Neuropsychopharmacology REVIEWS (2016) 41, 207–218

The Placenta as a Mediator of Stress Effects on Neurodevelopmental Reprogramming

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Adversity experienced during gestation is a predictor of lifetime neuropsychiatric disease susceptibility. Specifically, maternal stress during pregnancy predisposes offspring to sex-biased neurodevelopmental disorders, including schizophrenia, attention deficit/hyperactivity disorder, and autism spectrum disorders. Animal models have demonstrated disease-relevant endophenotypes in prenatally stressed offspring and have provided unique insight into potential programmatic mechanisms. The placenta has a critical role in the deleterious and sex-specific effects of maternal stress and other fetal exposures on the developing brain. Stress-induced perturbations of the maternal milieu are conveyed to the embryo via the placenta, the maternal–fetal intermediary responsible for maintaining intrauterine homeostasis. Disruption of vital placental functions can have a significant impact on fetal development, including the brain, outcomes that are largely sex-specific. Here we review the novel involvement of the placenta in the transmission of the maternal adverse environment and effects on the developing brain.
Neuropsychopharmacology Reviews (2016) **41,** 207–218; doi:10.1038/npp.2015.231; published online 26 August 2015

INTRODUCTION

Prenatal adversity is a risk factor for lifetime neuropsychiatric disease susceptibility. During gestation, rapid growth and plasticity render the brain sensitive to the effects of environmental factors that can confer adaptive advantages or lasting vulnerability. As the fetal origins of disease hypothesis was pioneered four decades ago by Barker (1997) and Dörner (1973), substantial advances have been achieved in understanding the neurodevelopmental consequences of intrauterine challenges, including maternal psychosocial stress, infection, and metabolic dysfunction (Bock *et al*, 2014, 2015; Brown and Derkits, 2010; Markham and Koenig, 2011; Weinstock, 2008). Maternal stress during pregnancy, in particular, has been identified in autism spectrum disorders (ASDs), attention deficit/hyperactivity disorder (ADHD), and schizophrenia risk (Beversdorf *et al*, 2005; Khashan *et al*, 2008; Kinney *et al*, 2008a; Li *et al*, 2010; Ronald *et al*, 2010). These neurodevelopmental disorders exhibit a strong sex bias, where boys are more likely to develop ASD, ADHD, and earlier-onset schizophrenia (Baio, 2012; Bloom *et al*, 2011; Froehlich *et al*, 2007; Zhang *et al*, 2012). Consistent with the male predominance of these disorders, recent epidemiological and preclinical studies suggest that males are uniquely vulnerable to prenatal adversity (Clifton, 2010; Davis and Pfaff, 2014). Although studies have revealed sex-specific changes in the developing brain (Bale, 2011; Kapoor and Matthews, 2005, 2008; Kapoor *et al*, 2009; Weinstock, 2011), the specific mechanisms by which perturbations in the maternal environment promote sex-biased fetal reprogramming remain unclear.

The programmatic effects of prenatal stress likely involve a complex interaction between the fetal genetic background, sex, and gestational age at the time of exposure (Bale, 2011). As the placenta resides at the interface between mother and fetus, it is uniquely positioned to modulate interactions within an adverse intrauterine environment. The placenta actively maintains intrauterine homeostasis through vital functions including exchange of nutrients, oxygen, and waste, immunoprotection of the semi-allogenic fetus, buffering from deleterious maternal factors, and secretion of hormones and growth factors into both maternal and fetal compartments (Jansson and Powell, 2007). Impairment of placental organogenesis and function can broadly have an impact on fetal development, conferring lasting effects on the brain (Myatt, 2006). The placenta comprises specialized cells derived from the embryo and thereby expresses the fetal genetic sex (Rossant and Cross, 2001). In uncomplicated pregnancies, sex differences in placental size and gene expression are present throughout gestation (Buckberry *et al*, 2014; Gabory *et al*, 2013; Mao *et al*, 2010; O'Connell *et al*, 2013; Sood *et al*, 2006). Such basal placental sex differences likely facilitate sex-specific responses to both

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Received 29 April 2015; revised 10 July 2015; accepted 30 July 2015; accepted article preview online 7 August 2015

normal and pathologic environments. Supporting this, sex differences in placental inflammatory responses, vascular remodeling, and placental size and efficiency have been reported in human pregnancies complicated by asthma, preeclampsia, and malnutrition (Clifton, 2010; Gabory *et al*, 2013). Such complications are also associated with altered neurodevelopment (Bale *et al*, 2010; Walker *et al*, 2015). In addition, prospective studies have found abnormal placental histology associated with an autism diagnosis (Anderson *et al*, 2007; Walker *et al*, 2013). Together, these data support the importance of the placenta, and changes in this tissue in response to perturbations across gestation, in the etiology of neurodevelopmental disorders.

In this review we will discuss the programmatic role of the placenta in the transmission of maternal adversity to the developing brain. We will broadly review the effects of maternal stress on offspring neurodevelopment and long-term changes in stress responsivity and behavior, discussing the placenta as a key orchestrator of this sex-specific programming.

LONG-TERM IMPACT OF MATERNAL STRESS

Prenatal Stress and Neuropsychiatric Vulnerability

Epidemiological evidence implicates maternal stress during pregnancy as a factor in poor offspring neuropsychiatric outcome across the lifespan. Children prenatally exposed to maternal stressors such as anxiety, depression, bereavement, and natural or manmade disasters are more likely to present with neurodevelopmental disorders and subclinical psychosocial problems (Beversdorf *et al*, 2005; King and Laplante, 2005; Kinney *et al*, 2008a, 2008b; Li *et al*, 2010; Rodriguez and Bohlin, 2005). For example, a higher prevalence of autism was associated with *in utero* exposure to severe tropical storms and ADHD risk was significantly increased following prenatal maternal bereavement (Kinney *et al*, 2008a; Li *et al*, 2010). In addition, children whose mothers experienced high stress levels during the 1998 Quebec Ice Storm exhibited reduced cognitive and language abilities and increased autistic-like traits (Laplante *et al*, 2008; Walder *et al*, 2014). Studies suggest susceptibility is greatest in the first half of gestation, a period of development where males and females appear differentially affected (Gerardin *et al*, 2011; Huttunen and Niskanen, 1978; Khashan *et al*, 2008; van Os and Selten, 1998; Walder *et al*, 2014). Although males present more frequently with childhood behavioral disorders and intellectual impairment associated with prenatal stress, females acquire more subtle later-onset anxiety and affective disorders (Davis and Pfaff, 2014). Such studies predict important sex differences in underlying mechanisms originating early in gestation.

Animal models of prenatal stress have demonstrated disease-relevant endophenotypes that recapitulate aspects of these clinical findings. In nonhuman primates, chronic maternal stress leads to deficits in attention, object permanence, and motor function in offspring, in particular when the stress was experienced early in gestation (Schneider and Coe, 1993; Schneider, 1992; Schneider *et al*, 1999). In rodent models, prenatal stress induces hypothalamic–pituitary–adrenal (HPA) stress axis dysregulation, heightened behavioral stress reactivity, depression-like behaviors, and cognitive deficits (Bock *et al*, 2015; Brunton and Russell, 2010; Cottrell and Seckl, 2009; Darnaudéry and Maccari, 2008; Kapoor and Matthews, 2005; Kapoor *et al*, 2009; Lemaire *et al*, 2000; Mueller and Bale, 2007, 2008; Weinstock, 2008). Similar to human studies, the gestational timing of the stress and fetal sex are key determinants in offspring outcome, where studies in both mice and guinea pigs found that prenatal stress produced HPA axis dysregulation and cognitive effects only in male offspring exposed during early or mid-gestation (Kapoor and Matthews, 2005, 2008; Kapoor *et al*, 2009; Mueller and Bale, 2007, 2008).

Reprogramming in the Prenatally Stressed Brain

Although the long-term effects of maternal stress in humans on disease outcomes have been studied, earlier assessment of the perinatal brain has been limited to noninvasive measures of growth and macrostructure (Beversdorf *et al*, 2005; Khashan *et al*, 2008; Kinney *et al*, 2008b; Li *et al*, 2010; Ronald *et al*, 2010). These studies reported delayed overall brain growth, limbic system-specific volumetric changes, and white matter abnormalities (Li *et al*, 2012; Lou *et al*, 1994; Qiu *et al*, 2013, 2015; Rifkin-Graboi *et al*, 2013). Such early observations appear to persist into childhood and adolescence, are correlated with affective problems, and may contribute to symptoms in patients with schizophrenia and autism (Buss *et al*, 2010, 2012; Davis *et al*, 2013; Du *et al*, 2013; Sarkar *et al*, 2014; Zikopoulos and Barbas, 2010).

Results from animal models of maternal stress support these data and indicate that volumetric abnormalities in prenatally stressed offspring reflect reduced numbers of both neurons and glia, in particular in the hippocampus and amygdala due, in part, to decreased neurogenesis (Coe *et al*, 2003; Fujioka *et al*, 2006; Kawamura *et al*, 2006; Kraszpulski *et al*, 2006; Lemaire *et al*, 2000; Rayen *et al*, 2011). Further, reduced synaptogenesis and hypo-myelination in limbic regions was found in male, but not in female, juvenile rats exposed to maternal stress (Murmu *et al*, 2006; Xu *et al*, 2013). Such changes appear to persist into adulthood, where, eg, decreased hippocampal cell proliferation and reduced dendritic length and complexity were detected in adult prenatally stressed male rats (Mandyam *et al*, 2008; Suenaga *et al*, 2012). These data suggest potential primary impairment of cell proliferation, growth, survival, and connectivity in the prenatally stressed brain, and more specifically in the male brain.

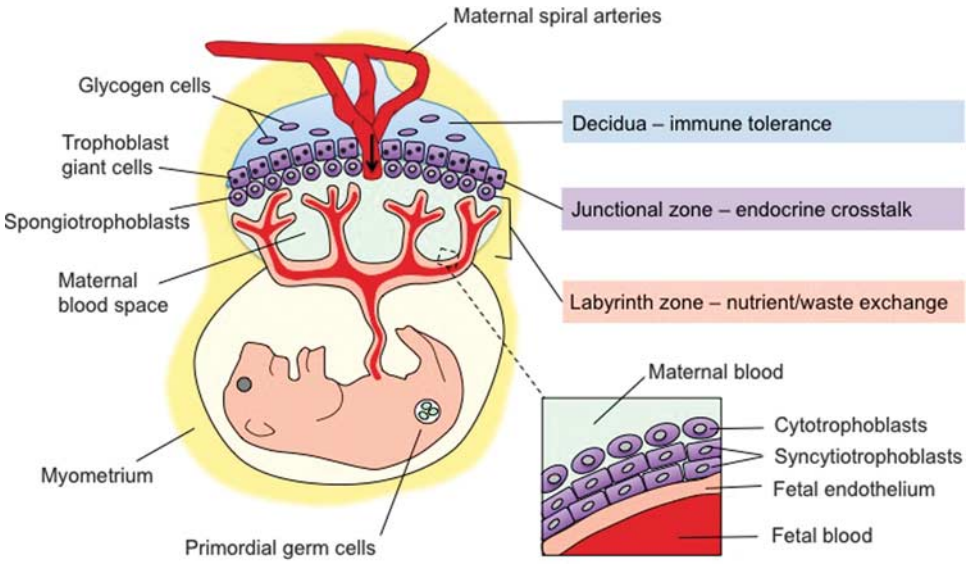

Figure 1. Morphology of the maternal–fetal interface: navigating a complex interaction between maternal and fetal compartments. Mid-sagittal schematic depicting the intricate arrangement of maternal tissue (blue), fetally derived trophoblasts (all five subtypes in purple), and fetal endothelial cells (tan) within the three major functional zones of the mature mouse placenta. The decidua, the most superficial layer from the maternal side (top), comprises maternal uterine and immune cells, as well as specialized glycogen-storing cells from the trophoblast lineage. The decidua is traversed by the maternal spiral arteries, veins, and the fetally derived endovascular trophoblasts that line it. The arrow indicates the direction of maternal blood flow. Bordering the decidua is the junctional zone (basal plate in humans), where maternal vasculature penetrates a layer of trophoblast giant cells and spongiotrophoblasts (extravillous cytotrophoblasts in humans) that secrete hormones to modulate maternal–fetal cross-talk, angiogenesis, and tissue remodeling. Finally, in the labyrinth zone (chorionic villous in humans), cytotrophoblasts and syncytiotrophoblasts residing between maternal blood spaces and fetal endothelial cells (inset) prevent direct blood contact while facilitating selective and essential nutrient/waste exchange. Environmental stimuli such as maternal stress can disrupt vital aspects of placental organogenesis and function, including decidual immune tolerance, vascularization and utero-placental blood flow, trophoblast hormone secretion, and nutrient exchange within the labyrinth zone. The neurodevelopmental consequences of stress depend on the maturational state of the entire maternal–placental–fetal unit at the time of exposure. Although implantation occurs early in gestation (embryonic day 4.5 in mice and the second week in humans), placental maturation and expansion continues throughout gestation, leaving this fetal lifeline and the somatic and germ cells it sustains continuously vulnerable to maternal stress signals.

PLACENTAL ORCHESTRATION OF FETAL BRAIN PROGRAMMING

The Programmatic Capacity of the Placenta

The mechanisms by which maternal stress confers lasting sex-specific neurobehavioral dysfunction likely initiate within the placenta. Stress-mediated perturbations of the maternal milieu must be conveyed to the embryo via interactions with the placenta. This transient organ is not simply a passive thoroughfare, but is an active maternal–fetal intermediary within which distinct functional zones collectively maintain intrauterine homeostasis (depicted in Figure 1). Although human and rodent placentas differ somewhat in their microstructure and developmental trajectory, the gross organization and functions of these zones are conserved (Georgiades *et al*, 2002). The decidua, comprising maternal uterine and immune cells, mediates immunological tolerance of the embryo (Arck and Hecher, 2013). Fetally derived trophoblast cells predominate in the basal plate (junctional zone in rodents), where they synthesize and secrete endocrine factors into both maternal and fetal circulations. Finally, in the chorionic villous (labyrinth zone in rodents), trophoblasts residing between the maternal and fetal vasculature control exchange of nutrients, oxygen, and waste via facilitated diffusion and macro- and micronutrient transporters (Georgiades *et al*, 2002; Rossant and Cross, 2001; Watson and Cross, 2005). Disruption of these critical functions can have an impact on fetal development, including the brain and primordial germ cells. Importantly, sex-specific reprogramming in response to maternal stress likely arises, owing to sex differences in trophoblasts derived from male (XY) and female (XX) embryos. Sex differences in placental size and gene expression have been identified in normal human and rodent placentas, and sex-specific placental abnormalities predict offspring outcome in pregnancies complicated by maternal asthma and preeclampsia (Buckberry *et al*, 2014; Clifton, 2010; Gabory *et al*, 2013; Howerton *et al*, 2013; Mao *et al*, 2010; O'Connell *et al*, 2013; Sood *et al*, 2006).

Stress at the Dynamic Maternal–Fetal Interface

Placental function is regulated by the collective responses of maternal decidual cells, trophoblastic cells, and fetal endothelial cells to the local environment (Fowden *et al*, 2008). Thus, disruption of the maternal milieu by stress and other stimuli can influence vital aspects of placental structure and function, including integrity of the protective

transplacental barrier, nutrient and oxygen exchange, and placental endocrine action (Jansson and Powell, 2007; Myatt, 2006). The specific consequences likely depend on the timing of exposure, as stress signals interact with dynamic events ongoing in maternal, fetal, and placental compartments. Environmental stimuli may modulate the onset, offset, or duration of these sequential events, resulting in distinct programmatic outcomes.

For example, perturbations in early pregnancy are more likely to produce prolonged effects on placental function via interference with organizational processes including trophoblast differentiation and vascular remodeling (Watson and Cross, 2005). Such changes would then have the potential to impact neurodevelopment across the duration of pregnancy, likely initiating broad programmatic consequences. Epidemiological studies support this unique early gestational vulnerability, as increased schizophrenia and autism risk were specific to first-trimester maternal stress and viral infection exposure, respectively (Atladóttir *et al*, 2010; Khashan *et al*, 2008). In contrast, late-pregnancy perturbations may have a more transient impact on placental actions, by impairing nutrient delivery during periods of high fetal demand or disrupting processes such as neurogenesis, synaptogenesis, and early myelination in the fetal brain. This timing would likely introduce region and cell-type-specific effects on the developing brain that vary depending on species-specific neurodevelopmental trajectories (Andersen, 2003; Avishai-Eliner *et al*, 2002). The capacity for reprogramming, however, is not limited to fetal somatic cells. Beginning in the second week of gestation in mice (3–10 weeks post conception in humans), the newly specified primordial germ cells migrate and undergo a wave of epigenetic remodeling, permitting a unique window during which stress effects may be transmitted to subsequent generations via new epigenetic marks (Bale, 2015; De Felici, 2013; Gapp *et al*, 2014; Saitou and Yamaji, 2012). Supporting this, male mice exposed to early prenatal stress and presenting with disease-relevant endophenotypes, including HPA axis dysfunction and hypothalamic reprogramming, transmitted this phenotype to their offspring in the absence of direct stress re-exposure (Morgan and Bale, 2011).

Human and animal studies have demonstrated timing-dependent and sex-specific effects of maternal stress on placental size, efficiency, and gene expression (summarized in Table 1). Recent studies using transgenic mouse lines to selectively target stress-sensitive placental genes, including *O*-GlcNAc transferase, were able to recapitulate the effects of prenatal stress on hypothalamic programming and function, and thereby provide strong evidence for the importance of placental function in brain development (Howerton and Bale, 2014; Howerton *et al*, 2013). In the next sections, we describe the effects of maternal stress on aspects of placental structure and function in more detail, and discuss potential mechanisms by which these changes may subsequently reprogram the developing brain.

Transplacental Barrier Permeability

One prominent hypothesis posits that stress compromises the transplacental barrier and, in turn, increases fetal exposure to selectively permeable factors such as steroid hormones and exogenous teratogens (Aye and Keelan, 2013; Seckl and Holmes, 2007). In addition to the structural separation within the labyrinth zone that prevents direct contact between maternal and fetal blood supplies (depicted in Figure 1, inset), metabolizing enzymes localized within trophoblasts facilitate fetal protection from excess glucocorticoids and amines (Brown *et al*, 1996; Nguyen *et al*, 1999). These barrier enzymes can be sensitive to maternal stress, where, eg, reduced placental expression of the glucocorticoid-inactivating enzyme, 11β-hydroxysteroid dehydrogenase type-2 (11βHSD2), has been associated with maternal anxiety and depressed mood in humans, as well as with chronic maternal stress in rodents (Blakeley *et al*, 2013; Jensen Peña *et al*, 2012; Mairesse *et al*, 2007; O'Donnell *et al*, 2012; Pankevich *et al*, 2009; Ponder *et al*, 2011). The result is for a potential fetal glucocorticoid overexposure to impact ongoing developmental events including a restriction of fetal growth, premature maturation of proliferative neural precursors, and altered HPA axis development (Seckl and Holmes, 2007). Notably, these predicted effects are consistent with the reduced perinatal brain volumetric findings in association with maternal stress described earlier (Li *et al*, 2012; Lou *et al*, 1994; Qiu *et al*, 2013). In addition to the potential for actions of excess glucocorticoids on the developing fetal brain, excess glucocorticoids also act within the placenta to have an impact on endocrine functions, thus compromising placental growth, vascularization, and nutrient transport (Hewitt *et al*, 2006; Wyrwoll *et al*, 2009). Further, known sex differences in placental 11βHSD2 expression, both at baseline and in response to environmental stimuli including stress, may contribute to sex-biased neurodevelopmental outcomes (Cuffe *et al*, 2011; Pankevich *et al*, 2009).

In addition to glucocorticoid release, stress increases levels of stress-related neurotransmitters, including serotonin, norepinephrine, and dopamine within both the maternal brain and circulation (Joëls and Baram, 2009). However, less is known about maternal stress effects on placental barrier proteins that may moderate passage of these amines to the fetus. Their fate within the placenta is controlled by their cell-surface transporters and intracellular metabolizing enzymes, such as monoamine oxidase (MAO) and catechol-*O*-methyl transferase, which regulate delivery to the fetus as well as local processes within the placenta (Nguyen *et al*, 1999). Recent human studies have associated maternal stress with increased levels of serotonin and norepinephine transporters, and a downregulation of MAO in villous trophoblasts at term (Blakeley *et al*, 2013; Ponder *et al*, 2011). As these cells reside between the maternal and fetal vasculature, such changes in transport would increase their intrauterine availability, especially that of serotonin, which is synthesized in maternal, placental, and fetal compartments

TABLE 1 Summary of Maternal Stress Effects on the Placenta

Species	Stress type	Stress timing	Sex	Placenta phenotype	Reference
Human	Anxiety	36 wpc	?	↑ Umbilical artery resistance, redistribution of fetal blood flow	Sjöström *et al*, 1997
Human	Anxiety	28–36 wpc	?	↑ Uterine artery resistance	Teixeira *et al*, 1999
Human	Anxiety	20 wpc	?	No association with uterine artery resistance	Kent *et al*, 2002
Human	Life stress	30 wpc	♂ and ♀	↑ Placenta weight	Tegethoff *et al*, 2010
Human	Anxiety and depression	Second to third trimester	♂ and ♀	↑ SLC6A4, trending↑SLC6A2 and 11βHSD2	Ponder *et al*, 2011
Human	Anxiety	Term	♂ and ♀	↓ 11βHSD2	O'Donnell *et al*, 2012
Human	Depression	Term	♂ and ♀	Trending↓11βHSD2	O'Donnell *et al*, 2012
Human	Depression	Term	♂ and ♀	↓ MAOA in villous trophoblasts	Blakeley *et al*, 2013
Human	Anxiety	Term	♂ and ♀	Trending↓MAOA in villous trophoblasts	Blakeley *et al*, 2013
Human	Depression	Pregnancy	♂ and ♀	↑ Methylation of glucocorticoid receptor	Conradt *et al*, 2013
Human	Anxiety	Pregnancy	♂ and ♀	↑ Methylation of 11βHSD2	Conradt *et al*, 2013
Mouse	Chronic variable (1/day)	1–7 dpc	♂ and ♀	↑ IGF2 in ♂ and ♀,↓11βHSD in ♀	Pankevich *et al*, 2009
Mouse	Chronic variable (1/day)	1–7 dpc	♂ and ♀	♂:↑PPARα, IGFBP1, GLUT4, HIF3α ♀:↓PPARα,↑DNMT1	Mueller and Bale, 2008
Mouse	Chronic variable (1/day)	1–7 dpc	♂ and ♀	↓ OGT in ♂ and ♀	Howerton *et al*, 2013
Mouse	Chronic variable (1/day)	1–7 dpc	♂ and ♀	♂:↑FASL, pro-inflammatory cytokines (IL6, IL1B, IL12RA, PTGS2), chemokines (CCR7, CCL5, CXCL10), cell surface antigens (H2-EB1, PTPRC), and endothelial molecules (EDN1, SELP). ♀:↑FASL,↓CCL2.	Bronson and Bale, 2014
Rat	Restraint (3/day)	10–21 dpc	♂	↓ GLUT1 and 11βHSD2,↑GLUT3 and GLUT4	Mairesse *et al*, 2007
Rat	Social defeat (1/day)+restraint (1/day)	5–20 dpc	?	↑ 11βHSD2 in low, but not high anxiety rat strains	Lucassen *et al*, 2009
Rat	Restraint (1/day)	14–20 dpc	?	↓ 11βHSD2,↑DNMT3a,↑11βHSD2 methylation	Jensen Peña *et al*, 2012

Abbreviations: 11βHSD, 11β-hydroxysteroid dehydrogenase 2; DNMT, DNA methyltransferase; dpc, days post conception; GLUT, glucose transporter; HIF, hypoxia-inducible factor; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; IL, interleukin; MAOA, monoamine oxidase A; OGT, *O*-GlcNAc transferase; PPAR, peroxisome proliferator-activated receptor; PTGS, prostaglandin; SLC6A4, serotonin transporter; SLC6A2, norepinephrine transporter; wpc, weeks post conception.
In human studies, stress timing refers to the gestational age of maternal stress assessment (wpc). In rodent studies, stress timing indicates the gestational age at maternal stress administration (dpc),

(Bonnin and Levitt, 2011; Nguyen *et al*, 1999; Verhaagh *et al*, 2001). Subsequent fetal overexposure may have deleterious effects on brain development, where, eg, serotonin excess impaired embryonic cortical interneuron migration in mice (Riccio *et al*, 2009; Velasquez *et al*, 2013). Serotonin, a potent vasoconstrictor, also elevates vascular resistance and reduces utero-placental blood flow, a mechanism thought to underlie hypertension in preeclampsia and gestational diabetes (Bolte *et al*, 2001; Li *et al*, 2014). Consistent with these vascular effects, maternal stress has been correlated with Doppler ultrasound indicators of restricted umbilical artery blood flow (Sjöström *et al*, 1997; Teixeira *et al*, 1999). Taken together, maternal stress-induced increased permeability of the transplacental barrier can influence fetal brain development via both direct and indirect actions, and aspects of placental function, such as nutrient transfer and endocrine actions.

Nutrient Exchange and Energy Homeostasis

The fetus relies on placental transfer of nutrients from the maternal circulation, which is achieved via diffusion or active transport across trophoblastic and endothelial cell membranes. The transfer capacity is determined by multiple factors including placenta size, vascularization, metabolism, and the availability of maternal-facing and fetal-facing transmembrane transporters. These factors are sensitive to the forces of maternal supply and fetal demand, and to adverse intrauterine conditions (Fowden *et al*, 2006; Jansson and Powell, 2006). Clinical studies suggest that placental transport capacity may be perturbed by maternal stress, owing to the utero-placental vascular dysfunction described in the previous section, which can impair bidirectional exchange of flow-limited substrates including oxygen and carbon dioxide (Myatt, 2006). The link between vascular function and nutrient delivery has been well established in uterine artery ligation models of placental insufficiency, where fetal hypoxia and oxidative stress are associated with reduced hippocampal size, abnormal neural migration, and hypomyelination in the offspring (Basilious *et al*, 2014; Lane *et al*, 2001; Reid *et al*, 2012). In addition, uterine artery ligation in rats disrupted striatal amino acid metabolism at term (Thordstein *et al*, 1992). Thus, fetal hypoxia, oxidative stress, and altered amino acid availability subsequent to stress-induced vascular dysfunction can adversely impact cell survival and differentiation within the fetal brain.

Although not yet investigated in humans, dysregulation of placental nutrient transporters has been demonstrated in animal models of prenatal stress (Mairesse *et al*, 2007; Mueller and Bale, 2008). Transporters are necessary for the

delivery of maternally derived glucose, amino acids, fatty acids, and cholesterol-containing lipoproteins, macronutrients essential for fetal development (Brett *et al*, 2014; Lager and Powell, 2012). Placental expression of the glucose transporter (GLUT) family is particularly sensitive to adverse conditions, such as psychosocial stress, diabetes, and malnutrition in both humans and rodents (Das *et al*, 1998; Illsley, 2000; Mairesse *et al*, 2007; Mueller and Bale, 2008). Further, maternal stress decreased GLUT1 in rat placentas at term (Mairesse *et al*, 2007; Mueller and Bale, 2008). As GLUT1 is the predominant isoform in late pregnancy, these data suggest that stress may reduce glucose transfer to the fetus (Brett *et al*, 2014; Illsley, 2000). In addition, the effects of stress on nutrient exchange are also sex dependent, where stress increased expression of GLUT4 as well as genes regulating fatty acid and oxygen availability in male, but not in female, placentas in rodents (Mairesse *et al*, 2007; Mueller and Bale, 2008). These changes, indicative of disrupted intrauterine energy homeostasis, were also associated with markers of delayed neurodevelopment in male neonates (Mueller and Bale, 2008).

Although changes in nutrient exchange in response to environmental stimuli promote adaptive advantages and maintenance of maternal–fetal homeostasis *in utero*, dysregulated availability of glucose, amino acids, and fatty acids initiates broad programmatic effects on the fetal brain (Innis, 2005; Morgane *et al*, 1993). For example, the fetus relies on fatty acids derived from the maternal circulation (Lager and Powell, 2012). Deficiency in long-chain polyunsaturated fatty acids during gestation, such as docosahexaenoic acid and arachidonic acid, which comprise 40%–50% of neuronal membrane phospholipids in the developing brain, resulted in altered neuronal membrane composition, increased neural inflammation, impaired microglia motility, and programmed long-term impairment in sensorimotor gating in offspring (Fedorova *et al*, 2009; Madore *et al*, 2014; Tam and Innis, 2006). Reduced fatty acid transport can also directly compromise placental function, owing to excess accumulation and subsequent oxidative stress (Jarvie *et al*, 2010). The high fetal demand for cholesterol in late gestation is met by both placental transfer from the maternal circulation and by fetal *de novo* synthesis (Lindegaard *et al*, 2008; Yoshida and Wada, 2005). Therefore, changes in placental cholesterol uptake and transfer are more likely to affect the fetal brain via further impact on placental function. For example, impaired trophoblast uptake of cholesterol may disrupt maternal–fetal cross-talk by reducing substrates for steroidogenesis as well as for synthesis of cholesterol-containing exosomes, non-hormonal communicators that regulate immune homeostasis (Beninson and Fleshner, 2014; Ouyang *et al*, 2014).

Endocrine Action

Bidirectional communication is achieved via hormone secretion by maternal-facing and fetal-facing trophoblasts. These cells synthesize and secrete growth factors, immunomodulators, sex steroids, metabolic mediators such as leptin and lactogen, and neuromodulators such as corticotropin-releasing factor (CRF) and serotonin (reviewed in Bonnin and Levitt, 2011; Bowen *et al*, 2002; Fowden *et al*, 2014; Reis *et al*, 2001; Sagawa *et al*, 2002; Sandman, 2015). Placental hormones act as endocrine, paracrine, and autocrine modulators of maternal and fetal physiology throughout pregnancy, in particular during implantation, at parturition, and in response to intrauterine conditions including stress signals. Their synthesis is regulated, in part, by gestational age and fetal sex, and some placental hormones are species specific (Carter, 2012; Fowden *et al*, 2014).

Perturbation of placental endocrine actions by stress can have profound effects on fetal neurodevelopment and subsequent disease risk. The role of placental-derived CRF in this reprogramming has been thoroughly investigated (reviewed in Avishai-Eliner *et al*, 2002; Sandman, 2015). Although placental synthesis of CRF in rodents has not yet been demonstrated, the human placenta produces CRF beginning in the seventh gestational week, the levels of which exponentially increase in the maternal circulation as pregnancy progresses (Emanuel *et al*, 1994; Goland *et al*, 1988; Petraglia *et al*, 1987; Robinson *et al*, 1989). Placental CRF is also released into the fetal circulation, where it has influence on nervous system development including regulation of proliferation and survival of neural progenitors (Koutmani *et al*, 2013). The bioavailability of CRF during pregnancy is determined by levels of a circulating binding protein (CRF-BP) (Bowman *et al*, 2001). Stress-related changes in CRF and CRF-BP can lead to neurotoxic effects, in particular in HPA and limbic circuits (Avishai-Eliner *et al*, 2002; Fujioka *et al*, 1999). Supporting this, negative correlations between placental CRF levels and fetal startle responses suggest that CRF overexposure delays maturation in humans (Sandman, 2015).

PLACENTAL INTEGRATION OF STRESS SIGNALS

Signal Detection and Response Coordination

Information about adverse intrauterine status is communicated to the placenta by maternally and fetally derived endocrine factors, which together determine placental adaptive responses and resource re-allocation. The placenta expresses receptors for numerous hormones including glucocorticoids, insulin, insulin-like growth factors (IGFs), leptin, gonadal hormones, cytokines, and prostaglandins (Bodner *et al*, 1999; Fowden *et al*, 2014; Hiden *et al*, 2006; Keelan and Mitchell, 2007; McCormick *et al*, 1981; Unlugedik *et al*, 2010). These signals are integrated by downstream cascades that ultimately influence placental growth, energy homeostasis, and endocrine action. For example, Jansson and Powell (2006) proposed that the mammalian target of rapamycin (mTOR) pathway serves as

a nutrient sensor that regulates transporter expression in order to facilitate compatibility between maternal supply and fetal demand. Circulating insulin and IGF1 activate the protein kinase activity of mTOR, leading to increased expression of genes promoting cell growth and metabolism (Roos *et al*, 2009).

Stress during pregnancy compromises the maternal hormonal milieu in humans and in animal models, where elevations in CRF, pro-inflammatory cytokines, and glucocorticoids have been reported (Parker and Douglas, 2010). The placenta integrates these signals and facilitates a coordinated, sex-specific response involving immune function, nutrient metabolism/transport, or its own endocrine actions (Fowden *et al*, 2014). For example, in mice, prenatal stress increased pro-inflammatory cytokines, including tumor necrosis factor-α and interleukin-6 in male, but not in female, placentas and the neurodevelopmental programming effects in this model were ameliorated by maternal anti-inflammatory treatment during stress exposure (Bronson and Bale, 2014; Mueller and Bale, 2008). The effects of immune dysregulation on the developing brain program endophenotypes of neurodevelopmental disorders, including autism and schizophrenia, and have been reviewed previously (Hsiao and Patterson, 2012).

A Common Programmatic Pathway

In addition to maternal psychosocial stress, fetal exposures involving stressful metabolic challenges are also associated with increased neuropsychiatric disease risk, including maternal diabetes, obesity, infection, and pre-eclampsia (Bale *et al*, 2010; Brown and Derkits, 2010; Walker *et al*, 2015). It is well established that maternal insulin is dysregulated in pregnancies complicated by diabetes, obesity, undernutrition, and preeclampsia, and insulin resistance also occurs in the placentas from diabetic, preeclamptic, and growth-restricted pregnancies (Colomiere *et al*, 2009; Rademacher *et al*, 2007; Scioscia *et al*, 2006; Street *et al*, 2011). Maternal infection during pregnancy increases cytokines within the placenta and is predicted to disrupt insulin signaling due to the inhibitory effects of cytokines on insulin action (Aguirre *et al*, 2002; Sykiotis and Papavassiliou, 2001; Tanti and Jager, 2009). This same mechanism is proposed to impair placental insulin signaling in pregnancies complicated by maternal psychosocial stress, as pro-inflammatory cytokines were increased in stress-exposed placentas and were associated with the male-biased endophenotype (Bronson and Bale, 2014). Programmatic effects in these conditions likely depend on the gestational age at which placental insulin signaling is affected, as insulin receptors are expressed in mammalian placental trophoblasts and fetal endothelial cells in a spatiotemporal pattern (Desoye *et al*, 1994). Functional analysis of insulin-responsive genes suggests that maternal insulin regulates placental metabolism (predominately of lipids and fatty acids) in early pregnancy, whereas fetal insulin communicates demand for growth and cell proliferation/survival near term (Hiden *et al*, 2006). Therefore, insulin perturbation can influence placental function, nutrient availability, and intrauterine homeostasis throughout gestation (depicted in Figure 2) and vastly have an impact on neurodevelopmental programming.

Encoding of Stress Memories in the Epigenome

Epigenomic remodeling is increasingly recognized as a molecular bridge linking placental adaptive responses to adversity with long-term phenotypic outcomes. Epigenetic processes including DNA methylation, histone modifications, and changes in small noncoding RNA expression are dynamic mechanisms by which the environment can shape gene expression and placental function, and when maintained within the fetal germ cells can influence the phenotype of future generations (reviewed in Bale, 2015; Franklin *et al*, 2010; Maccani and Marsit, 2009; Marsit, 2015; Monk *et al*, 2012). Tight epigenetic regulation of gene expression is essential for normal developmental processes, including placentation, cell fate determination, genomic imprinting, and X-inactivation, in particular throughout critical developmental periods during which imprinted epigenetic marks are erased and re-established (Gabory *et al*, 2011; Rugg-Gunn, 2012).

Intrauterine conditions, especially perturbations in nutrient availability and metabolism, have dramatic effects on epigenetic machinery (Tarrade *et al*, 2015). For example, maternally derived micronutrients such as folate and choline serve as substrates for DNA methyltransferases (DNMT) and their deficiency decreases placental DNA methylation (Kim *et al*, 2009). In calorie-restricted as well as high-fat diet-exposed mice, distinct hypomethylation patterns were detected in male and female placentas, including at imprinted loci, suggesting sex-specific placental adaptive responses to nutritional state (Chen *et al*, 2013; Gallou-Kabani *et al*, 2010). Similarly, maternal stress in humans and rodents elicits sex-specific placental epigenetic adaptations, including changes in DNA methylation and DNMT expression that were associated with neurodevelopmental outcomes (Table 1, (Conradt *et al*, 2013; Jensen Peña *et al*, 2012; Mueller and Bale, 2008). Differential methylation of the placental 11βHSD2 promoter has been the epigenetic mark most consistently correlated with gene expression levels and maternal stress (Conradt *et al*, 2013; Jensen Peña *et al*, 2012). Although the effects of stress on histone modifications and microRNA expression within the placenta have yet to be fully elucidated, it is clear that placental epigenetic processes maintain important sex differences in homeostatic strategies at the maternal–fetal interface. Sex-dependent molecular memories of the prenatal environment can then be encoded by the fetal epigenome and, when incorporated into the germline, communicated to future generations.

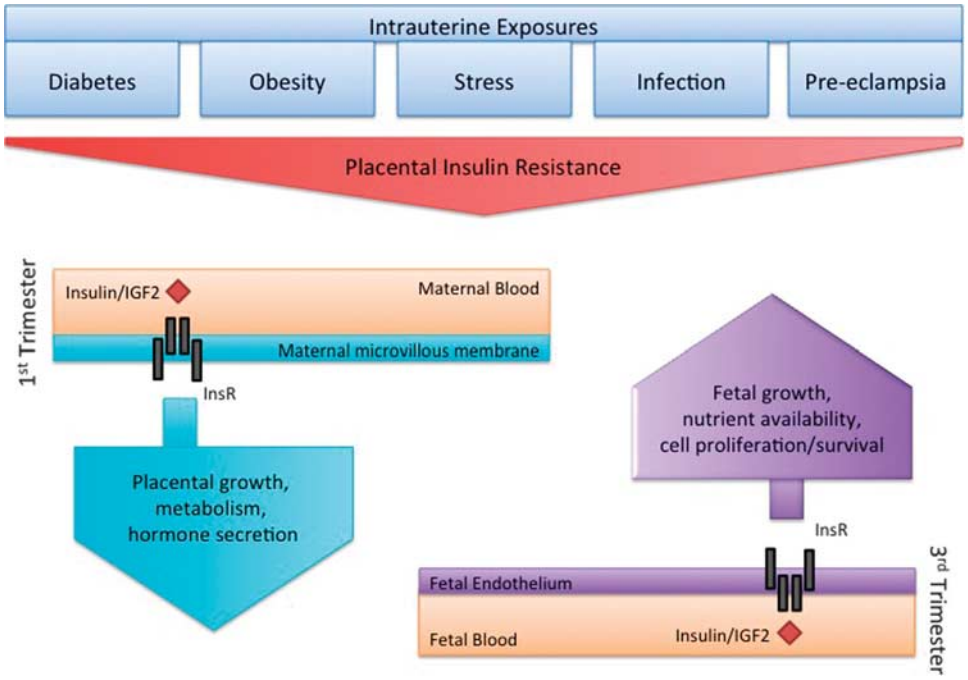

Figure 2. Insulin signaling as potential common programmatic placental pathway. A simplified schematic depicting the predicted impairment of insulin signaling within placentas complicated by diverse fetal exposures. In diabetes, obesity, and pre-eclampsia, changes in insulin receptor (InsR) localization, kinase activity, and substrate availability lead to placenta insulin resistance. Maternal stress and infection are predicted to also elicit insulin resistance, owing to the inhibitory effects of cytokines on insulin action. Predicted programmatic effects of placenta insulin resistance depend on exposure timing. In early pregnancy, InsRs are localized to maternal-facing trophoblasts and predominately regulate expression of genes related to metabolism of lipids and fatty acids. Such changes may have an impact on placental growth, trophoblast survival, and hormone secretion in early pregnancy. Later in gestation, their expression is restricted to the fetal endothelial cells where insulin communicates fetal demand for growth, cell proliferation, and cell survival.

CONCLUSIONS

Nearly 20%–40% of pregnancies are complicated by adverse intrauterine conditions, including maternal mental health disorders, diabetes, obesity, and preeclampsia (Ananth *et al*, 2013; Bennett *et al*, 2004; Dawson *et al*, 2015; DeSisto *et al*, 2014; Goodman *et al*, 2014; Rubertsson *et al*, 2014). These fetal exposures are significant risk factors for neuropsychiatric disease predisposition, in particular in male offspring. Growing evidence supports a critical role for the placenta in the deleterious and sex-specific effects of these fetal exposures on the developing brain. Although a great deal more investigation is necessary to elucidate the specific mechanisms by which the placenta imparts these critical signals to the developing embryo, the potential importance of the placenta as a biomarker of maternal stress and its potential for determining neurodevelopmental and neuropsychiatric disease risk is enormous.

FUNDING AND DISCLOSURE

The work described was funded by grants from NIH MH073030, MH087597, MH091258, MH099910 and MH104184. The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank Ali Rodgers and Katie Morrison for reading of the manuscript.

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