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Prenatal programing: At the intersection of maternal stress and immune activation

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Abstract

Exposure to prenatal insults such as maternal stress and pathogenic infections has been associated with an increased risk for neurodevelopmental disorders. The mechanisms by which these programing events occur likely involve complex interactions between the maternal hormonal milieu, the placenta, and the developing fetus, in addition to compounding factors such as fetal sex and gestational stage of development. Despite the diverse biological processes involved, examination of common pathways in maternal stress and immune activation offers intriguing possibilities for elucidation of mechanistic insight. Further, the endocrine and sex-specific placenta is a tissue poised to be a key mediator in fetal programing, located at the intersection of the maternal and embryonic environments. In this review, we will discuss the potential shared mechanisms of maternal stress and immune pathway activation, with a particular focus on the important contribution and role of the placenta.

Keywords

Maternal stress; Immune-activation; Fetal programming; Neurodevelopment; Epigenetic; Sex; Placenta; Glucocorticoids

Introduction

Exposure to prenatal insults such as maternal stress and pathogenic infections has been associated with an increased risk for neurodevelopmental disorders. The mechanisms by which these programing events occur likely involve complex interactions between the maternal hormonal milieu, the placenta, and the developing fetus, in addition to compounding factors such as fetal sex and gestational stage of development (Bale, 2011; Dunn et al., 2011; Mao et al., 2010). Despite the diverse biological processes involved, examination of common pathways in maternal stress and immune activation offers intriguing possibilities for elucidation of mechanistic insight. Further, the endocrine and sex-specific placenta is a tissue poised to be a key mediator in fetal programing, located at the intersection of the maternal and embryonic environments. In this review, we will discuss the potential shared mechanisms of maternal stress and immune pathway activation, with a particular focus on the important contribution and role of the placenta.

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Disruptions in maternal homeostasis and fetal programing

Effects of prenatal stress

Many studies of human populations have linked maternal stressors, such as death of a family member, unwantedness of the pregnancy, military invasion, natural disaster and reported maternal depression or anxiety with an increased offspring risk for disruptions in neurodevelopment (Beversdorf et al., 2005; Buka et al., 2000; Goldstein et al., 2000; Khashan et al., 2008, 2009; Kinney et al., 2008; Li et al., 2009; Myhrman et al., 1996; van Os and Selten, 1998). Additionally, both the timing of these stressors and the sex of the offspring have been identified as key factors in the increased incidence of offspring disease development associated with maternal stress. For example, male offspring of mothers suffering from depression during pregnancy showed deficits in both motor skills and behavioral state regulation, whereas changes in behavior were not detected in female offspring (Gerardin et al., 2011). Extreme stressors during pregnancy, such as the loss of a spouse or a military invasion, produced a temporally specific effect on offspring where the gestational age was a key factor. Children born from pregnancies where the father died during mid-gestation (months 3–5) were at a higher risk for developing schizophrenia than those whose father died during late pregnancy or the first year postpartum (Huttunen and Niskanen, 1978). Similarly, children born from pregnancies that were afflicted by a military invasion were at a higher risk for the development of schizophrenia, an effect more pronounced if the invasion occurred during the first trimester (van Os and Selten, 1998).

Animal models of maternal stress across a diverse range of species, including mice, rats, guinea pigs and nonhuman primates have demonstrated that prenatal stress increases offspring hypothalamic–pituitary–adrenal (HPA) axis sensitivity, anxiety and depressive-like behaviors and cognitive deficits; endophenotypes associated with neuropsychiatric disease (Darnaudery and Maccari, 2008; Kapoor and Matthews, 2005; Kapoor et al., 2008, 2009; Lemaire et al., 2000; Mueller and Bale, 2007, 2008; Schneider et al., 2002; Weinstock, 2001). Similar to epidemiological findings, a temporal specificity of stressor exposure and fetal sex were predictive factors in animal models of maternal stress (as reviewed in Bale et al., 2010). Work in our lab and by others has demonstrated that stress during gestation results in sex-dependent HPA stress axis dysregulation and behavioral or cognitive deficits, and that there was an important temporal specificity in these outcomes (Kapoor and Matthews, 2005; Kapoor et al., 2009; Mueller and Bale, 2007, 2008). In mice, male offspring that experienced stress early in gestation showed heightened corticosterone production in response to an acute stressor, increased immobility responses in both the forced swim and tail suspension tests, and deficits in the performance and strategy used in the modified Barnes maze, a spatial learning and memory task (Mueller and Bale, 2007, 2008). Similar timing effects have also been reported in guinea pigs where gestational stress during periods of rapid brain development produced impaired learning performance, increased anxiety-like behaviors and higher basal levels of cortisol in males. Taken together, these sex and temporal specific outcomes of maternal stress offer potential mechanisms and time points to be further investigated in the search for novel targets and biomarkers predictive of disease.

Effects of maternal immune activation

Intriguingly, similar to maternal stress, maternal infection also has a strong association with increased offspring risk for neuropsychiatric and neurodevelopmental disorders. Clinical studies have found that exposure to *Toxoplasma gondii*, influenza or herpes simplex viruses during pregnancy increases offspring risk for schizophrenia, psychosis and autism spectrum disorders (Brown et al., 2004a, 2005; Buka et al., 2001a, 2008). Increased maternal levels of pro-inflammatory cytokines, such as TNF-α and IL-8, resultant from infection are the most

likely mediators of increased offspring risk of disease development (Brown et al., 2004b; Buka et al., 2001b). Further, there is an established temporal specificity for these outcomes associated with maternal infection similar to studies on maternal stress. For instance, exposure to influenza during the first trimester or elevated levels of IL-8 during the second trimester produced an increased the risk for offspring schizophrenia development (Brown et al., 2004a, 2004b). While not directly investigated in these epidemiological datasets, there is a gender bias in the symptomatic presentation and timing of the onset of schizophrenia, likely to be recapitulated in the association with maternal immune activation (Aleman et al., 2003).

Numerous animal models of maternal infection show similar relationships where maternal immune activation produces offspring endophenotypes that are associated with neurodevelopmental disorders, especially schizophrenia (as reviewed in Meyer and Feldon, 2010). This body of research demonstrates offspring programing by several models, including maternal influenza viral infection, injection of the pathogen mimics Poly I:C and lipopolysaccharide (LPS) and the pro-inflammatory cytokine IL-6 (Borrell et al., 2002; Coyle et al., 2009; Fortier et al., 2007; Makinodan et al., 2008; Meyer et al., 2005; Romero et al., 2007; Shi et al., 2003; Smith et al., 2007). The most consistent phenotype produced in these models is a deficit in offspring pre-pulse inhibition (PPI) in response to an acoustic startle, a change that is reversed by the administration of antipsychotic drugs haloperidol or clozapine (Borrell et al., 2002; Fortier et al., 2007; Meyer et al., 2005; Romero et al., 2007; Shi et al., 2003; Smith et al., 2007). Sensorimotor gating deficiencies, a phenotype measured by PPI, is commonly associated with schizophrenia, but has also been demonstrated in numerous other psychiatric or affective disorders such as obsessive compulsive disorder, Tourette's syndrome and post-traumatic stress disorder (Braff et al., 2001). Again, highlighting the importance of gestational timing for immune activation in producing long-term outcomes, a single administration of IL-6 at embryonic day 12.5 (E12.5) in mice was sufficient to produce deficits in both PPI and latent inhibition, while administration of an anti-IL-6 antibody following Poly I:C injection rescued this effect (Smith et al., 2007). Further, mice deficient in IL-6 failed to produce these phenotypes in response to prenatal maternal immune activation supporting an important involvement of maternal pro-inflammatory cytokines in offspring central nervous system programing (Smith et al., 2007). Similar to models of maternal stress, there is evidence to support that offspring responses to maternal immune activation are also sex-dependent. For example, male offspring of pregnant rats challenged with LPS late in gestation showed deficits in PPI, whereas females or offspring exposed earlier in pregnancy were unaffected (Fortier et al., 2007).

The intersection between immune and stress pathway activation

Beginning with classic work by famed endocrinologist Hans Selye (e.g., 1955), there has been a firm understanding that there is a suppressive role of glucocorticoids on the immune system. More recent work has highlighted a complex interplay between the HPA stress axis and immune system activation. These interactions can occur both peripherally and centrally, and depending on the context can lead to either immune activation through prevailing pro-inflammatory signaling or an immunosuppressive effect by glucocorticoid suppression of macrophages and Th1-type T cells or direct actions of CRF on peripheral CRF receptors (Goetzl et al., 2008). Likely participants in these interactions from the HPA axis include corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH) and glucocorticoids.

CRF, the central upstream mediator of stress pathway activation, can have a myriad of context-and concentration-dependent effects upon the immune system. For example, CRF can decrease T cell proliferation and natural killer (NK) cell cytotoxicity as a centrally

mediated effect, as ICV injection of CRF antibodies prevents this suppression (Jain et al., 1991; Pawlikowski et al., 1988). Peripherally, CRF can also act as an anti-inflammatory molecule by reducing inflammatory exudate volume in various models of injury (Karalis et al., 1995; Wei et al., 1986). Despite these apparent immunosuppressive effects, CRF can also be an immune stimulant, enhancing B and T cell proliferation in response to various antigens and increasing interleukin-2 receptor numbers (Singh, 1989; Wei et al., 1986). In the context of psychological stressors, such as placement of rats in open-field settings or conditioned aversion stress, CRF triggers cytokine release and associated fever response prior to a rise in glucocorticoid levels (LeMay et al., 1990; Morrow et al., 1993). Additionally, prenatal maternal stress is positively correlated with higher circulating levels of the pro-inflammatory cytokines IL-6 and TNFα, particularly during the first trimester; potentially linking stress and maternal immune activation that could affect fetal programing (Coussons-Read et al., 2005, 2007). These effects may be mediated in part by CRF receptors found at peripheral sites of the immune system, serving to promote pro-inflammatory signaling in addition to effects of the downstream glucocorticoids (Cao et al., 2005; Karalis et al., 1991). The effects of glucocorticoids on the immune system are complex, and have been well summarized by Sapolsky et al. (2000). There is a temporal specificity in the effects glucocorticoids have on the immune system; in the acute phase glucocorticoids suppress immune responses, yet if they are present for up to a week prior to an immune challenge, glucocorticoids may serve to enhance pro-inflammatory responses. Glucocorticoids also have tissue specificity in their effects. For example, chronic elevations of glucocorticoids have suppressive effects on the peripheral immune system, yet promote a pro-inflammatory state on the immune cells in the brain (Sorrells and Sapolsky, 2007). These dynamic effects of glucocorticoids should therefore be examined in any tissue of interest.

Certainly, a reciprocal interaction of these two systems also occurs. From the immune system, pro-inflammatory cytokines can also have potent effects upon the HPA axis. For example, IL-1β promotes CRF release from the hypothalamus and ACTH from the pituitary (Berkenbosch et al., 1987; Bernton et al., 1987; Sapolsky et al., 1987). Other cytokines, including IL-2, IL-6, TNF-α, and interferon-γ (IFN-γ), are capable of stimulating the HPA axis, although none with the potency of IL-1 (as reviewed by Irwin and Miller, 2007; Wick et al., 1989). Taken as a whole, these reciprocal interactions between immune activation and HPA stress axis responses offer common mechanisms whereby the maternal environment in response to such fetal antecedents such as maternal stress or infection can affect offspring development and generate similar offspring phenotypes.

The placenta as a key mediator of offspring programing

The placenta is a conserved eutherian mammalian adaptation to facilitate in vivo gestation that has diverse functions ranging from nutrient and oxygen transport to complex endocrine and paracrine signaling. One function of critical importance is to protect the developing fetus from maternal environmental insults. For example, during either prolonged or short-term maternal nutritional deprivation, the placenta maintains fetal growth by sacrificing itself through autophagy (Alwasel et al., 2010; Broad and Keverne, 2011). Therefore, responses of the placenta to the maternal environment should be interpreted in this context of increasing offspring survival in the short-term, with the unfortunate consequence being long-term fetal developmental changes that may involve an increased risk for stress pathway dysregulation and neurodevelopmental disorders. Alternatively, the Barker hypothesis suggests that changes in offspring programing during development as a result of fetal antecedents attempts to predict the postnatal environment; this suggests that disease results when the predicted environment and the actual postnatal environment do not match (Barker and Osmond, 1986). Given that maternal cytokines and glucocorticoids are important

effectors of aberrant offspring development that have been associated with neurodevelopmental disorders, the impact these molecules have on placental development and gene expression is likely important in our understanding of the etiology of disease risk. Additionally, the placenta is a tissue derived from both maternal and fetal contributions, with the majority of the tissue of fetal origin, specifically the trophoblast cell lineage, a derivative of the trophectoderm (Rossant and Cross, 2001). Therefore the placenta is sex-specific, which may in part suggest a point of convergence for effects of fetal antecedents to produce a gender bias in any effect found in the developing fetus (Bale, 2011). Prenatal stress not only has sex-specific effects on the developing fetuses, but also upon the fetal-placental unit as a whole. For example, chronic restraint stress in pregnant rats produced dramatic changes specifically in the male fetal-placental unit (Mairesse et al., 2007). Male rat fetuses exposed to this prenatal stress exhibited decreased body, pancreatic and testis weights, as well as reduced β-cell mass, plasma glucose, growth hormone and ACTH. Additionally, in the placenta associated with these fetuses there was reduced glucose transporter 1 (GLUT1) expression and 11-beta hydroxysteroid dehydrogenase 2 (11βHSD2) activity and expression. We have found similar sex-specific effects of prenatal stress on the male placenta in mice. Placentas were collected from both male and female E12.5 embryos and mRNA levels of genes related to the response to hypoxia, inflammation and nutrient transport were assessed. Compared to non-stressed controls, early prenatal stress produced male specific increases in placental gene expression of peroxisome proliferator-activated receptor α (PPARα), insulin like growth factor binding protein 1 (IGFBP-1), glucose transporter 4 (GLUT4), and hypoxia-inducible factor 3α (HIFα), all genes known to be critically important in regulating fetal growth and development (Mueller and Bale, 2008).

Glucocorticoids, members of the steroid class of hormones and thus lipophilic in nature, readily pass through the placenta. However, high levels of placental expression of the enzyme 11βHSD2, which converts active glucocorticoids to an inactive metabolite (Drake et al., 2007), protects the developing fetus from high maternal levels of this hormone (Beitins et al., 1973). Glucocorticoids are necessary for various aspects of fetal brain development including subcellular reorganization of neuron–neuron and neuron–glia interactions, as well as late gestational lung maturation. Clearly, close modulation of mechanisms involved in maintenance of appropriate hormone levels is necessary to create this differential (Matthews, 2000). Studies in humans and in animal models have linked reduced placental 11βHSD2 activity or expression with fetal exposure to increased glucocorticoids, birth complications and fetal programing of adult hypertension and hyperglycemia (Lindsay et al., 1996a, 1996b; Shams et al., 1998; Stewart et al., 1995). In rodents and humans, the activity and sensitivity of placental 11βHSD2 to maternal stimuli are sex-specific. In females, 11βHSD2 activity is reduced in response to either inflammation associated with asthma or prenatal exposure to ethanol, but in male placentas activity is actually increased (Burton and Waddell, 1994; Clifton et al., 2006; Wilcoxon and Redei, 2004). This sex specificity may therefore provide one mechanism by which sex biases in neurodevelopmental programing occurs. Finally, studies in animal models have demonstrated that placental 11βHSD2 expression and activity are also reduced by chronic maternal stress, linking this enzyme to an environment known to affect fetal programing associated with neurodevelopmental disease (Fig. 1) (Mairesse et al., 2007).

While changes in the activity of placental 11βHSD2 may contribute to increased glucocorticoid levels within the fetal compartment, there are also important direct effects of increased maternal glucocorticoids upon programing of the placenta itself. One example of this is the regulation of placental glucose transporters by glucocorticoids. Altered placental glucose transport from the maternal to fetal compartment has been implicated in birth complications such as intrauterine growth restriction, adult phenotypes such as diabetes and also has far reaching effects on general fetal development due to the fundamental

importance of glucose as an energy substrate (Myatt, 2006). In cultured human trophoblast cells and in vivo rat placental tissues there was a significant reduction of both the mRNA and protein levels of the glucose transporters GLUT1 and GLUT3 (Hahn et al., 1999). A more recent report using spiny mice (*Acomys cahirinus*) reiterates these findings where the immediate response to exogenous glucocorticoid administration was a reduction in GLUT1 levels in both male and female placentas. However, observations later in gestation reveal a divergence between the sexes where males have a continued suppression of GLUT1, but females actually show an increased expression (O'Connell et al., 2011). In addition to altering the expression and activity of nutrient transporters, glucocorticoids also affect the oxidative state of both the placental and fetal compartments. Oxidative stress is exacerbated during conditions that complicate pregnancy, including inflammation and placental insufficiency, leading to developmental diseases with higher incidence in males (Auten and Davis, 2009; Myatt, 2010). Perhaps explaining the difference in disease presentation, antenatal glucocorticoids have sex-specific effects on the oxidative state of human placental tissue. In females, exogenous glucocorticoid exposure promotes antioxidant activity and reduces signs of oxidative stress postpartum, yet in males this exposure promotes a pro-oxidant state (Stark et al., 2011; Vento et al., 2009). As stated earlier, as there are temporal and tissue specific effects of glucocorticoids so careful examination of the placental specific response to these hormones should be further examined, with particular emphasis on the differences across pregnancy between the maternal and fetal components of the placenta.

The mechanism of fetal transmission of maternal cytokines is not well understood. There are several reports that support the ability for maternal cytokines to reach the fetal compartment or for the fetus to mount its own response to maternal inflammatory states. The latter would suggest an interaction at the level of the placenta that promotes fetal immune activation. As described above, maternal immune activation in pregnant mice can lead to offspring endophenotypes associated with neurodevelopmental disease, but blocking pro-inflammatory cytokine production ameliorates effects on offspring adult behaviors, therefore pro-inflammatory cytokines are likely key molecules in these programing events (Patterson, 2009). Dammann and Leviton report that maternal infection was correlated with high levels of several pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6, not only within the maternal circulation, but also within the fetal circulation and CNS (1997). Another study found that maternal immune activation leads to increased levels of pro-inflammatory cytokines within the amniotic fluid and placenta (Lin et al., 2003). TNF-α and IL-1β expression was upregulated in a dose dependent manner in the fetuses of pregnant rats exposed to LPS (Gao and Cai, 2003). Additionally, maternal IL-6 was found in the fetal compartment by midgestation, whether this occurred through active transport by the placenta or passive permeability was not clear (Dahlgren et al., 2006). Activational changes at the level of the placenta were detected where knockout mouse strategies demonstrated that maternal IL-6 production was necessary for the programing effects of maternal immune activation, and that this effect occurred by placental JAK/STAT3 signaling to reduce growth hormone, insulin-like growth factor I and insulin-like growth factor binding protein 3 (Hauguel-de Mouzon and Guerre-Millo, 2006; Hsiao and Patterson, 2011). Taken together, these data suggest that maternal immune activation is a powerful effector of fetal programing, and that the signals associated with maternal inflammation may in part be transduced through direct and indirect actions at the placenta.

An important consideration is that in most placental mammals X-inactivation is a random process, yet in rodents there are at least 150 loci that escape this process, thereby leading to expression of the genes from both X-chromosomes which can account for basal sex differences of X-linked genes (Carrel and Willard, 2005). Of relevance to the above discussion on the intersection of maternal stress and immune activation, many components of the pro-inflammatory pathway are X-linked, pointing to a potentially interesting sex

chromosome involvement in sex differences in immune responsivity. One such X-linked gene in NEMO (NFκB essential modulator), an X-linked regulatory protein that participated in the IKK complex that promotes nuclear translocation of NFκB dimers. Following cytokine production, NFκB binds to its target gene consensus sequence and promotes transcription of cytokine receptors and prostaglandins. Interestingly, children born with hypomorphic NEMO mutations frequently show intrauterine growth restriction, which may support a dysregulation of cytokine signaling in the placenta during development in these pregnancies (Hanson et al., 2008). Therefore the sex-specific contribution of the placenta to fetal programing may be resultant from differential expression of sex-linked traits, such as NEMO, as opposed to the traditionally held view of the influences of gonadal hormones.

Conclusion

Both maternal stress and immune activation serve as potentiating factors for alterations in offspring programing and increasing disease risk. This impressive coordination likely results from the multi-level reciprocal interactions found in these pathways where stress can serve as an immune activator and vice versa. Additionally, and perhaps even more intriguing are the seemingly temporal- and sex-specific effects of these fetal antecedents. Careful consideration of these sensitive periods of increased vulnerability that are dependent on fetal sex will likely elucidate important mechanisms by which the maternal environment invokes long-term outcomes. Finally, it is clear that the endocrine placenta is a key target tissue in need of further analyses for its important roles in fetal development including: sex-specificity of the placenta, its dynamic changes in early development, and its role in endocrine signaling for factors critical in determining somatic growth and programing. Strategies to investigate the placenta in these programing events should focus on common factors of both the stress and immune pathways, as their activation during pregnancy promote similar offspring phenotypes.

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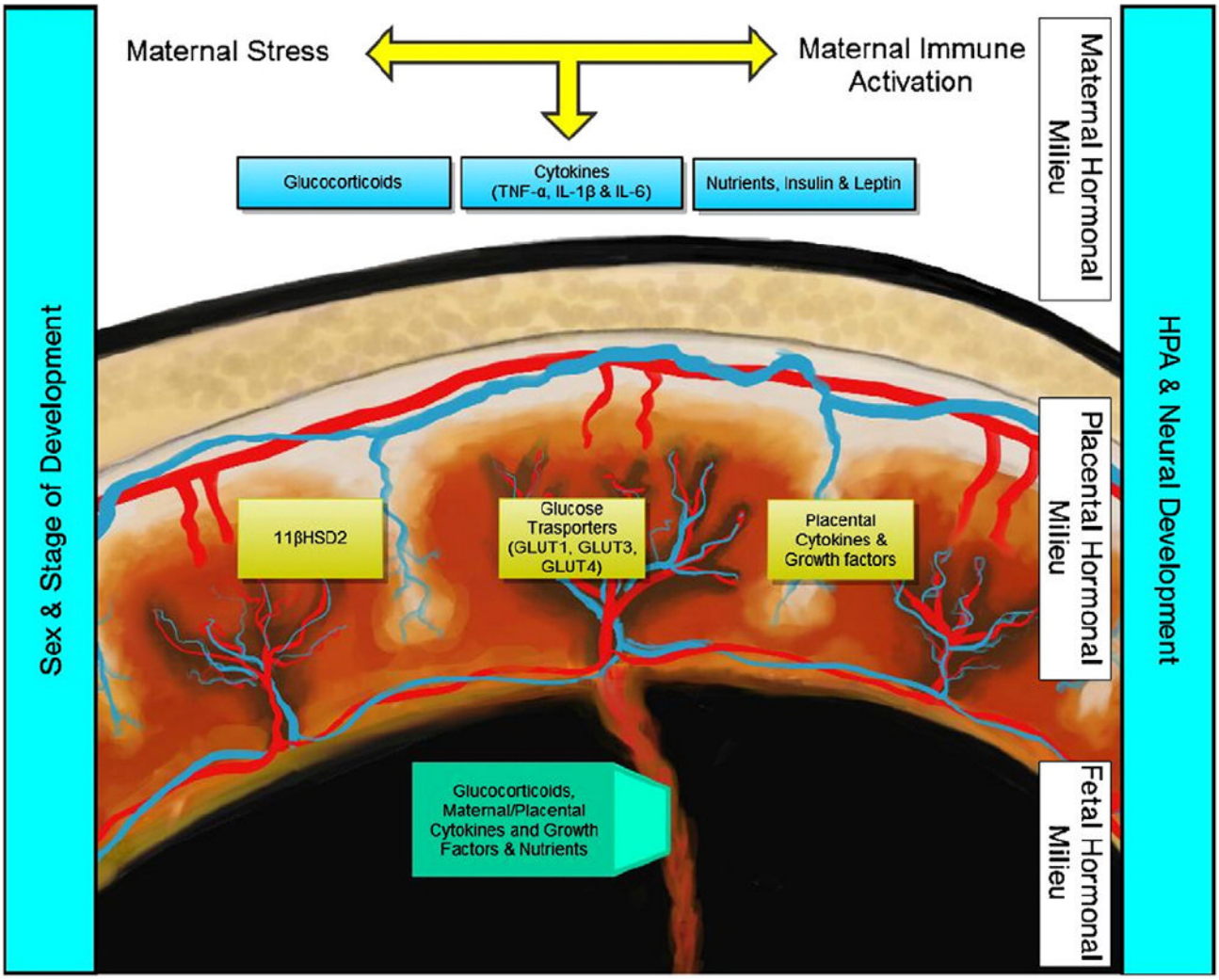

Fig. 1.

Schematic representing the proposed interaction between maternal, placental and fetal factors that may underlie aspects of programing of neurodevelopmental disease. Both maternal stress and immune activation have been associated with altered fetal programing of the developing hypothalamic–pituitary axis (HPA) and nervous system. Putative maternal contributions include increased glucocorticoids, pro-inflammatory cytokines, altered nutrient availability and dysregulated leptin and insulin signaling. In eutherian mammals, these maternal contributions are transmitted to the fetal compartment via the placenta. This transmission is achieved through passive permeability (i.e. glucocorticoids), active transport (e.g. glucose and other nutrients) and perhaps most intriguingly through endocrine and paracrine signaling within the endocrine placenta (e.g. glucocorticoid inactivation via 11-beta hydroxysteroid dehydrogenase 2 [11βHSD2] and local production of cytokines and growth factors). The resulting fetal hormonal milieu as transmitted via the placenta directly interacts with the developing embryo to shape the ontogenetic trajectory. Changes in programing are likely affected by developmental differences as well as embryo sex, which leads to chromosomal and somatic differences in both the placenta and embryo.