

The studies in humans investigating the effects of exposure to stressful events during pregnancy like war, however, are confounded by changes in food availability and variation in the severity of exposure within and between studies. Furthermore, data from a Swedish study indicated that the perceived level of stress may be an important factor was well. During the Chernobyl disaster, the perceived level of stress predicted the offsprings' risk of emotional and cognitive disorders better than the actual experience level of radiation (Kolominsky et al., 1999). In order to understand the underlying mechanism of prenatal stress exposure on the offspring's health, better controlled studies are necessary. Better control of environmental factors can be obtained by using animal models in a laboratory setting. The most common models of prenatal stress either use repeated restraint stress or chronic variable stressors. However, there are some studies that have specifically targeted social stress using a social defeat paradigm.

Exposure to prenatal stress (PNS) has been associated with higher risk of affective disorders in humans (Brown et al., 1995; Watson et al., 1999). Rodent models support this association, as decreased exploration in an elevated plus maze and increased reactivity to novelty was shown in PNS-exposed rats (Vallee et al., 1997), indicative of increased anxiety-like behavior. Additionally, in behavioral tests designed to assess depression-like phenotypes, prenatally-stressed rats display increased immobility, suggesting increased depression-like behavior (Morley-Fletcher et al., 2003, 2004). Furthermore, PNS rats showed decreased social interaction (Lee et al., 2007), however, there were no differences in sucrose intake in this study (Lee et al., 2007). These studies suggest that, at least in males, PNS exposure may predispose towards a depression- and anxiety-like phenotype. In addition to alterations in affective behaviors, PNS also has effects on cognitive functioning and neurodevelopmental disorders. Deficits in spontaneous spatial recognition and working memory performance have been reported (Vallee et al., 1999). Additionally, PNS offspring have been shown to have impaired prepulse-inhibition responses and increased locomotor activity after amphetamine administration, both of these phenotypes have been associated with development of a schizophrenia-like phenotype (Koenig et al., 2005).

There is a large body of literature on the effects of PNS on stress responsivity and hypothalamus-pituitary-adrenal (HPA)-axis functioning. Exposure to prenatal stress has been shown to alter corticosterone levels throughout the circadian cycle; in adult male rats increased corticosterone levels have been found at the end of the light phase, a time period where typically the highest corticosterone levels are observed (Koehl et al., 1999). Consistent with heightened corticosterone levels, hypertrophy of the adrenals has been reported (Lemaire et al., 2000). Furthermore, several studies showed increased glucocorticoid levels and associated decreased negative feedback of the HPA-axis after acute stress (Koehl et al., 1999; Henry et al., 1994; Barbazanges et al., 1996; Maccari et al., 1995). At the level of the brain, alterations in the glucocorticoid system have been shown; the binding capacity of both the mineralocorticoid receptor and the glucocorticoid receptor were decreased in PNS offspring (Koehl et al., 1999; Maccari et al., 1995).

In addition to effects on stress-related traits, prenatal stress has also been reported to affect the metabolic phenotype of the offspring. Lesage and colleagues showed that chronic restraint stress during the last week of pregnancy induced hyperphagia and impaired glucose tolerance in adult male offspring (Lesage et al., 2004). Similar to the human studies, PNS offspring had lower birth weights than control, which may have contributed to their metabolic phenotype later in life. Metabolic syndrome-predisposing effects of PNS in rats were confirmed in a study that used a variable stress paradigm during the last week of pregnancy and in this study differences in birth weight were not found. Tamashiro and colleagues showed that offspring of prenatally stressed dams were also impaired in an oral glucose tolerance test. However, these differences were only apparent in PNS rats that were weaned onto a high fat diet (Tamashiro et al., 2009). Stress exposure earlier during pregnancy seems to have some contrasting effects, offspring of mice exposed to stress during the first week of pregnancy were shown to gain less weight on a high fat diet, whereas they were hyperphagic on a standard chow diet (Pankevich et al., 2009). This suggests that the timing of the stress is an important variable in the metabolic risk associated with prenatal stress exposure.

3.2. Individual variation in the phenotype

Although a clear effect of PNS on the phenotype is shown in most experiments, large variation is observed among individuals within a study, suggesting that there might be vulnerable and resistant individuals within PNS populations. These individual differences have become apparent in rodent models selectively bred for specific traits. The Lewis and Fischer 344 rats are rodents with heightened (Fischer 344) or attenuated (Lewis) HPA-axis reactivity, and have been shown to differ in a wide range of HPA-axis-related behavioral and physiological traits (Sternberg et al., 1992). Stohr and colleagues showed that PNS had differential effects in the Lewis and Fischer 344 rats. In Lewis rats, PNS improved acquisition of active avoidance, decreased immobility in the forced swim test, and reduced novelty-induced locomotion, whereas in Fischer 344 rats PNS had no effect in the active avoidance or forced swim test, and increased novelty-induced locomotion (Stohr et al., 1998). Studies in rats selectively bred for High and Low anxiety traits suggest that PNS has opposite effects in anxious versus non-anxious rats. Rats bred for high anxiety traits became less anxious after PNS, whereas rats bred for low anxiety traits became more anxious (Bosch et al., 2006). In a similar fashion, rats selectively bred for low novelty seeking behavior were reported to show less anxiety than their controls, whereas those rats selectively bred for high novelty seeking behavior were not affected by PNS (Clinton et al., 2008). Taken together these studies suggest that PNS may have opposite effects dependent on the genetic background of the individual.

In addition to the differences in anxiety traits or HPA-axis responsivity, the way a stressor is perceived may play an important role in effects of PNS. The stress-coping style of an individual determines the behavioral and physiological response of an organism to stress. Two clear stress-coping phenotypes can be distinguished, the proactive and passive stress-coping styles. Behaviorally, proactive stress-copers are characterized by active responses to stressors; they will attempt to modulate the environment to reduce the stress (Koolhaas et al., 1999). This proactive stress response is illustrated in rodents during a defensive burying test. In this test proactively coping rats will bury an electrified prod that is placed in their cage with saw dust in order to avoid a shock. In contrast, passive stress-copers respond to stress in a more inhibited manner. In the defensive burying test, passive rodents

will sit as far away from the prod as possible to avoid being shocked (de Boer and Koolhaas, 2003). These stress-coping phenotypes are highly correlated with other behavioral responses. Proactive stress-coping individuals tend to show more aggression and impulsivity and are less behaviorally flexible than passive stress-copers (Coppens et al., 2010). Physiologically, the stress response of proactive stress-copers includes greater activation of the sympathetic nervous system and little activation of the HPA axis. In contrast, stress response of passive stress-copers is characterized by a large contribution of the HPA-axis and relatively little activation of the sympathetic nervous system (Koolhaas et al., 2011). Previous studies reported that rats differing in stress-coping style also differed in their susceptibility for anxiety- and depression-like behavioral phenotypes, as well as in their metabolic phenotypes. Typically, rats characterized by passive stress-coping styles display higher levels of anxiety- and depression-like behavior (Koolhaas et al., 1999). Additionally, passively coping rats derived from either selective breeding or wild rat colonies were prone to weight gain and hyperinsulinemia when fed a high fat diet compared to proactive rats (Boersma et al., 2011, 2010, 2009).

In our recent studies, we found that PNS may modulate the stress-coping phenotype of the offspring. We showed that the distribution of the stress-coping behavior, expressed as the percentage time spent burying during the defensive burying test, was altered within the PNS rat population (Boersma et al., 2014a). In contrast to the control population, where about 16% of the rats were characterized as intermediate, there were no rats showing an intermediate stress-coping phenotype within the PNS offspring population (Fig. 1A). Additionally, among those rats characterized as proactive coping, PNS rats spent more time burying that the control rats (Fig. 1B). Because the defensive burying behavior is set up to measure proactive stress-coping behavior, it is difficult to conclude whether PNS also altered passive stress coping behavior. It is possible that if a behavioral test targeted towards passive stress-coping behavior is used, a similar shift in phenotype will be observed. Overall, the data presented in Fig. 1 suggest that PNS may result in a more distinct expression of an individual's stress-coping phenotype.

Consistent with the studies in rats selected for stress-coping style, we found that passive coping PNS offspring gained more body weight, were hyperleptinemic and had impaired glucose tolerance compared to proactive coping PNS offspring after being fed a high fat diet for three weeks in adulthood (Boersma et al., 2014a). No differentiation in the metabolic phenotype was observed between passive and proactive rats derived from unstressed control dams thus, in this case, the metabolic phenotype is not solely dependent on the stress-coping style (Boersma et al., 2014a). It seems that PNS modulates the stress-coping style, inducing a more extreme phenotype, and that this in turn results in the increased body weight and glucose impairment observed in the passive coping PNS offspring. This hypothesis is consistent with the observation that the percentage time spent immobile during the defensive burying test, a proxy for the degree of passive coping, correlates positively with the area under the curve for insulin in an oral glucose tolerance test (Fig. 2A) and with plasma leptin levels (Fig. 2B).

These data suggest that susceptibility to metabolic disorders may indeed be mediated by the presence or absence of a match between prenatal and postnatal environments. When the postnatal environment matches the prenatal environment, adaptations to the phenotype of the offspring to match the prenatal environmental conditions are beneficial. However, when the postnatal environment is mismatched compared to the prenatal environment these adaptation may become maladaptive, and lead to pathology development. Like in the case of passively-coping PNS rats where adaptations to reserve energy in preparation for stressful environmental conditions lead to increased risk to obesity and insulin resistance when the rats are postnatally exposed to conditions of energy abundance.

4. Potential mechanisms underlying the PNS phenotype

4.1. Hormones

4.1.1. Glucocorticoids

Increased maternal glucocorticoid levels have been suggested to be causal to the prenatal stress phenotype. In mice, for example, chronic stress exposure during pregnancy increases levels of circulating glucocorticoids in the dam and in the amniotic fluid (Abdul Aziz et al., 2012; Misdrahi et al., 2005). Data derived from studies using exogenous glucocorticoid administration during gestation, show that heightened maternal glucocorticoids may indeed induce alterations in HPA-axis functioning in offspring similar to those observed in PNS rats (reviewed in (Drake et al., 2007)). Furthermore, offspring of dams treated with dexamethasone, a synthetic glucocorticoid, during pregnancy had increased

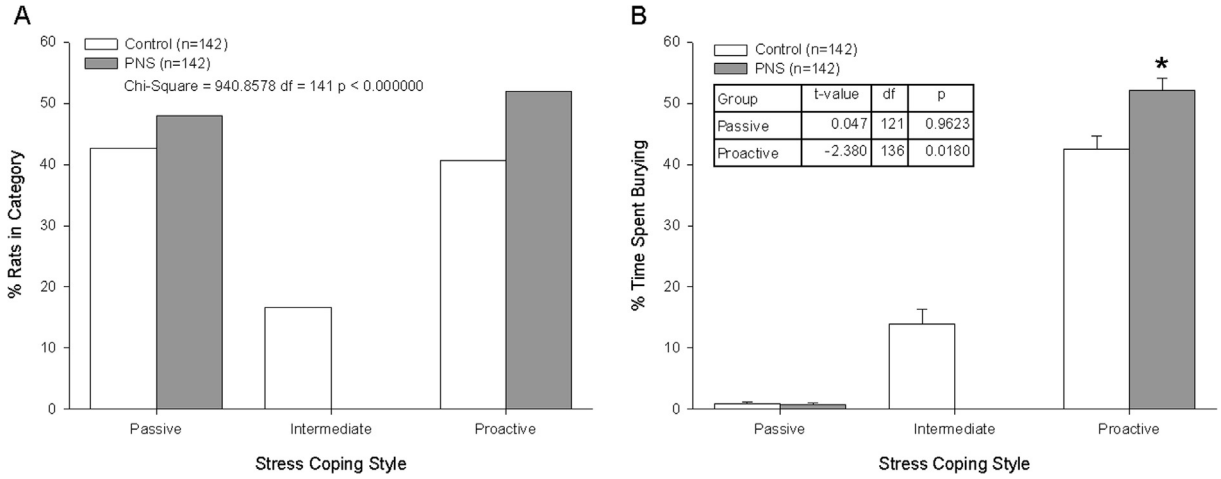

Fig. 1. Stress coping behavior in the control and prenatal stress population. A: Distribution of stress coping style within the control and prenatal stress. Passive = less than 10% time spent burring, Intermediate = between 10 and 20 % time spent burying, proactive = more than 20% time spent burying. B: Time spent burying during a defensive burying test within each stress coping style. * indicates a significant difference between the control and PNS groups.

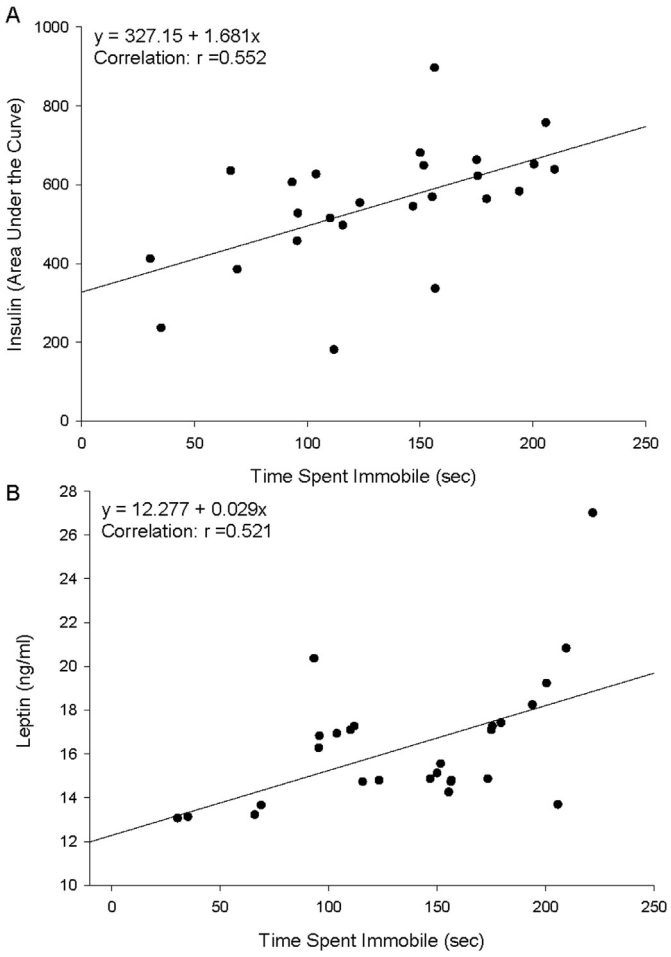

Fig. 2. Correlations with "immobility" behavior during a defensive burying test after 3 weeks of HFD in control and PNS offspring. A: Correlation between Immobility and the area under the Insulin response curve during an oral glucose tolerance test (2 mg/kg Glucose). B: Correlation between Immobility and leptin levels after 3 weeks of HFD exposure. Data extrapolated from (Boersma et al., 2014a).

weight gain on a high fat diet and impaired insulin signaling (O'Brien et al., 2008), suggesting that glucocorticoid exposure during pregnancy may indeed induce increased risk to metabolic disruptions in PNS offspring.

Heightened glucocorticoid exposure in the fetal brain, could affect brain development through several glucocorticoid response elements found on genes important for brain development (Polman et al., 2013). PNS is associated with increased corticotrophin-releasing hormone (CRH or *Crh*) in the paraventricular nucleus and central nucleus of the amygdala (Welberg et al., 2005). Data on the glucocorticoid (GR or *Nr3c1*) and mineralocorticoid (MR or *Nr3c2*) receptors indicate decreased maximal binding capacity of both GR and MR in the hippocampus (Koehl et al., 1999; Henry et al., 1994; Maccari et al., 1995). Additionally, prenatal dexamethasone treatment increases *Nr3c1* expression in liver and adipose tissue, and this has been associated with increased phosphoenolpyruvate carboxykinase (PEPCK or *Pck1*) expression in liver, important for the regulation of gluconeogenesis (Nyirenda et al., 1998). PNS may not only alter glucocorticoid levels through GR and MR directly, but may also influence sensitivity of these receptors. Prenatal stress has been shown to reduce negative feedback of the GR in the offspring leading to higher circulating levels of corticosterone (Weinstock, 1997). The sensitivity of the GR is dependent on the formation of a GR heterocomplex that facilitates transcription. FK506 binding protein 5 (FKBP5 or *Fkbp5*), is a part of this heterocomplex and is known to mediate GR sensitivity. When bound to the steroid receptor, FKBP5 decreases its affinity for the ligand and prevents translocation to the nucleus, and studies suggest that *Fkbp5* expression may be sensitive to early life environmental factors (Binder et al., 2008). Future studies on the effects of prenatal stress on the functioning of FKBP5 and other genes regulating GR signaling are needed to elucidate the role of glucocorticoid signaling on the PNS-induced phenotype.

Dexamethasone is a glucocorticoid analog and may be transported across the placenta more readily than corticosterone which is broken down by 11-beta-hydroxysteroid dehydrogenase 2 (11β-HSD2 or *Hsd11b2*) that is highly expressed in the placenta (Edwards et al., 1996). Therefore, the concentrations of glucocorticoids that dexamethasone-treated offspring are exposed to *in utero* may be several-fold higher than the *in utero* glucocorticoid exposure in PNS rats. Differences between prenatal dexamethasone treatment and prenatal stress were further studied by Franko and colleagues who compared glucose tolerance in offspring of dexamethasone-treated dams, undisturbed control dams and mildly stressed dams (daily saline injections) on a standard chow diet. Their data suggest that on the standard diet, female offspring of dexamethasone treated dams showed hyperglycemia during an intraperitoneal glucose tolerance test, whereas no effect of mild prenatal stress was observed (Franko et al., 2010). This may suggest intrauterine exposure to glucocorticoids does impair glucose tolerance in female rat offspring, and that the maternal levels of glucocorticoids may be an important parameter to take into account.

4.1.2. Sympathetic activation

The role of maternal sympathetic activation during stress on the offspring phenotype has been less studied. Increased sympathetic activation in the pregnant dam may alter several physiological parameters that might affect the fetus. For example, sympathetic activation may increase maternal heart rate and blood pressure, which in turn may influence the blood flow to the placenta (Erkinaro et al., 2009). Furthermore, the uterus contains alpha-adrenergic receptors, and stimulation of these receptors has been shown to increase both uterine blood flow and uterine contractility (Sato et al., 1996). To what extent these effects also occur during pregnancy and how this may affect the fetus' development remains to be assessed. In addition to alterations in blood flow, stress-induced activation of the sympathetic nervous system leads to the release of epinephrine and norepinephrine. In pregnant rats lower epinephrine levels are reported during stress compared to non-pregnant females, suggestive of reduced stress responsivity during this period (Douglas et al., 2005). An increase in norepinephrine levels is observed in pregnant rats in response to stress, although the response is dampened. Therefore, increased maternal norepinerphine may play a role in the PNS phenotype. This hypothesis is strengthened by the observations in the offspring of dams treated with propranolol, a beta-adrenoreceptor antagonist, showing up-regulation of fetal beta 1-adrenoceptors, and increases in norepinephrine activity in adulthood (Erdtsieck-Ernste et al., 1993). To what extent antagonism of the beta-adrenergic receptor also alters the behavioral phenotype of the offspring remains to be studied. Apart from direct effects on the offspring, sympathetic activation may affect the offspring's phenotype by altering glucocorticoid transport across the placenta. A study in human cell culture suggests that heightened norepinephrine decreased expression of *Hsd11b2* (Sarkar et al., 2001).

4.1.3. Cytokines

Another pathway through which maternal stress could impact the development of the offspring is altered immune system

activity. In general, stress exposure leads to increased immune activation and subsequent higher levels of pro-inflammatory cytokines in the dams. In humans, immune activation during pregnancy, such as viral infection during pregnancy, has been associated with heightened risk for neuropsychiatric disorders like schizophrenia and autism (Brown and Derkits, 2010; Chess, 1977; Wilkerson et al., 2002). However, the immune response induced by infection may be different from the response induced by stress. A study in mice showed that increases in interleukin-6 and interleukin-8 during pregnancy predicted higher maternal weight which is associated with an increased metabolic risk for the offspring, however, no significant correlations were found between maternal cytokine levels and fetal adiposity. This study did not assess if the maternal cytokine levels during pregnancy predict the metabolic phenotype of the offspring in adulthood (Farah et al., 2012). Overall, the data on the effects of maternal immune activation due to stress on the offspring phenotype is limited. In future studies a thorough investigation of the cytokine levels in both dam and fetus may advance our knowledge on the underlying mechanisms.

4.2. Brain development

PNS has been shown to alter the development of the amygdala, prefrontal cortex and hippocampus (Coe et al., 2003; Fujioka et al., 2006; Kawamura et al., 2006; Kraszpulski et al., 2006). In summary, prenatal stress was shown to decrease neurogenesis (Coe et al., 2003; Fujioka et al., 2006), neuronal arborization (Kraszpulski et al., 2006),neuronal density (Kawamura et al., 2006) these brain areas. Furthermore, dendritic architecture was shown to be altered in PNS rats (Jia et al., 2010). Finally, PNS exposure resulted in decreased neuronal connectivity (Goelman et al., 2014).

In addition to amygdala, prefrontal cortex and hippocampal development, it may be that exposure to prenatal stress induces changes in development of the hypothalamus. Changes in hypothalamic development might play an important role in the metabolic characteristics of PNS offspring. Influences of the prenatal environment on the development of the hypothalamus were indicated in studies investigating the effects of prenatal high fat diet exposure. Perinatal high fat diet exposure was shown to alter the development of hypothalamic leptin and insulin signaling (reviewed in (Coupe and Bouret, 2013)). Our studies showed that adult offspring of PNS rats had decrease expression of neuropeptide-Y and agouti-related peptide, and increased expression of proopiomelanocortin in the arcuate nucleus of the hypothalamus, but these increases correlated with the increased adiposity and leptin in these animals, making it hard to distinguish cause and consequence (Boersma et al., 2014a). Neuronal development of the hypothalamus takes place primarily during the early postnatal period (Coupe and Bouret, 2013), therefore direct effects of PNS on the development of this brain area is unllikely. In studies investigating the effects of prenatal diet, it has been shown that leptin levels and signaling *were* altered in offspring from high fat diet fed dams (Sun et al., 2012). During development leptin acts as a trophic factor, which in turn may alter neuronal development (reviewed in (Sun et al., 2012; Bouret, 2009)). Whether PNS also alters the development of the leptin signaling pathways remains to be determined. While circulating leptin levels were not different between control and PNS offspring (Tamashiro et al., 2009) in this study, other hormones related to energy homeostasis, such as insulin, ghrelin and amylin have critical roles during development and may have been altered by PNS and have had significant influences on brain maturation. Future studies into neuronal development of feeding related brain areas are needed to investigate this.

4.2.1. Brain derived neurotrophic factor

PNS may alter development of brain areas involved in emotion and reward through alterations in expression of trophic factors such as brain derived neurotropic factor (BDNF or *Bdnf*). PNS was shown to decrease expression of *Bdnf* in hippocampus (Neeley et al., 2011) and amygdala (Boersma et al., 2014b). With its important role in neuronal development, a decrease in *Bdnf* may have consequences for the development of a wide variety of neuronal pathways (reviewed in (Park and Poo, 2013)) and thereby it may affect the phenotype of the PNS offspring. Neeley and colleagues showed that the effects of PNS on *Bdnf* expression in the hippocampus are strain dependent. They showed that baseline *Bdnf* expression was increased in PNS offspring of the Sprague Dawley and Lewis rat strains, but that PNS did not affect baseline *Bdnf* expression in the Fischer 344 strain (Neeley et al., 2011). As mentioned previously, the Lewis and Fischer strains were differentially *affected* by PNS: PNS Lewis rats showed alterations in depression-like behaviors, whereas the Fischer 344 strain seems relatively unaffected by PNS (Stohr et al., 1998). Overall these data suggest that *Bdnf* may affect neuronal development and the subsequent phenotype of the PNS rat. Additionally these data suggest that these effects may be dependent on the innate vulnerability of the individual.

4.2.2. Serotonin

With its role in brain development during the perinatal period, serotonin (5-HT) may be another neurotransmitter playing an important role in the PNS phenotype. During early development serotonin acts as a trophic factor stimulating cell differentiation, migration, myelination and dendritic pruning (reviewed in (Gaspar et al., 2003)). Maternal stress has been shown to increase 5-HT turnover in the dam, and to increase fetal brain levels of tryptophan, 5-HT and 5-hydroxyindoleacetic (Peters, 1990). These changes in fetal serotonin level may in turn affect brain development. Furthermore, prenatal stress has been shown to alter serotonin receptor binding in rat offspring. In the cerebral cortex the number of serotonin 2C receptor binding sites was increased after PNS exposure (Peters, 1988). Furthermore, in the ventral hippocampus PNS was shown to decrease serotonin 1A receptor binding (Van den Hove et al., 2006). A recent study in mice may suggest that the effects of PNS on the 5-HT system may be dependent on the individual's response to prenatal stress. In prenatally stressed mice that did not show PNS-induced alterations in stress responsivity, tryptophan hydroxylase (a 5-HT synthesizing enzyme) levels were increased, whereas in PNS mice with impaired stress responsivity tryptophan hydroxylase level were decreased (Miyagawa et al., 2014). Furthermore, the effects of PNS were shown to differentially affect the phenotype of mice serotonin transporter knockout mice and their control litter mates, suggesting a modulatory role of the serotonin system on the PNS phenotype (van den Hove et al., 2011). It is of interest to note here, that rodents genetically selected for their stress-coping style, were shown to differ in their serotonin regulation during stress (Veenema et al., 2004), suggesting that serotonin may also underlie the differential response to PNS between passive and proactive stress copers. Overall these data imply that serotonin may play an important role in the neurodevelopmental phenotype of PNS-exposed individuals, and that serotonin may, in part, explain some of the individual differences seen in the PNS phenotype.

4.2.3. Glucocorticoids

We previously discussed a role for glucocorticoids in the PNS phenotype. In addition to the previously mentioned mechanism, glucocorticoids may alter neuronal development and thereby induce the PNS phenotype. Cortisol administration during

pregnancy was shown to inhibit fetal brain growth in sheep (Huang et al., 1999). In humans it was shown that glucocorticoid treatment reduced cortical folding and brain surface area (Modi et al., 2001). In a mouse model, prenatal dexamethasone treatment was shown to decrease neuronal cell proliferation in the hippocampus in the offspring (Noorlander et al., 2008). Offspring of dexamethasone-treated pregnant rats have a reduction in cell volumes and cell numbers in the nucleus accumbens (Leao et al., 2007). In addition to dexamethasone treatment during pregnancy, PNS rats were show to have reduced amygdala volume and decreased numbers of both neurons and glia compared with controls (Kawamura et al., 2006). Taken together these data clearly indicate that glucocorticoid exposure during PNS may alter neuronal development, which in turn may mediate the adult PNS phenotype.

The discussed mechanisms indicate that during prenatal stress signals from the dam, like heightened glucocorticoid levels, heightened sympathetic activation, may inform the fetus about the external environmental conditions leading to alterations to neuronal development. Although the placenta may buffer some of these signals, one may argue that the buffering function of the placenta may serve to distinguish between short term and moderate environmental disturbances from long term, more severe environmental disturbances. Again, these adaptations may be beneficial under matching prenatal and postnatal environments, however, when a mismatch occurs this may lead to pathology.

4.3. Epigenetic factors

Epigenetics refers to chemical modifications to the DNA that result in alterations in gene expression without changing the DNA sequence itself. Epigenetic alterations can occur through different mechanisms such as DNA methylation, histone modification and non-coding RNAs (reviewed in (Berger et al., 2009)).

Effects of exposure to early life stress (via reduced maternal licking and grooming during the neonatal period) on glucocorticoid receptor (GR, *Nr3c1*) DNA methylation has been reported (Weaver et al., 2004). Rats reared by low licking and grooming dams had a higher percentage of DNA methylation of the exon 1_7 of the GR promoter and had associated lower nr3c1 expression in the hippocampus (Weaver et al., 2004). Decreased hippocampal GR may result in decreased negative feedback through GR leading to a prolonged elevation of corticosterone after stress. Mice exposed to PNS (via variable stress) during the first week of gestation were shown to have increased DNA methylation of the GR promoter region in the hypothalamus (Mueller and Bale, 2008). To date, similar effects on the GR DNA methylation in the offspring of dams stressed during the last week of gestation have not been reported.

In the previous paragraphs we introduced FKBP5 as a potential modulator of GR signaling in the PNS model. To date no direct evidence has been presented that PNS alters DNA methylation of the FKBP5 gene. However a study in mice suggested that FKBP5 DNA methylation was decreased in mice treated with corticosterone (Lee et al., 2011). This suggests that the FKBP5 gene is susceptible to epigenetic alterations induced by glucocorticoids. Further research is needed to elucidate whether PNS exposure alters the epigenetic profile of this gene.

Corticotrophin releasing hormone (*CRH*) is another gene that may be epigenetically altered during PNS exposure. Early life stress, in the form of maternal deprivation was shown to decrease DNA methylation of the CRH promoter (Chen et al., 2012). Additionally, in adult mice it was shown that stress responsivity in adulthood was correlated with methylation of the CRH promoter (Elliott et al., 2010). The effects of PNS exposure on CRH DNA methylation remains to be studied.

Another candidate gene through which epigenetic mechanisms may affect the PNS associated phenotype is BDNF. Roth and colleagues showed that early postnatal stress increased DNA methylation of BDNF exon IV (Roth et al., 2011). We recently showed that prenatal stress also increased DNA methylation of both exons IV and VI of the BDNF gene (Boersma et al., 2014b), implying that the decrease in expression of *Bdnf* in PNS offspring may be mediated by increased DNA methylation. The expression of the coding *Bdnf* exon IX has an inverted U-shape developmental pattern with peak levels between postnatal day P14 through P21, suggesting that this might be the critical period for BDNF action (Das et al., 2001). Following this peak, *Bdnf* exon IX expression levels decrease until P28 and then *Bdnf exon IX expression* levels remain stable through adulthood. Alterations in specific *Bdnf* exon expression may be important for neuronal development since the different *Bdnf* exons show different temporal expression patterns through development. Interestingly, the postnatal surge in BDNF protein seems to coincide with an increase in *Bdnf* exon IV expression suggesting that this exon might be important for BDNF levels during this period. Developmental patterns of expression of the specific *Bdnf* exons in response to PNS in brain regions important for stress related behaviors have not been studied. Therefore the roles of specific *Bdnf* exons in the neuronal development of those specific brain regions after PNS exposure needs further study.

4.4. Trans-generational effects

In addition to having direct effects on the exposed offspring, prenatal stress exposure may also have effects on subsequent generations. Although the mechanism by which epigenetic modifications are transmitted to the next generation is not fully understood, more evidence has arisen indicating that, at least for some imprinted genes, epigenetic profiles can be maintained or reprogrammed in the progeny (Borgel et al., 2010). In mice, it was shown that the effects of early postnatal maternal separation on social and depression-like behaviors were transmitted to both the F2 and F3 generations (Franklin et al., 2010, 2011; Weiss et al., 2011). Roth and colleagues showed that alterations in *Bdnf* gene expression and DNA methylation in the prefrontal cortex associated with reduced maternal care were found in both the F1 and F2 generations concurrent with altered maternal behavior in daughters (F1) and granddaughters (F2). Thus, epigenetic signatures and associated behaviors may be transmitted over multiple generations (Roth et al., 2009). Some evidence that prenatal stress exposure may also have trans-generational effects comes from a study by Morgan and colleagues, who showed that maternal stress during the first week of pregnancy induced dysmasculination in the F2 generation (Morgan and Bale, 2011). In addition, in Sprague Dawley rats antepartum maternal behavior, which was decreased as a result of PNS, was decreased in the granddaughters of the prenatally stress rats as well (Ward et al., 2013). In guinea pigs trans-generational effects on the HPA-axis function of PNS were shown; F2 offspring of PNS guinea pigs were shown to have higher fecal cortisol metabolites than F2 control offspring (Schopper et al., 2012). Overall these studies suggest that prenatal stress may not only affect the exposed offspring, but may alter the phenotype of the following generations. This, in turn, suggests that prenatal stress may affect the disease risk in multiple generations. More research is needed to understand the mechanism underlying these trans-generational effects.

From a gene-environment mismatch theory perspective these trans-generational effects pose an interesting question. It seems that exposure to standard environmental conditions do not normalize the now mal-adaptive alterations in the F1 or F2 offspring. From an evolutionary standpoint, one may argue the

absence of an environmental stressor in the current generation that was present in the previous generations may indicate variable environmental conditions, and since most of these mis-match pathologies develop after reproductive age, and thus will not diminish the population fitness, reversal of the phenotype has no priority. However, the "original" phenotype has to have some fitness advances otherwise this phenotype would have been lost during evolution. Thus one may wonder which environmental cues would lead to "normalization" of the phenotype, and whether we can mimic these environmental cues as a preventative strategy.

5. Final thoughts

Prenatal stress exposure alters the phenotype of the offspring, and when the postnatal environment does not match the prenatal environmental conditions these alterations may have pathological consequences. The studies discussed in this manuscript clearly indicate that there are some innate differences in stress vulnerability, like the stress-coping style, that may impact an individuals' risk of developing metabolic and other pathologies. Furthermore, this innate risk seems to be modulated by the prenatal environment, dependent on the genotype of the fetus, prenatal stress exposure may have adverse or protective properties. Additionally, to make risk prediction even more complex, the postnatal environment also interacts with both the genotype, and the prenatal environment. Using the stress-coping style model as an example, rats genetically selected for a passive stress-coping style have an increased risk to develop obesity. Exposure to prenatal stress in unselected rats induces a more extreme stress-coping style compared to those not exposed to prenatal stress and therefore increases obesity risk. However, this obesity phenotype in the passively coping rat only becomes apparent when the animals are exposed to a high fat diet. One may reason here that having a more extreme stress coping style is advantageous under threatening environmental conditions, and having a stressed mother may indicate future environmental conditions that the developing fetus must prepare for. Additionally, under these predicted stressful environmental conditions, energy conservation will be adaptive. However, when the animal is postnatally exposed to energy rich environments, like high fat diet access; this adaptive strategy backfires and places the animal at risk for obesity. In this case there is a mismatch between the prenatal environment and the postnatal environment leading to pathology. Since these adaptations seem to be mediated by epigenetic processes ongoing during development, some of the effects may be irreversible. However, understanding these neuromolecular adaptations may present us with new targets to develop pharmacological interventions. Furthermore, understanding the mismatch of environments may inform us about environmental interventions, like environmental enrichment, that can be targeted towards both the phenotype and the early life environmental conditions of the individual.

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