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Fetal Stress and Programming of Hypoxic/Ischemic-Sensitive Phenotype in the Neonatal Brain: Mechanisms and Possible Interventions

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Abstract

Growing evidence of epidemiological, clinical and experimental studies has clearly shown a close link between adverse *in utero* environment and the increased risk of neurological, psychological and psychiatric disorders in later life. Fetal stresses, such as hypoxia, malnutrition, and fetal exposure to nicotine, alcohol, cocaine and glucocorticoids may directly or indirectly act at cellular and molecular levels to alter the brain development and result in programming of heightened brain vulnerability to hypoxic-ischemic encephalopathy and the development of neurological diseases in the postnatal life. The underlying mechanisms are not well understood. However, glucocorticoids may play a crucial role in epigenetic programming of neurological disorders of fetal origins. This review summarizes the recent studies about the effects of fetal stress on the abnormal brain development, focusing on the cellular, molecular and epigenetic mechanisms and highlighting the central effects of glucocorticoids on programming of hypoxicischemic-sensitive phenotype in the neonatal brain, which may enhance the understanding of brain pathophysiology resulting from fetal stress and help explore potential targets of timely diagnosis, prevention and intervention in neonatal hypoxic-ischemic encephalopathy and other for brain disorders.

Keywords

Fetal stress; brain development; reprogramming; hypoxic-ischemic encephalopathy; glucocorticoids; epigenetics

1. Introduction

Fetal growth and development are a complex and dynamic process that depends on sophisticated interactions among the mother, placenta and fetus to ensure optimal growth

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and survival conditions (Warner and Ozanne, 2010). Numerous epidemiological, clinical and experimental studies have shown clearly that a compromised intrauterine environment may have subtle or drastic impact on tissue/organ ontogeny, structure and function, and alter the vulnerability or resiliency to some challenges and diseases in later life (Cottrell and Seckl, 2009; Dudley *et al.*, 2011). Indeed, there is a wealth of evidence indicating that an adverse fetal environment, mostly manifested as intrauterine growth restriction (IUGR), is closely associated with increased risks of development of hypertension, coronary heart disease, insulin resistance, type 2 diabetes, central obesity, hyperlipidaemia, and other neurobehavioral, neuropsychological and neuropsychiatric disorders in adulthood (Barker *et al.*, 1993a; Barker *et al.*, 2009; Dudley *et al.*, 2011; Gluckman and Hanson, 2004; Gluckman *et al.*, 2008; Harris and Seckl, 2011). The hypothesis of "developmental programming of health and disease" or "fetal origins of adult disease" was put forward to elucidate these links between adverse intrauterine environment, fetal growth and development, and disease later in life (Figure 1) (Barker *et al.*, 1993a; de Boo and Harding, 2006; Langley-Evans and McMullen, 2010; Seckl, 1998; Wadhwa *et al.*, 2009; Warner and Ozanne, 2010). As being stated, environmental signals can be transmitted from the mother to the fetus, impacting specific vulnerable tissues in their sensitive developmental stage, modulating normal development trajectory, remodeling their structure and function and reprogramming the resiliency or susceptibility to diseases in postnatal life (Harris and Seckl, 2011). Such programming processes may be determined by multiple factors including gestational age, duration and mode of exposure and nature of the stressor, and these processes are tissue/organ specific (Harris and Seckl, 2011). Genetic traits, epigenetic modifications and central stress mediators such as glucocorticoids may underpin such phenotypic plasticity.

Brain is one of the critical targets of stressors and is also the central organ responsible for stress responses, determining the adaptive or maladaptive responsiveness to various acute and chronic stressful events *via* making corresponding alterations in its structure and function (McEwen, 2008). The developing brain in the fetal stage is also highly plastic, flexible, and especially sensitive to numerous adverse environmental factors. Combined with its specific genetic traits, these changes of fetal brain contribute to high incidence of a wide spectrum of neurodevelopmental disorders in the postnatal life. It has been well documented that fetal stresses, such as hypoxia, malnutrition, substances exposure (nicotine, alcohol and cocaine) and excess glucocorticoids (endogenous or exogenous), have long lasting impact on the developing brain; altering brain's ontogeny, organization, structure and function; remodeling brain's development trajectory, and reprogramming brain's vulnerability or resiliency of some neurobehavioral, neuropsychological and neuropsychiatric disorders in later life (Archer, 2011; Chen and Zhang, 2011; Chiriboga, 1998; Harris and Seckl, 2011; Seckl and Meaney, 2004; Zhang *et al.*, 2005).

Neonatal hypoxic ischemic encephalopathy (HIE) is one of major causes of acute mortality as well as chronic neurological disability in newborns (Chen *et al.*, 2009b; Vannucci, 2000). Up to 25% of survivors demonstrate permanent neurological deficits such as cerebral palsy, mental retardation, learning disability and epilepsy (Perlman, 2006; Vannucci, 2000). However, there is no universally accepted therapy available for HIE except that a few studies implied that moderate hypothermia, administered in the early phase for full term neonates with mild or moderate encephalopathy, may reduce mortality and disability at 18 months (Perlman, 2006; Rees *et al.*, 2011). Before the availability of more potent effective therapy emerges, it is essential to explore all potential modifiable risk factors that may provide us with promising targets to prevent or improve the outcome of this encephalopathy. There is strong evidence suggesting that various prenatal stress insults may be the promising candidates meriting exploration.

In this review, we summarize recent studies about the programming effects of prenatal stress on fetal brain development and its associated diseases in later life, especially the programming effects of sensitive phenotype to neonatal hypoxic ischemic encephalopathy, particularly highlighting the cellular and molecular mechanisms and emphasizing the critical roles of glucocorticoids and epigenetic modification, which may enrich us with the knowledge of its underlying pathophysiology and contribute to exploration of some potential preventive and therapeutic interventions for neonatal HIE injury.

2. Fetal stress, abnormal brain development and associated diseases

2.1. Fetal hypoxia

Prenatal hypoxia-ischemia (HI) refers to a reduced level of oxygen (hypoxia) and a decreased blood flow (ischemia) during fetal development, which can cause various complications during pregnancy associated with neurological deficits and long-term neurodevelopmental disabilities in later life. One of these complications is cerebral palsy that occurs in 2 per 1,000 babies (Graham *et al.*, 2008). Of these, 15% - 20% will die during the postnatal period, and another 25% will develop permanent severe neuropsychological conditions.

The hypoxia-inducible transcription factors (HIFs) are one of the adaptive mechanisms activated during the HI insult. Hypoxia stabilizes HIF-1α subunit that binds to HIF-1β subunit and induces target genes transcription to regulate oxygen homeostasis. Some of these genes associated with the HIF-1 regulation include erythropoietin (EPO) that plays an important role in cell survival, vascular endothelial growth factor (VEGF) that activates endothelial cells leading to capillary sprouting (Vazquez-Valls *et al.*, 2011) and glucose transporter-1 (GLUT-1) that affects the cellular glucose metabolism (Wood *et al.*, 2009). HIFs play a crucial role in stimulating vascular development, angiogenesis and metabolic adaptation during brain development, which have been demonstrated in gene knockout experiments (Milosevic *et al.*, 2007; Tomita *et al.*, 2003).

Fetal hypoxia affects normal brain development and induces abnormal behavioral presentations. The cerebral cortex, hippocampus and sub-ventricular zone are the most vulnerable regions to the hypoxic insult (Northington *et al.*, 2001). A mouse model study has indicated that prenatal hypoxia produces a mild neurological deficit in a variety of behavioral tests. For example, the duration in an accelerating rotarod test was shorter for the offspring with prenatal hypoxic exposure compared to the control offspring, and they traveled a shorter distance and spent most of their time stationary compared with the control group (Ireland *et al.*, 2010). Some structural proteins of the white matter were measured in adult offspring with prenatal hypoxic exposure during gestational days 7 to 21. These structural proteins were associated with normal development of myelin and axon, and their expression levels decreased due to maternal hypoxia while the expression of protein related to astroglia increased, predisposing the individual to white matter changes later in life (Wang *et al.*, 2010). Hippocampus is one of the most common targets in the brain during ischemic injury. Phospholipase A2 (PLA_2) plays an important role in the underlying mechanism associated with the neuronal degeneration as was found in a study performed with hippocampal slices of Wistar/ST rats. The PLA_2 activity was evaluated in an oxygen-glucose deprivation environment in which the most vulnerable sub-region of the hippocampus was CA1 and cytosolic PLA_2 ($cPLA_2$) was associated with neuronal death (Arai *et al.*, 2001). Another possible mechanism of fetal brain injury due to prenatal hypoxia could be associated with inflammation. A recent work reported that chronic hypoxia exposure induced an increase in the lactate:pyruvate ratio and a decrease in the GSH:GSSG ratio, a favorable pro-oxidant state, in the brain of Duncan-Harley guinea pigs. Additionally,

the expression levels of pro-apoptotic proteins Bax, Bcl-2 and p53 increased as well as the levels of some pro-inflammatory cytokines (Guo *et al.*, 2010).

Prenatal hypoxia exposure also affects other vital organs/tissues in addition to the brain, which may contribute to various pathologies in later life. Studies in rats have shown that gestation hypoxia causes fetal heart remodeling and increases heart susceptibility to ischemia and reperfusion injury in offspring (Tong *et al.*, 2011; Tong and Zhang, 2011; Li *et al.*, 2003; Patterson *et al.*, 2010; Rueda-Clausen *et al.*, 2009). In mice, maternal hypoxia resulted in a significant increase in pulmonary mRNA levels of angiotensin converting enzyme (ACE) 1, 2 and angiotensin II Type 1b (AT-1b) receptors and the protein levels of renin and ACE-2, but a decrease in protein levels of ACE-1 (Goyal *et al.*, 2011). These results demonstrated that prenatal hypoxia affected the expression patterns of pulmonary renin-angiotensin-system (RAS) and suggested a possible mechanism contributing to the pathophysiology of pulmonary hypertension in offspring. Hypoxia may also be associated with fetal inflammatory response syndrome (FIRS). Maternal hypoxia has been shown to increase protein levels of interlukin-6 (IL-6) and tumor necrosis factor alpha (TNF-a) in fetal guinea pig sera and the mRNA expression in the lung, heart and brain (Yafeng *et al.*, 2009). In the placenta, 11-beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2) that catalyzes the conversion of cortisol to inactive cortisone, plays an important role in protecting the fetus from exposure to a high level of maternal glucocorticoids. Studies in human trophoblast cells demonstrated that hypoxia inhibited the activity of 11β-HSD2 and decreased its protein expression (Homan *et al.*, 2006).

2.2. Maternal malnutrition

One of the most common hostile environmental insults for the fetus is maternal malnutrition during the gestational period. Maternal malnutrition includes maternal overnutrition (high-fat, high-energy and high-protein diets) and maternal undernutrition (caloric and protein restriction diets or low-vitamin intake), both of which may contribute to perinatal programming (Elahi, *et al.*, 2009; Erkkola *et al.*, 2011; Gniuli, *et al.*, 2008; Guilloteau *et al.*, 2009; Rasch *et al.*, 2004).

In addition to its well-studied effects on programming of metabolic and cardiovascular disease (Barker and Osmond, 1986; Bateson *et al.*, 2004; Gluckman *et al.*, 2008; McMillen and Robinson, 2005), maternal malnutrition during pregnancy causes permanent brain dysfunction, especially cognitive and behavior deficits accompanied by alterations of neuronal excitability as well as structural changes in the developing and adult brain (Grantham-McGregor and Baker-Henningham, 2005; Levitsky and Strupp, 1995; Morgane *et al.*, 1993; Morley and Lucas, 1997; Olness, 2003; Walker *et al.*, 2007). A recent study evaluated the impact of global 30% maternal nutrient reduction on early fetal baboon brain maturation and found major cerebral developmental disturbances including neurotrophic factor suppression, cell proliferation and cell death imbalance, impaired glial maturation and neuronal process formation, down-regulation of gene ontological pathways and related gene products, and up-regulated transcription of cerebral catabolism without fetal growth restriction or marked maternal weight reduction (Antonow-Schlorke *et al.*, 2010). This finding suggests that moderate nutrient reduction during pregnancy is an important epigenetic factor that provides suboptimal conditions for appropriate fetal brain development with potential life-long consequences.

Maternal undernutrition causes marked epigenetic changes in hypothalamic genes and increases both glucocorticoid receptor (GR) and proopiomelanocortin (POMC) gene expression in the fetal brain, which is likely to contribute to fetal programming of a predisposition to obesity *via* altered GR regulation of POMC and neuropeptide Y as well as to altered regulation of food intake, energy expenditure, and glucose homeostasis later in life

(Stevens *et al.*, 2010). Additionally, maternal undernutrition may affect sensorimotor functions *via* its action on the CNS (Sanches *et al.*, 2011; Ba, 2005), the growth of major and minor cranial components (Cesani *et al.*, 2006), the structure of the brain (Torres *et al.*, 2010), and brain development itself (Melse-Boonstra *et al.*, 2010; Ohishi *et al.*, 2010; Ranade *et al.*, 2011). Maternal malnutrition may selectively decrease the number of neurons in some regions of the hippocampus, for example, CA2, CA4 and DG but not in CA1 and CA3 (Florian *et al.*, 2010). In addition to global maternal nutrient reduction, maternal choline deficiency during pregnancy alters neurogenesis and angiogenesis in fetal hippocampus (Albright *et al.*, 1999a, b, 2005; Craciunescu *et al.*, 2003; Mehedint *et al.*, 2010; Niculescu *et al.*, 2004, 2006).

Not only does maternal undernutrition have a negative impact on fetal brain development, but maternal overnutrition during gestation has also been shown to permanently alter brain structure and function in the offspring. Studies in pregnant rats fed a high-fat diet showed increased neural progenitor proliferation in the hypothalamus of fetal and neonatal brains (Chang *et al.*, 2008). Additional studies in mice demonstrated that maternal high-fat diet altered fetal hippocampal development as indicated by region-specific changes in proliferation of neural precursors, decreased apoptosis and neuronal differentiation within the dentate gyrus, resulting in the decreased neurogenesis in the dentate gyrus in young adult offspring (Niculescu and Lupu, 2009; Tozuka *et al.*, 2009). Neonates exposed to maternal high-fat diets also showed a negative impact on the brain development (Walker *et al.*, 2008).

2.3. Fetal nicotine exposure

Although the negative effects of cigarette smoking on the development of the fetus and the newborn are well-known, it is estimated approximately 22% of mothers and 45% of fathers continue to smoke during the time of their children's birth (Nelson and Taylor, 2001). Studies indicate there are about 250 million female smokers around the world and over 700,000 children born with exposure to cigarette smoking each year in the United States (Pauly and Slotkin, 2008). Thus, cigarette smoking may represent the single largest modifiable neuropharmacological exposure for the fetus and newborn (Wickstrom, 2007). Currently, nicotine replacement therapy (NRT) is recommended by some obstetricians to help women quit smoking during pregnancy although there are serious concerns about its effectiveness and safety to the mother and her fetus (Pauly and Slotkin, 2008; Wickstrom, 2007).

There are more than 4,000 chemicals in tobacco including carbon monoxide, cyanide, etc., of which nicotine is the major compound with neurotoxicity (Dwyer *et al.*, 2009). Nicotine can easily cross the placental barrier and concentrate in fetal circulation, brain, amniotic fluid and even breast milk during lactation (Wickstrom, 2007). Directly or indirectly, nicotine can exert a variety of adverse effects on fetal development. Nicotine may induce poor nutritional status of mothers *via* its anorexigenic effect and compromise blood flow to the placenta through enhanced release of catecholamine from adrenals and sympathetic nerve terminals, which may also contribute to chronic placenta insufficiency. More importantly, nicotine can directly affect fetal developmental patterns through the activation of nicotinic acetylcholine receptors (nAChRs). Ample human studies have revealed nicotine exposure during pregnancy is associated with a spectrum of adverse fetal and obstetrical outcomes: spontaneous abortion, placenta previa, placental abruption, preterm birth, stillbirth, fetal growth restriction, low birth weight, and, more severely, sudden infant death syndrome (SIDS) (Archer, 2011; Bruin *et al.*, 2010; Eppolito and Smith, 2006; Slotkin, 1998).

Epidemiological, clinical and experimental studies indicate that adverse effects of prenatal nicotine exposure are far beyond the pregnancy outcomes and neonatal morbidity or

mortality. Long-term adverse neurodevelopmental consequences of perinatal nicotine exposure constitute the greatest impact on society. A large amount of evidence suggests that nicotine plays a key role in mediation of long-term neurological developmental deficits resulting from maternal smoking. As one of the major psychoactive agents, nicotine exerts its effects *via* interaction with various subtypes of nAChRs localized in specific brain regions with programmed temporal and spatial distribution patterns, affecting a multitude of neurotransmitters' synthesis, release, reuptake and turnover; modulating neural proliferation, differentiation, migration and apoptosis, etc.; altering brain structure, organization and morphology; disrupting normal brain development, which finally contributes to heightened vulnerability to various neurobehavioral, neuropsychological and neuropsychiatric disorders in postnatal life (Bruin *et al.*, 2010; Dwyer *et al.*, 2008; Dwyer *et al.*, 2009; Ernst *et al.*, 2001; Pauly and Slotkin, 2008; Wickstrom, 2007).

Growing epidemiological studies have revealed that prenatal nicotine exposure is associated with various levels of motor and sensory deficits, high incidence of externalizing behavioral problems (such as oppositional, aggressive, overactive), increased risk of attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD), cognitive function impairment in memory, attention and learning, and the risk for developing drug dependence (e.g. nicotine, cocaine) (Eppolito and Smith, 2006; Ernst *et al.*, 2001; Wickstrom, 2007). Consistently, animal studies, mostly in rodents with prenatal nicotine exposure, also demonstrate similar presentations including hyperactivity, cognitive and somatosensory impairment, exaggerated anxiety, neurochemical imbalance, nicotine self-administration, reduction of neural cell survival and aberrant synaptogenesis (Dwyer *et al.*, 2008; Dwyer *et al.*, 2009; Eppolito and Smith, 2006; Levitt, 1998). These detrimental brain effects can be induced without apparent birth weight reduction, a crude marker of poor intrauterine environment, implying the threshold of brain damage by nicotine is much lower than that of inducing IUGR (Slotkin, 1998).

Another problem deserving concern is the NRT during pregnancy. Recently, the NRT is widely accepted and recommended to pregnant smokers although there is a lack of convincing solid evidence for its efficacy and safety. Pharmacologically, the plasma half-life of nicotine is about 2 h (Wickstrom, 2007). However, nicotine is metabolized more quickly during pregnancy, which indicates that higher doses of NRT may be needed to attain an effect for cessation of smoking (Wickstrom, 2007). In addition, most formulations of NRT deliver nicotine continuously compared to episodic smoking in smokers. The total exposure dosage of nicotine by NRT may actually exceed those of pregnant women with mild or moderate cigarette smoking (Wickstrom *et al.*, 2002). Furthermore, given the fact of lower threshold for altering brain development by nicotine, more extensive studies should be conducted to justify the efficacy and safety of NRT to the fetus before its continued application in pregnancy (Pauly and Slotkin, 2008; Wickstrom, 2007).

2.4. Fetal cocaine exposure

Cocaine has been one of the most popular illicit drugs over the past 30 years. It is estimated that approximately 30% of young adults reported having used cocaine at the height of the epidemic years (O'Malley *et al.*, 1991). In some urban areas, about 10-45% of women consume cocaine during pregnancy (Chiriboga, 1998; Gressens *et al.*, 2001). Although cocaine abuse began to decline in recent years, it is still one of the major concerns of public health because of its potential long-term adverse effects, especially for the offspring prenatally exposed to cocaine.

Similar to nicotine, cocaine is a highly psychoactive stimulating agent with various effects but has much shorter half-life compared with nicotine (Slotkin, 1998). The most prominent pharmacological effect of cocaine is the inhibition of synaptic reuptake of monoamines,

such as catecholamine, dopamine and serotonin, which may contribute to disturbance of autonomic function and aberrant neurotransmission (Chiriboga, 1998; Seidler and Slotkin, 1992; Slotkin, 1998). Like nicotine, cocaine can also easily cross the placenta and concentrate in the fetus with variable levels (Chiriboga, 1998). In addition to its direct inhibitory effects on cell replication, cocaine can induce intense vasoconstriction and compromise maternal cardiovascular system, leading to significant fetal hypoxia/ischemia and/or malnutrition, exerting great impact on fetal development (Anderson-Brown *et al.*, 1990; Chiriboga, 1998; Seidler and Slotkin, 1992).

Although there are some controversies about its negative effects on fetal development recently, large epidemiological, clinical and animal studies have shown the correlation of prenatal cocaine exposure with numerous obstetrical, pediatric and neurobehavioral abnormalities (Ackerman *et al.*, 2010; Chae and Covington, 2009; Chiriboga, 1998; Gressens *et al.*, 2001). For example, in early epidemic years, the term “crack/cocaine baby” was widely employed to depict the infants born to women with cocaine abuse during pregnancy although such a term lacked solid substantiation and was challenged by careful analysis (Chiriboga, 1998). Intrauterine cocaine exposure has been linked to increased risk of spontaneous abortion, abruption of placenta, stillbirth, fetal stress, meconium staining, and premature delivery (Chiriboga, 1998). More importantly, prenatal cocaine exposure is associated with microcephaly, cerebral malformation, focal hypoxic/ischemic or intraventricular hemorrhage damage and perturbation of cerebral cytoarchitecture (Chiriboga, 1998; Gressens *et al.*, 2001; Kandall *et al.*, 1993; Levitt, 1998). After delivery, the offspring with cocaine exposure demonstrates sleep disturbances, feeding difficulties, hypertonic tetraparesis and in some cases with seizure attacks (Chiriboga, 1998; Gressens *et al.*, 2001). Some studies even suggested a possible correlation of cocaine exposure with SIDS (Durand *et al.*, 1990; Gressens *et al.*, 2001; Kandall *et al.*, 1993). These clinical presentations are usually associated with transiently abnormal neurophysiological tests, which may disappear within the first year (Gressens *et al.*, 2001).

It seems that the effects of cocaine exposure on the developing brain are more subtle than those of nicotine (Slotkin, 1998). However, behavioral studies in animal models and recent clinical findings in humans have revealed that prenatal cocaine exposure may also produce long-term neurodevelopmental consequences although its outcome may be subtle and need more sophisticated or challenging methodologies to revelation. The children with cocaine exposure often demonstrate some moderate but significant neuropsychological deficits at school age including difficulty in concentration, weak resistance to distracters, aggressive behavior and impulsivity (Ackerman *et al.*, 2010; Gressens *et al.*, 2001). However, their IQ score may be within the normal range. In addition, these children are vulnerable to development of anxiety or depression (Gressens *et al.*, 2001). Alteration of anatomical structure and perturbation of neurotransmission induced by prenatal cocaine exposure may contribute to such deficits. In addition to its neurological effects, animal studies showed that fetal cocaine exposure resulted in programming of cardiovascular dysfunction in offspring (Bae and Zhang, 2005; Bae *et al.*, 2005; Xiao *et al.*, 2009a, b).

2.5. Fetal alcohol exposure

As a well-known teratogen, consumption of alcohol (ethanol) at different gestational stages can produce a wide range of adverse effects on the normal growth and development of the fetus. Fetal alcohol spectrum disorders (FASD) is the term used to describe many problems associated with prenatal alcohol exposure (PAE) (Jones *et al.*, 2010). In the USA, 1 in 12 pregnant women drink during the gestational period and each year around 40,000 babies are born with FASD. Fetal alcohol syndrome (FAS) is the most severe form of the alcohol spectrum disorders, associated with pre- and postnatal growth retardation and delayed neurological development, and occurs in 0.3-2.2 per 1,000 babies in the USA for the past

half-century (Ripabelli *et al.*, 2006). Ethanol crosses the placenta and circulates in the bloodstream of the fetus, affecting the development of fetal cells and tissues. The effect of ethanol in the fetus depends on a series of factors such as doses, exposure time, gestational age and others (de Licona *et al.*, 2009; Maier and West, 2001).

Neurocognitive deficits have been related constantly to PAE. Epidemiology studies also reported that adults with FAS exhibit various neurobehavioral problems. FAS patients present a lot of social problems and don't have friends, but on the other hand, they feel vulnerable and need care and assistance. Their academic performance is also very poor, most of them drop out or fail school, while aggressiveness is the most common emotional disorder in them (Freunscht and Feldmann, 2011). Rats in PAE demonstrate anxiety- and depressive-like behaviors similar to FAS, and a mechanism that involved oxidative stress has been suggested to induce this effect (Brocardo *et al.*, 2011). Low levels of human alpha-fetoprotein (HAFP) in pregnant women have been associated with FAS in the offspring (Halmesmaki *et al.*, 1987). Although the physiological role for HAFP is not clear, it is known that this protein binds to some transcription factor initiators (e.g., Retinoic acid and estradiol). Thus it may be associated with gene regulation as part of epigenetic mechanisms (King, 2011).

2.6. Fetal glucocorticoids exposure

Glucocorticoids during development are essential for normal maturation of various vital organs and contribute to immediate survival after birth. However, overexposure of the fetus to glucocorticoids at the critical developmental window of specific organs may alter normal developmental trajectory and lead to permanent reprogramming of structure and function (Cottrell and Seckl, 2009; Harris and Seckl, 2011; Seckl and Meaney, 2004). Glucocorticoids bind to their specific intracellular receptors (glucocorticoid receptor, GR and mineralocorticoid receptor, MR, respectively), acting as nuclear transcription factors to control target gene expression, regulating cell proliferation, differentiation, apoptosis and survival.

Maternal stress, psychosocial or adverse environmental factors can easily trigger the release of various levels of glucocorticoids or disrupt uteroplacental barrier, such as 11β-HSD2 (Mairesse *et al.*, 2007). During glucocorticoids therapy, which is usually employed in conditions such as preterm delivery when immature lung may threaten neonatal survival or antenatal treatment of congenital adrenal hyperplasia (CAH), synthetic glucocorticoids (dexamethasone, betamethasone) may be administered prenatally (Whitelaw and Thoresen, 2000). Although the antenatal glucocorticoids treatment is critical for facilitating the maturation of vital organs and tissues and favoring short-term survival, it may also confer on the fetus adverse levels of glucocorticoids and impair normal fetal development with long-term adverse consequences.

A plethora of evidence has indicated that overexposure to glucocorticoids during vulnerable periods of fetal development correlates with low birth weight, increased risk of premature delivery and adverse outcomes in the offspring. In human studies, there are substantial descriptions of linkage between low birth weight and increased risk of development of cardio-metabolic syndrome, such as hypertension, coronary heart disease, obesity, hyperlipidaemia, insulin resistance, type2 diabetes, stroke, etc., in adulthood (Barker *et al.*, 1993a; Barker *et al.*, 1993b; Cottrell and Seckl, 2009; Fall *et al.*, 1995; Harris and Seckl, 2011; Moore *et al.*, 1996; Rich-Edwards *et al.*, 1997). Such association is independent of other adult life-style risk factors, including smoking, alcohol abuse, lack of exercise, obesity, and poor socioeconomic status (Harris and Seckl, 2011; Leon *et al.*, 1996; Levine *et al.*, 1994; Osmond *et al.*, 1993). Consistently, a wide variety of animal studies also supported these results. For example, enhanced exposure of cortisol from maternal or fetal origins is

associated with elevated blood pressure in sheep fetuses (Tangalakis *et al.*, 1992). Dexamethasone treatment during pregnancy in rats demonstrates lower birth weight, increased blood pressure and glucose intolerance in adulthood (Benediktsson *et al.*, 1993). Similar results are found in pregnant baboons treated with repeated doses of betamethasone (Koenen *et al.*, 2002). Lower birth weight may not be the cause of these diseases, which may be considered as a crude indicator of suboptimal intrauterine environment and predictor of increased risk of pathophysiology in later life.

The brain is a major target of glucocorticoids. Both types of glucocorticoid receptors (GR, MR) are widely expressed in the brain, such as in hippocampus, amygdala, lateral septal nuclei and some other cortical areas. Glucocorticoids play a crucial role in normal fetal brain development *via* initiating terminal maturation, remodeling axon and dendrite growth and affecting cell survival (Harris and Seckl, 2011; Meyer, 1983; Yehuda *et al.*, 1989). Sustained high levels of glucocorticoids in the fetus may exert an adverse impact on brain cell and structure by disturbing the hypothalamic-pituitary-adrenal (HPA) axis, neurotransmitter balance and synaptic plasticity, which may contribute to abnormal neurodevelopment and the heightened brain vulnerability to diseases in the postnatal life (Weinstock, 2008). Studies including a wide range of species demonstrate that prenatal glucocorticoids exposure impairs intrauterine growth, re-sets the HPA axis sensitivity, and increases the risk of cardio-metabolic and affective disorders in later life. The greatest effects of glucocorticoids on birth weight usually occur in late pregnancy when fetal growth is accelerating. Prenatal glucocorticoids exposure may result in programming of heightened HPA axis sensitivity to stressful events in later life, leading to permanently increased levels of cortisol or corticosterone in offspring. Higher HPA axis activity confers enhanced response to stress and challenge, underpinning some neurobehavioral and psychiatric abnormalities (Cottrell and Seckl, 2009; Harris and Seckl, 2011; Seckl and Meaney, 2004).

Numerous studies also revealed the correlation between low birth weight and affective, psychiatric and cognitive disorders, such as schizophrenia, attention deficit/hyperactivity (ADHD), antisocial behavior, increased susceptibility to post-traumatic stress disorder (PTSD), anxiety disorders, lower IQ score or learning disability, and depression-like behaviors (Cannon *et al.*, 2002; Famularo and Fenton, 1994; Harris and Seckl, 2011; Jones *et al.*, 1998; Lahti *et al.*, 2009; Raikkonen *et al.*, 2008; Thompson *et al.*, 2001; Wiles *et al.*, 2005; Wust *et al.*, 2005). These findings in humans have been corroborated in substantial animal model studies. For example, maternal prenatal stress is correlated with attention deficits in offspring of non-human primates. Rodent model studies demonstrated increased anxiety and depressive-like behavior and compromised cognitive capability in adulthood (Meaney and Szyf, 2005). It seems plausible that excess fetal glucocorticoids exposure may at least partly represent one common pathway in which adverse environmental cues transferred from the mother to the fetus, altering brain developmental trajectory, permanently affecting cerebral structure and function, and reprogramming the vulnerability to later challenges and diseases (Cottrell and Seckl, 2009).

3. Mechanisms of fetal stress-mediated programming

3.1. Aberrant cell behavior and structure remodeling in the brain

Brain development consists of a series of progressive and regressive events tightly regulated by the interaction between cellular and environmental factors. Fetal brain development is especially susceptible to environmental perturbations. Prenatal stress exposure affects various neurotransmitters, neuromodulators, neurotrophic factors and cell adhesion molecules, etc., at specifically susceptible stages to alter neuronal development *via* both acute and chronic effects on cellular behavior and gene expression patterns (Levitt, 1998).

Aberrant cellular behavior and gene expression confer permanent structure remodeling and function reprogramming, which may lead the brain to be more vulnerable to later challenges.

Nicotine exerts effects mainly through triggering the release of acetylcholine *via* stimulation of specific subtypes of nAChRs. The most abundant subtypes of nAChR in vertebrate brain are α4β2 and α7, of which α7 is highly expressed in the immature brain. These are implicated in the response to brain injury and inflammation and participate in regulating the rate of apoptosis, and thus may be a potential candidate mechanism in abnormal fetal brain development caused by nicotine exposure (Pauly *et al.*, 2004; Pauly and Slotkin, 2008; Verbois *et al.*, 2000). Acetylcholine acts as a neurotrophic factor in brain development and is involved in cell proliferation, cell differentiation, survival, apoptosis, neuritic outgrowth, neuronal migration, synaptogenesis, and establishment of neuronal circuitry and modulation of other neurotransmitters releasing. Inappropriate premature stimulation of nAChRs during fetal development may disrupt normal prescheduled program of time and/or intensity of these neurotrophic effects and induce abnormal brain development with long-term consequences.

Human and animal studies have shown that prenatal nicotine exposure can up-regulate nAChRs' density in specific brain regions. However, such up-regulation may be only a compensatory response accompanied by lower function (Wickstrom, 2007). Fetal nicotine stimulation may cause target cells to prematurely switch from proliferation to differentiation and thus alter synaptogenesis. Additionally, nicotine stimulation can induce inappropriate apoptosis in several cell types, such as undifferentiated hippocampus progenitor neurons, dentate gyrus neurons in rats and murine neurons in olfactory bulb (Pauly and Slotkin, 2008). These cellular damages may be dependent on distribution patterns of nAChRs in the brain, leading to region specific abnormality of cell number and other macromolecular contents. The damages of nicotine to cells in the brain can be indicated by increased levels of cell damage markers (ornithine decarboxylase activity) and reduced DNA levels. In addition, these damages may be accompanied by increased gliogenesis, in which glial cells not neuronal cells replace the missing cells and lead to abnormal function (Pauly and Slotkin, 2008; Slotkin, 1998). Thus, structural alterations such as reduction of brain weight, thinner cortical thickness and smaller cell size ensue.

The adverse effects of prenatal cocaine exposure on brain development are more controversial among major drug abuse. Some clinical data suggest that cocaine might exert minimal effects on body size, brain structure and behavioral abnormality compared with alcohol and nicotine (Levitt, 1998; Richardson, 1998). However, recent animal studies revealed some consistent adverse changes in brain development. Experimental studies in mice and monkeys demonstrated that prenatal cocaine exposure resulted in attenuation of neuronal production, disturbance of neuronal migration and differentiation, aberrant gliogenesis and long-term anatomical, molecular and biochemical changes of aminergic systems (Gressens *et al.*, 1992; Gressens *et al.*, 2001; Kosofsky *et al.*, 1994; Levitt, 1998; Lidow, 1995). Most of studies suggest that these neuroanatomical changes are consistent with the distribution patterns of the dopamine (DA) system in the brain, and DA rich brain regions such as the anterior cingulated cortex (ACC) and medial prefrontal cortex (MPF) are predominantly affected, implying that the DA system is the major target of cocaine and confers its major adverse effects on behavior and emotion programming (Dewar and Reader, 1989; Goldman-Rakic and Brown, 1982; Jones *et al.*, 1996; Levitt, 1998; Levitt *et al.*, 1984). Prenatal glucocorticoids exposure also exerts pronounced effects on brain cellular behavior and structure alteration, which will be discussed in the following part.

Maternal protein restriction (MPR) adversely affects fetal brain development by altering astrocytogenesis, the extracellular matrix, neuronal differentiation and programmed cell

death (Gressens *et al.*, 1997). In a recently study, it was reported that maternal protein-restricted diet during pregnancy altered the expression patterns of proteins and mRNA related with brain RAS in the fetus, which could be associated with pathogenesis of hypertension (Goyal *et al.*, 2010). Additionally, maternal low-protein diet decreases the activity of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), in fetal rat cerebellums,, which in turn increases the lipid oxidation damage, affecting normal cerebral functions such as coordination control, posture, fine adjustment and cognition process (Bonatto *et al.*, 2006; Torres *et al.*, 2010). It has been further demonstrated that maternal protein-restricted diet decreases lipid levels and DHA in fetal rat brains. These studies suggest that MPR may have a negative impact on fetal brain development. The neuronal metabolic activity is decreased by a low iron diet, and this may affect the recovery of the brain after a brain injury (Rao *et al.*, 1999). MPR also affects the expression of proteins involved in the mitochondrial function, neurogenesis and synaptogenesis. The expression of proteins associated with oxidative pathways in the hippocampus was regulated by MPR (Alexandre-Gouabau *et al.*, 2011). For example, Bcs1L is down-regulated, which is consistent with a decrease in cytochrome c oxidase activity. The expression of NdUf8, a subunit of mitochondrial complex I, is also suppressed by MPR. Another group of proteins involved in the regulation of cellular processes, known as 14-3-3, were also down-regulated as well as PrdX 3, a protein with antioxidant function localized in the mitochondria. It has also been reported that MPR downregulated the expression of Arp3 in the fetal brain, which is part of the Arp2/3 complex involved in the regulation of actin cytoskeleton, as well as Arp1, the fascin and the MAPKK1. Interestingly, MPR upregulated MAP2 and TCP1, playing a significant role in the synaptic activity.

Brain cells consume 20% of the total oxygen available for all the organs, which makes the brain one of the organs with a significant production of reactive oxygen species (ROS) (Sokoloff, 1999). Additionally, the brain tissue is rich in unsaturated fatty acids, which could be the substrate for lipid peroxidation (Halliwell, 1992). Another reason that makes the brain an organ that could produce high levels of ROS is due to the oxidization of neurotransmitters such as DA, serotonin and norepinephrine. In the fetus, brain cells are prone to be affected by neurotoxic effect due to oxidative stress than in adults because the levels of antioxidant agents are lower in fetal brains than those in adult brains (Bergamini *et al.*, 2004; Henderson *et al.*, 1999). Liver is the organ where ethanol is mostly metabolized, and this process can affect the intracellular redox state of the central nervous system due to a direct dysregulation of mitochondrial bioenergetics. Interestingly, mitochondrial dysfunction has been found in cerebral tissues of fetal mice exposed to ethanol (Xu *et al.*, 2005). One of the enzymes that can metabolize ethanol in the liver is cytochrome P450 2E1 (CYP2E1). It was reported that PAE increased the activity of CYP2E1 in the fetal liver and mitochondrial fractions in guinea pigs (Hewitt *et al.*, 2010). Neuronal loss is one of the most prominent alcohol-induced pathological changes. PAE could make the brain more vulnerable by affecting the expression or neuroprotective role of nitric oxide (NO) (Bonthius *et al.*, 2004) associated with the cGMP pathway (Karacay *et al.*, 2007). Studies in mice have shown that deficiency in nNOS may induce neuronal loss and microencephaly (de Licona *et al.*, 2009).

3.2. Dysregulation of the HPA axis and perturbation of neurotransmitters

Intrauterine programming of the HPA axis may be one of the key common mechanisms underpinning prenatal stress and increased risk of diseases later in life (Figure 2). Fetal HPA axis is highly susceptible to programming actions during development. Prenatal stress, such as nicotine, cocaine, alcohol, hypoxia, malnutrition and glucocorticoids, can directly or indirectly alter the “set point” of the HPA axis, and enhance the activity of the HPA axis in basal and stressful conditions throughout life. Glucocorticoids play the pivotal role in such programming processes, which may be also associated with other stress mediators, such as

catecholamines (Lee *et al.*, 2008). Structures of the limbic system, including hippocampus, hypothalamus, anterior pituitary and amygdala, express high levels of GR, constituting the major target of endogenous or exogenous glucocorticoids in the brain. These GRs, particularly in hippocampus, exert crucial negative feedback regulation on the activity of the HPA axis. Maternal stress or synthetic glucocorticoids administration result in high levels of glucocorticoids exposure to the fetus, leading to down-regulation of GR in hippocampus and attenuation of negative feedback of the HPA axis and enhancement of the HPA axis activity. The overall effects of programming allow body being exposed to sustained elevated endogenous glucocorticoids in both basal and stress conditions, resulting in alteration of behavior, cognition, learning, memory, emotion and predisposing the individual to a variety of cardiovascular and metabolic syndromes in later life (Harris and Seckl, 2011).

The programming effects of HPA function by prenatal stress may be correlated to the exposure's severity, time, duration, and genetic factors (Harris and Seckl, 2011). Notably, some studies indicate there is a transient period of blunted HPA response during pre-weaning stage in ethanol-exposed offspring followed by a long-term hyper-responsive property (Zhang *et al.*, 2005). Importantly, postnatal events including early handling or maternal behaviors also exert profound effects on programming of HPA function. Weaver (2004) reported the association between early maternal behaviors (licking and grooming, LG and arched back nursing) and alteration of behaviors and HPA responses in adult offspring. The offspring with high LG manipulation demonstrate low levels of fearful behaviors and better-adjusted HPA responses to stress compared with that of offspring with low LG manipulation. Such differences are correlated with altered expression of GR in hippocampus and involve two epigenetic programming mechanisms: demethylation in promoter region of GR gene and hyperacetylation of histones surrounding GR gene. Early maternal behaviors (LG) (within 2 weeks after delivery) can lead to demethylation of the exon 1_7 promoter region of GR in rat hippocampus, enhance the binding of NGFI-A to exon 1_7 promoter, up-regulate the expression of GR, strengthen negative feedback regulation of the HPA axis, and result in more optimal glucocorticoids and HPA response to stress challenges in adulthood. These changes between adult offspring with high LG and low LG manipulations can be eliminated by the central infusion of histone deacetylase inhibitor, trichostatic A (TSA), suggesting a reversible potential for genes with long-lasting epigenetic modification (Weaver *et al.*, 2005).

The activity of HPA axis in the fetus can be altered by maternal alcohol exposure. In a study of sheep model, it was reported that PAE during third-trimester-equivalent increased the levels of ACTH and cortisol in the fetus (Cudd *et al.*, 2001). Interestingly, the HPA axis of females is more susceptible to be affected by insults in the fetal environment (McCormick *et al.*, 1995; Szuran *et al.*, 2000). Prenatal alcohol exposure induced sexually dimorphic effects as reported in some studies where females were found more susceptible than males to some effects of maternal exposure (Nelson *et al.*, 1986; Weinberger and Martinez, 1988). One possible mechanism associated with these effects was examined in a study of rat models in which the level of 11β-HSD2 in the placenta of the female pups was found lower than that in the placenta of the male pups (Wilcoxon and Redei, 2004). Additionally, PAE has shown some sexually dimorphic effects on the glucocorticoids-regulated genes where ethanol increases the expression of corticotropin-releasing hormone (CRH) in female but not in male pups, and. interestingly, the mRNA levels of pro-opiomelanocortin were suppressed in male but not in female pups (Aird *et al.*, 1997).

Growing evidence indicates that various neurotransmitters are also profoundly implicated in the programming effects of fetal brain. Appropriate neurotransmitter signals are essential for normal brain development. Perturbation of the time and intensity of neurotransmitter signals at critical developmental stages may result in aberrant cell behavior, changing

developmental trajectory and alteration of brain structure and function. Normally, *via* interaction with their specific receptors, neurotransmitters exert a variety of fundamental effects on brain development through inducing neural cell proliferation, promoting the switch between proliferation and differentiation, modulating axonogenesis and synaptogenesis, triggering or inhibiting apoptosis, initiating appropriate migration and accurate localization of cell groups in specific brain regions (Pauly and Slotkin, 2008). There are a number of neurotransmitters including acetylcholine, dopamine, norepinephrine, serotonin, glutamate and GABA, most of which present in early stages of fetal development. Prenatal stress may directly or indirectly affect the release, synthesis, reuptake and turnover of these neurotransmitters and/or modify their receptors to program fetal brain development. By direct activation of nAChRs, nicotine triggers the release of acetylcholine. Indirectly, nicotine can also regulate other neurotransmitter release by modulation of the presynaptic nAChRs (Wickstrom, 2007). Brain slice preparation studies have shown that nicotine increases presynaptic release of acetylcholine, dopamine, norepinephrine, serotonin, glutamate and GABA (Gauda *et al.*, 2001; Xu *et al.*, 2001). Furthermore, prenatal nicotine exposure can exert more extensive effects through altering some receptor-mediated signaling pathways (Yanai *et al.*, 2002). Compared with nicotine, the major targets of cocaine are the monoaminergic system. Cocaine can act as a competitive antagonist of the transporters of dopamine, serotonin and norepinephrine, resulting in disturbance of dopaminergic circuits in the brain. Chronic prenatal alcohol exposure increases glucocorticoids concentration and induces glutamate release in hippocampus of fetal guinea pigs, presumably as a consequence of enhanced glucocorticoids receptor expression (Iqbal *et al.*, 2006). Additionally, alcohol increases the expression of NMDA receptors, which could be neurotoxic for brain development (Naassila and Daoust, 2002).

3.3. Central effects of stress hormones

3.3.1. Glucocorticoids and fetal programming—Glucocorticoids are extraordinary hormones with numerous effects affecting many vital organs/systems, including the brain, heart and kidney, etc., and may regulate expression patterns of approximately 10% of human genes (Buckingham, 2006). Glucocorticoids are essential for life and play a crucial role in the regulation of growth and development, but also are implicated in various pathogenesis. There are two major endogenous glucocorticoids, cortisol and corticosterone, both synthesized in mammalian species but with different distribution predominance between species. Cortisol is predominant in humans while its counterpart corticosterone is principally produced in rodents. As the key mediators of stress responses, glucocorticoids are mainly synthesized from cholesterol in cells of zona fasciculate of adrenal cortex (Buckingham, 2006). In normal conditions, glucocorticoids levels are strictly regulated by negative feedback of glucocorticoids on the HPA axis. Disturbance of such feedback regulation loop may result in maladaptive impacts on the brain and other organs, contributing to numerous pathophysiological changes throughout life.

The effects of glucocorticoids are mainly mediated *via* binding to their intracellular receptors. There are two receptors with distinct affinity, glucocorticoid and mineralocorticoid receptor (GR and MR, respectively), both belonging to the nuclear receptor superfamily and modulating target gene expression. Normally, before binding to their specific receptors, about 95% of endogenous glucocorticoids are bound to a carrier protein (corticosteroid-binding globulin, CBG) in circulation, which allows only a small part of free glucocorticoids reaching target cells. Some transporter proteins, belonging to the ATP-binding cassette (ABC) family, also called multidrug-resistant P-glycoproteins (MDR P-glycoproteins), can actively extrude steroids from cells and lower intracellular levels of glucocorticoids (Buckingham, 2006). However, the most important regulation mechanism of glucocorticoids to their receptors is local pre-receptor metabolism within the target cells by

11β-hydroxysteroid dehydrogenase (11β-HSD) that catalyzes the interconversion of cortisol/corticosterone and its inactive metabolites cortisone/11-deoxycorticosterone, respectively. Two isoforms of 11β-HSD have been identified, 11β-HSD1 and 11β-HSD2, showing counteracting effects (Buckingham, 2006). 11β-HSD2, mainly acting to inactivate endogenous glucocorticoids, presents in some tissues such as the placenta and developing brain, which may offer crucial protection for fetus from exposure to excess of glucocorticoids. However, most synthetic glucocorticoids, such as dexamethasone or betamethasone, are not the selective substrates for 11β-HSD2, which may readily cross the utero-placental barrier and add additional detrimental effects on the fetus compared with the same levels of endogenous or other 11β-HSD2 sensitive glucocorticoids (Buckingham, 2006; Holmes *et al.*, 2003; Seckl and Meaney, 2004).

Glucocorticoids are highly lipophilic and easily cross biological barriers. However, in most normal pregnant conditions, glucocorticoids levels in the fetus are much lower than those in the maternal circulation. Such transplacental concentration gradient is principally maintained by placental 11β-HSD2, which actively captures and converts endogenous glucocorticoids into its inactive metabolites and acts as a primary “barrier” to prevent untimely premature and/or inappropriate intensity of glucocorticoids exposure to sensitive tissues during fetal development (Seckl, 2001; Seckl and Meaney, 2004). However, this enzyme is not a perfect barrier, and it varies considerably with progression of gestation in both placenta and brain under physiological conditions and is readily influenced by various environmental factors (Holmes *et al.*, 2003; Seckl and Meaney, 2004; Seckl and Walker, 2001). For example, *in vivo* and/or *in vitro* studies have indicated that the level/activity of 11β-HSD2 is downregulated by malnutrition (e.g., maternal protein restriction), hypoxia, catecholamine, pro-inflammatory cytokines and other endocrine factors (Chisaka *et al.*, 2005; Hardy and Yang, 2002; Homan *et al.*, 2006). Given the significant concentration gradient underlying between the mother and her fetus, only a little alteration of 11β-HSD2 in the placenta may result in a great impact of glucocorticoids on the fetal brain development. Indeed, increased fetal glucocorticoids exposure may result from maternal administration (exogenous), increased maternal levels due to prenatal stress, decreased placental 11β-HSD2 level/activity or increased synthesis by fetal adrenal in late gestational stage (Fowden and Forhead, 2004). Inhibition of 11β-HSD2 during pregnancy is closely correlated with reduced birth weight, the increased risk of hypertension and glucose intolerance, elevated HPA axis activity and anxiety-related behaviors, very similar to actions of excess glucocorticoids exposure. Furthermore, the programming effects of 11β-HSD2 inhibition can be reversed by maternal adrenalectomy and metyrapone administration to block glucocorticoids synthesis, implying the critical role of maternal endogenous glucocorticoids in fetal development (Cottrell and Seckl, 2009; Fowden and Forhead, 2004; Seckl and Meaney, 2004).

Glucocorticoids affect fetal brain development mainly *via* interaction with their receptors, GR and MR. GR and MR are highly expressed in the developing brain with dynamic and complicated ontogeny. During fetal development, GR presents from the early embryonic stage in most tissues, but expression of MR is relatively limited and presents during later stages of development (Holmes *et al.*, 2003). MR is responsible for mediating effects of very low concentrations of glucocorticoids usually in physiological conditions, and GR mediates effects of relatively high levels of glucocorticoids when MR has been saturated, especially in stress response (Buckingham, 2006). Synthetic glucocorticoids are relatively selective for GR. Therefore, GR is likely to be the major player in glucocorticoids overexposure. After processes such as ligand binding, dimerization and phosphorylation, the glucocorticoid receptor-ligand complex translocates into the nucleus and binds to various GREs (glucocorticoids response elements) in the gene promoter region, resulting in activation or repression of target gene expression. These genomic effects usually occur slowly in onset

compared with the rapid nongenomic effects possible mediated by novel membrane receptors (Buckingham, 2006).

Genomic studies have identified a large-scale profile of glucocorticoids responsive gene classes in neural tissues that are implicated in diverse functions of neural plasticity and brain development. These genes mediate processes including neurotransmitter release and exocytosis (PCLO, SYT1, SYT4, CLTB, AP2B1, SNAP25); neurotransmitter turnover (MAO-A); neuronal structure, neurite outgrowth, spine formation (GPM6A, LIMK1, TUBB2, MAP1B, NEFL, CHN1); axonal transport; motor activity (DNCLC1, DNCIC1, LIS1, KIF5C, SYT4); and neural cell adhesion molecules (OBCAM, SC1, LAMP, ICAM5, NRXN3, CX3CL1) (Datson *et al.*, 2008; Datson *et al.*, 2001; Morsink *et al.*, 2006). The effects of glucocorticoids on these gene expressions are time, cell, and environmental context dependent, showing significant disparity between specific brain regions under different types of stressors (Datson *et al.*, 2008).

Glucocorticoids exert effects at cellular and molecular levels to affect tissue/organ growth and differentiation. During fetal development, high levels of glucocorticoids exposure change the expression patterns of various receptors, enzymes, ion channels and transporters in most of cell types as well as alteration of various growth factors, cytoarchitecture proteins, binding proteins and other essential components of the intracellular signaling pathways (Fowden and Forhead, 2004). Such changes significantly impact the basal cellular functions and their responses to numerous stimuli, contributing to alteration of cell size, number, proliferation rate and terminal differentiation. Indirectly, glucocorticoids can also affect tissue proliferation and differentiation *via* altering cellular secretion of proteins, hormones, growth factors and metabolites, which can greatly amplify its programming effects on fetal development (Fowden and Forhead, 2004). At the molecular level, glucocorticoids regulate target gene transcription, mRNA stability, translation/post-translation modifications, etc., which may be mediated by directly controlling *via* GREs in promoter regions of responsive genes or indirectly *via* other transcription factors or glucocorticoids dependent hormones (Fowden and Forhead, 2004). All of these changes induced by glucocorticoids will confer an integration of function at the system level, suggesting that glucocorticoids-mediated programming may result in dynamic, multifaceted, co-ordinated and interdependent changes in different tissues (Fowden and Forhead, 2004).

Sufficient glucocorticoids are vital for normal maturation in most regions of the developing CNS. However, during vulnerable stages of development, inappropriate levels of glucocorticoids may remodel developmental trajectories of specific brain structures and alter corresponding functions accompanied by long-lasting adverse consequences, notably disturbance of behavior, cognition and disease susceptibility in later life (Harris and Seckl, 2011; Seckl and Meaney, 2004). For example, prenatal glucocorticoids administration reduces brain weight at birth, delays myelination of the corpus callosum, retards astrocyte and vasculature maturation in sheep, and decreases cortex convolutions index and surface area in humans (Antonow-Schlorke *et al.*, 2009; Modi *et al.*, 2001). Prenatal stress can also diminish dendritic spine density in the anterior cingulated gyrus and orbitofrontal cortex in rats (Murmu *et al.*, 2006). Studies in both humans and animals have revealed that hippocampus is a highly vulnerable structure particularly sensitive to prenatal glucocorticoids exposure, leading to variable memory and behavior deficits. For example, prenatal stress in rats can reduce synaptic spine density in hippocampus, which is associated with impairment of reversal learning (Hayashi *et al.*, 1998). Betamethasone administration in fetal baboons inhibits neurogenesis and impairs neuronal plasticity *via* downregulation of critical proteins such as cytoskeletal microtubule-associated proteins and synaptophysin, resulting in cognition deficits (Antonow-Schlorke *et al.*, 2003). In addition, antenatal administration of dexamethasone results in neuronal degeneration in the hippocampus

subfields and reduces the hippocampus volume in a dose-dependent manner (Uno *et al.*, 1990). It seems that chronic low levels of glucocorticoids exposure may be more deleterious than its short, sharp impact on fetal brain development (Harris and Seckl, 2011). Thus, the alteration of hippocampus structure and function may offer a plausible neuroanatomical basis for the programming effects of glucocorticoids on cognitive ability, behavior and the risk of psychological and psychiatric disorders in later life.

Long-term prenatal glucocorticoids exposure may permanently alter the "set point" and sensitivity of endocrine axis, such as the somatotrophic and hypothalamic-pituitary-adrenal axes (Fowden and Forhead, 2004; Meaney *et al.*, 2007). The HPA axis is an important programming target in the brain. It is strictly controlled by a negative-feedback mechanism in which glucocorticoids from peripheral adrenal cortex interact with GR in hippocampus, hypothalamus and pituitary to modulate its final level and activity of HPA axis in stress. Maternal malnutrition, inhibition of 11β-HSD2 and other prenatal stress may reduce tissue-specific expression of GR, particularly in hippocampus and impair the negative feedback regulation of glucocorticoids, thus altering the "set point" of the HPA axis (Harris and Seckl, 2011; Meaney *et al.*, 2007; Seckl and Meaney, 2004). A large variety of animal studies have shown prenatal glucocorticoids exposure permanently increases basal corticosterone/cortisol levels in plasma and enhances the activity of HPA axis in adult rats, sheep, guinea pigs and primates (Hawkins *et al.*, 2000; Levitt *et al.*, 1996; Seckl and Meaney, 2004; Uno *et al.*, 1994). Such changes are dependent on gestational age of exposure and also show sex-specific features. Prenatal dexamethasone exposure also stimulates CRH expression in the paraventricular nucleus of hypothalamus (PVN) and in central nucleus of the amygdala, increasing corticosterone and ACTH levels in rat offspring (Levitt *et al.*, 1996). Additionally, prenatal stress may heighten the vulnerability of CRH neuron in PVN and also program the development of the HPA axis (Tobe *et al.*, 2005). HPA programming may be a common pathway shared by other prenatal challenges. Furthermore, prenatal glucocorticoids exposure may have effects beyond the CNS and elevate 11β-HSD1 levels in hepatic, visceral adipose tissues, which regenerates more active glucocorticoids from its inactive metabolites and further enhances adverse effects of glucocorticoids on the developing brain (Cleasby *et al.*, 2003; Nyirenda *et al.*, 2009). Given its wide spectrum of physiological and pathophysiological functions, it is predictable that chronic excess of glucocorticoids during fetal development and overactivity of the HPA axis may increase risks of development of hypertension, hyperglycemia, obesity, other metabocardiovascular syndrome, stroke, cognitive impairment, affective and other neuropsychiatric disorders in later life, similar to what is expected in Cushing's syndrome (Harris and Seckl, 2011).

Excessive glucocorticoids exposure may also lead to reprogramming of offspring behavior in postnatal life. Glucocorticoids can reprogram expression patterns of several key molecules implicated in the regulation of neuronal development, HPA axis and other higher cerebral functions (Drake *et al.*, 2007). For example, prenatal glucocorticoids exposure increases CRH and GR expression in the amygdala, a central structure mediating emotional response such as fear and anxiety (Welberg *et al.*, 2000, 2001). Through elevated CRH and GR, amygdala may positively drive the HPA axis activity, which has been supported by transgenic study in mice (Tronche *et al.*, 1999). Prenatal glucocorticoids exposure can also influence the development of dopaminergic system, contributing to the development of schizo-affective, attention-deficit hyperactivity, extrapyramidal disorders and drug addiction (Drake *et al.*, 2007). Some studies also suggest that prenatal dexamethasone treatment may enhance vulnerability of cholinergic neurons to toxic challenges in later life (Diaz *et al.*, 1995). Human studies have revealed the correlation between stressful events during the second trimester of pregnancy and incidence of schizophrenia. Of importance, such programming effects are also time-dependent (Koenig *et al.*, 2002).

3.3.2. Catecholamines and fetal programming—Given its deep involvement in various acute and chronic stress responses, it is easy to assume the critical position of catecholamines in programming of fetal development by prenatal stress. However, up to now, only a few studies are available to indicate the effects of catecholamines (norepinephrine and epinephrine) in fetal stress-mediated programming of the developing brain. Predictably, prenatal stress can evoke enhanced maternal release of norepinephrine *via* activation of the sympathetic-adrenal-medullary system, resulting in significant maternal vasoconstriction and/or disturbance of maternal cardiovascular function. This will lead to compromised delivery of oxygen and nutrients to the fetus and exaggerate adverse effects of other stress stimuli on the fetus. More importantly, Sarkar (2001) reported that both norepinephrine and epinephrine rapidly repressed 11β-HSD2 mRNA expression in early and late gestational human trophoblast cell lines, which might increase exposure levels of glucocorticoids to the fetus in uterus. The downregulation of 11β-HSD2 by catecholamines is mainly mediated by activation of α1 and α2 adrenoreceptors and is not dependent on β-adrenergic stimulation. However, no similar studies in vivo have been reported yet. There are studies implying that catecholamines may exert programming effects on the HPA axis in offspring of a fetal ethanol exposure model (Lee *et al.*, 2008). However, most of these studies only confer indirect evidence of programming effects of catecholamines. Notably, some studies have indicated that maternal catecholamines can cross the placenta, and catecholamines are released by the fetus of later stage in stress (Morgan *et al.*, 1972; Thomas *et al.*, 1995), suggesting it is plausible that catecholamines may exert direct programming effects on fetal brain and other organ development via interaction with their specific regionally expressed α and/or β adrenoceptors. Indeed, a recent study in pregnant rats demonstrated a key role of increased norepinephrine in nicotine-mediated promoter methylation and PKCε gene repression in the developing heart and its sustained effect on heightened cardiac vulnerability to ischemic and reperfusion injury in adult offspring (Lawrence *et al.*, 2011).

3.4. Epigenetic mechanisms in fetal programming

One of the important adaptive mechanisms that the human body could be evoked to react to some adverse environments is through epigenetic modification of gene expression patterns. The fetal developmental stage is the most critical period for the human being because in the uterus the fetus could be exposed to inadequate or inappropriate environments that could be chemical/nutritional or non-chemical. These epigenetic changes could be associated with conditions or diseases during adulthood (Joss-Moore *et al.*, 2011; Nistala *et al.*, 2011; Pinney and Simmons, 2010).

The fetus is a critical developmental stage in which different events occur in a way to induce repression or activation of gene transcription *via* epigenetic mechanisms (Chen and Zhang, 2011). Epigenetic modifications regulate the expression of genes without altering the DNA sequence. The chromatin-based epigenetic is very important to ensure the correct integration of developmental signals at gene regulatory regions in which chromatin modifications play very important roles. Some of these chromatin modifications are mediated by DNA methylation and histone posttranslational modifications (HPTMs), including histone methylation, acetylation, phosphorylation, ubiquitylation, sumoylation and propionylation (Jungel *et al.*, 2010; Ouvry-Patat and Schey, 2007). Other important chromatin modifications and processes are the histone variants, the chromatin remodeling and RNA interference.

Many of these modifications have been associated with disease programming. Studies in mice showed that a low-protein diet in pregnant animals during the second trimester of gestation induced hypomethylation in the CpG islands of the ACE-1 gene promoter in the

fetal brain (Goyal *et al.*, 2010). It has also been reported that low-protein diet during pregnancy alters the expression of mmu-mir-27a, mmu-mir27b and mmu-mir-330, which are important miRNAs in the regulation of mRNA stability. These results suggest that the effect of these epigenetic changes may play an important role in the manifestation of brain dysfunction and other disorders later in life. Studies in pregnant rats showed that a low-protein diet during gestation decreased the expression of DNA methyl transferase (DNMT) 1 and the methylation levels of exon 1_{10} at glucocorticoids receptor gene promoter and increased the expression of GR in offspring at postnatal day 34 (Lillycrop *et al.*, 2007).

Other examples of fetal stress-mediated epigenetic modifications of gene expression patterns include the regulation of PKCε gene expression in the developing heart. Several animal models of fetal stress, including hypoxia, cocaine, and nicotine exposure, have demonstrated PKCε gene repression in the developing heart and increased heart vulnerability to ischemia and reperfusion injury in offspring, suggesting a common mechanism of PKCε in fetal programming of heart disease in later adult life (Lawrence *et al.*, 2011; Meyer *et al.*, 2009; Patterson *et al.*, 2010; Zhang *et al.*, 2009). It has been well-documented that PKCε plays a critical role in cardioprotection during cardiac ischemia and reperfusion injury (Heusch *et al.*, 2010; Murriel and Mochly-Rosen, 2003). Fetal stress caused highly specific changes in CpG methylation patterns at PKCε gene promoter and induced subtle epigenetic modifications of PKCε gene repression in the developing heart with pathophysiological consequences in the offspring heart (Lawrence *et al.*, 2011; Meyer *et al.*, 2009; Patterson *et al.*, 2010; Zhang *et al.*, 2009).

Epigenetic regulation is also associated with programming of type 2 diabetes mellitus (T2DM). Chromatin remodeling has been found in cells of IUGR rats. A decrease on histone acetylation in H3 and H4 at the proximal promoter Pdx1, which plays a critical role in the development of endocrine and exocrine pancreas, was observed in the islets isolated from IUGR fetuses (Park *et al.*, 2008). This modification affected the binding of USF1, an activator of Pdx1, and the resulting decrease of Pdx1 transcription causes a significant repercussion in the aberrant development of the pancreas (Li *et al.*, 2006).

Brain-derived neurotrophic factor (BDNF) plays a vital role in the brain development. An epidemiologic study in adolescents whose mothers smoked during pregnancy revealed that prenatal nicotine exposure increases DNA methylation of the BDNF-6 exon, and this may lead to changes in the plasticity and development of the brain (Toledo-Rodriguez *et al.*, 2010). A recent study evaluated the DNA methylation patterns of the genes coding GR, 11β-HSD2, neuronatin and reelin in hippocampus of the offspring rats from pregnant animals that had been treated with a deficient methyl donor diet (MDD). Though the behavior differences were demonstrated between MDD and the control groups, the DNA methylation patterns of these genes were not altered (Konycheva *et al.*, 2011). However, it has been shown that maternal stress of pregnant rats during gestational days 12-16 increases the levels of DNA methylation in frontal cortex and hippocampus in offspring, which is associated with behavioral changes in offspring rats (Mychasiuk *et al.*, 2011). Additionally, it has been found that fetal exposure to bisphenol A (BPA), a xenoestrogen, induces changes in DNA methylation patterns in the 2500 Notl loci, suggesting that the maternal BPA exposure may also exert some programming effects on brain development (Yaoi *et al.*, 2008).

4. Fetal stress reprograms the vulnerability of neonatal hypoxic-ischemic encephalopathy

4.1. Neonatal hypoxic-ischemic encephalopathy

The most common cause of neonatal brain damage is HIE, which is also the most clearly recognized cause of cerebral palsy (Bracci *et al.*, 2006; Perlman, 1997, 2006). Severe HIE

disrupts normal brain development, leading to a wide variety of neurodevelopmental deficits presented as various motor and sensory abnormality, learning disability, mental retardation and seizure attacks (Vannucci, 1990; Vexler and Ferriero, 2001). The incidence of asphyxia is approximately 20% in full-term infants and up to 60% in premature infants with low birth weight, of which 20 – 50% asphyxiated infants showing HIE symptoms and signs will die and about 25% of the survivors will be accompanied by permanent severe neuropsychological disability (Vannucci, 2000).

Compromised cerebral blood flow (CBF) is the dominant pathogenetic mechanism for neuropathophysiology due to hypoxia-ischemia, which may arise from acute reduced materno/feto-placental blood flow or from chronically compromised fetal oxygen and energy supply (Perlman, 2006; Terzidou and Bennett, 2001). The resulting patterns of HIE injury consist of periventricular white matter lesions in preterm newborn; cortico-subcortical lesions, particularly in the sensomotor cortex, parasagittal region, and deep gray matter lesions of basal ganglia and thalamus in near-term and term newborns. Such patterns of injury are associated with brain maturation stage and nature of hypoxic-ischemic injury.

The etiology of brain damage secondary to HIE is complicated and multifaceted. It is well documented that energy failure due to reduction of CBF and oxygen delivery initiates the principal pathways contributing to brain cell death. In acute phase, energy depletion (primary energy failure) results in increased neuronal release of glutamate and reduced reuptake of glutamate by astrocyte, lactate acidosis, glutamate receptor (NMDA) activation, intracellular calcium accumulation, generation of ROS, lipid peroxidation, NO formation and neurotoxicity, disruption of cell essential components, and immediate or delayed cell death. Typically, about 6 – 48 h later, a second phase of injury (secondary energy failure) ensues. During this phase, accumulated mitochondrial dysfunction secondary to extended injury from primary insults (calcium influx, excitotoxicity, oxygen free radicals or NO nitrosative stress) leads to release of various cytotoxic enzymes and pro-apoptotic proteins from mitochondria causing delayed cell death (Perlman, 2006; Rees *et al.*, 2008, 2011; Vexler and Ferriero, 2001). Evidence suggests that some circulatory and endogenous inflammatory cells/mediators may also contribute to such ongoing brain injury (Palmer, 1995; Perlman, 2006).

It is also notable that compared with the adult brain, the neonatal brain shows some differences in physiological structure organization, ontogeny, function, cellular composition and signaling pathway related to gene and protein expression, demonstrating more sensitive and plastic features to challenges (Chen *et al.*, 2009b). Such features determine that its response to brain injury is also significantly different from the adult brain, resulting in distinct acute and chronic neurological consequences, which deserves a careful consideration in experimental and clinical studies. For example, the neonatal brain shows more permeable immature blood-brain barrier (BBB) that allows readily cross of various solutes and small insoluble molecules in blood (Chen *et al.*, 2009b). The major responses to injury and cell death mechanisms are different in the neonatal brain, favoring more apoptotic features (Vexler and Ferriero, 2001). Additionally, the response to the treatment in the neonatal brain may be also different from that in the adult brain. In general, compared with the adult brain, the neonatal brain is more resistant to HI damage (Vannucci and Hagberg, 2004).

Up to now, no universally definite effective therapy is available to intervene with this severe neonatal encephalopathy. The only accepted therapy for HIE in clinical practice is moderate hypothermia. A recent meta-analysis of 10 randomized controlled trials confirmed the neuroprotective effects of moderate hypothermia administered within 6 h after birth for full-term newborns with mild or moderate HIE, showing reduced mortality and neurological

deficits at 18 months of age (Edwards *et al.*, 2010; Rees *et al.*, 2011). However, it does not improve mortality and neurological outcomes in neonates with severe HI brain injury and is contraindicated in pre-term neonates. Furthermore, the narrow administration time window also greatly restricts its clinical application. Other intervention strategies, such as application of excitatory amino acid antagonists, oxygen free radical inhibitors and scavengers, inhibition of nitric oxide formation, blockade of apoptosis cascades, application of growth factors and neurosteroids, are either still in the experimental stage or in early, ongoing, small scale clinical studies or have already failed in clinical trials, showing the lack of solid evidence to justify their extensive application (Perlman, 2006; Rees *et al.*, 2011).

4.2. Fetal stress enhances the vulnerability of neonatal hypoxic-ischemic encephalopathy

A wealth of human and animal studies has indicated the close link between prenatal stress and enhanced risk of development of cardiometabolic syndrome, stroke, neurobehavioural, neuropsychological and neuropsychiatric pathogenesis in adolescence and/or adulthood. However, little research concerns the potential harmful effects of fetal stress on the susceptibility of neonatal HIE. Given the profound impact of prenatal stress on programming of brain structures and functions as discussed above, it is plausible to presume that fetal stress may induce the sensitive phenotype of HIE in the neonatal brain *via* reprogramming expression patterns of some key functional genes and/or proteins involved in the pathophysiology of HIE. Indeed, recent studies lend necessary supports to such a hypothesis.

Multiple mechanisms may be involved in the fetal stress-mediated increase in the susceptibility of neonatal HIE (Figure 3). Prenatal stress may enhance the vulnerability of neonatal HIE *via* reprogramming expression patterns of essential components of the reninangiotensin system (RAS) in the brain (Mao *et al.*, 2009a). It is well accepted that RAS is both a circulating and tissue/organ specific hormonal system implicated in various physiological and pathophysiological processes *via* the major peptide angiotensin II (Ang II) stimulating its specific AT_1R and AT_2R, which demonstrate opposite effects in many conditions (Sokol *et al.*, 2004; Dasgupta and Zhang, 2011; Shi *et al.*, 2010). Both AT_1R and AT_2R are present in the brain with different expression patterns and signaling pathways during different developmental stages. Clinical trials and experimental studies indicate that RAS plays an important role in the development and progression of cerebrovascular diseases, but most of these studies were conducted in the mature brains. For example, clinical trials such as LIFE and MOSES have demonstrated that chronic blockade of RAS can offer neuroprotection with the prevention of first or recurrent stroke in high-risk populations, independent of its blood pressure-lowering effects (Lindholm *et al.*, 2002; Schrader *et al.*, 2005). Numerous studies have revealed that AT_1R antagonists exhibit anti-apoptotic, anti-inflammatory, anti-oxidant effects and improve cerebral perfusion, demonstrating vascular-dependent and -independent neuroprotection in acute stroke (Ando *et al.*, 2004; Dai *et al.*, 1999; Lou *et al.*, 2004; Zhou *et al.*, 2005). Less is known about the role of AT_2R in neurological pathophysiology. Emerging evidence indicates that AT_2R also confers beneficial effects in a variety of pathologies including various neurological disorders. Some studies reported that AT_2R was up-regulated in stroke, particularly in the ischemic area of the brain, implying its potential role in neuroprotection (Mogi *et al.*, 2006). Increased activation of AT_2R may be responsible for some neuroprotective effects of AT_1R antagonism (Li *et al.*, 2005). *In vitro* stimulation of AT_2R promotes intense neurite outgrowth, which can be antagonized by PD123319 (Laflamme *et al.*, 1996). Moreover, McCarthy et al. (2009) demonstrated centrally direct stimulation of AT_2R with CGP42112 conferred a neuroprotective role in a conscious rat model of stroke, which was beyond blood pressure regulation. The underlying mechanisms of AT_2R in neuroprotection remain to be elucidated. Some studies indicated that it may be related to its complicated interaction with

AT_1R in apoptotic modulation, neuronal regeneration and vasodilation in ischemic regions following stroke (Jones *et al.*, 2008; Saavedra *et al.*, 2006). Stressful stimuli in pre- or perinatal developmental stages may reprogram the expression patterns of AT_1R and AT_2R in vital organs such as the heart, vasculatures, kidney and brain, contributing to later pathologies. Such programming effects may be glucocorticoids dependent and sometimes with sex diversity and involve complex epigenetic mechanisms. For example, nicotine exposure alters expression patterns of AT_1R and AT_2R in the kidney and vessels, and enhances vascular response to vasoconstrictors, which maybe contribute to development of hypertension in adulthood (Mao *et al.*, 2009a, b; Xiao *et al.*, 2007, 2008, 2011). In addition, maternal hypoxia during gestation can downregulate glucocorticoid receptors in the heart of fetuses and offspring and decrease GR binding to the GREs at the AT_2R promoter region, resulting in increased expression of AT_2R and heightened cardiac susceptibility to ischemicreperfusion injury in adult offspring (Xue *et al.*, 2011). Our recent preliminary studies have shown the neuroprotective effects of stimulation of AT_2R in the brain by intracerebroventricular injection of its selective agonist and antagonist in postnatal 10 day rat pups with HIE. More importantly, we have revealed that perinatal nicotine exposure significantly affects expression patterns of AT_2R in postnatal 10 day neonatal brain in a sex-dependent manner, suppression in male pups and upregulation in female pups, which closely parallels to the exaggerated brain HI-induced infarction size in male pups in nicotine-treated animals. This sex-dependent difference of heightened brain HI injury in neonate rats induced by nicotine can be reversed by intracerebroventricular administration of AT_2R agonist or antagonist, which further confirms a key role of AT_2R in fetal stress-mediated programming of ischemic-sensitive phenotype in the neonatal brain and suggests a novel mechanism in heightened vulnerability of HIE in neonates. Interestingly, similar findings were obtained in a rat model of fetal hypoxia, showing that prenatal hypoxic stress also enhanced HI-induced infarction size in neonatal pups of HIE model, which was accompanied by significant alteration of expression patterns of AT_1R and AT_2R in the brain. These studies suggest a common mechanism of Ang II receptors in programming of the vulnerability of neonatal HIE.

Another promising candidate mediator with potential role in heightened vulnerability of neonatal HIE is glucocorticoids, either cortisol or corticosterone. As discussed above, glucocorticoids exert profound effects on the programming of fetal stress and brain development, particularly their programming effects on the HPA axis activity as well as other important organs and tissues. Sustained overexposure to glucocorticoids down-regulates GR levels in hippocampus, attenuates negative feedback of the HPA axis, permanently resets the activity of HPA axis and enhances basal and stressful glucocorticoids responses in the postnatal life. These will cause the brain to be exposed to chronically high level of glucocorticoids, resulting in aberrant gene regulation and cell behavior and programming of vulnerability of HIE injury. Paradoxically, glucocorticoids show bidirectional effects on the brain, which may be implicated in both neurodegenerative and neuroprotective processes (Abraham *et al.*, 2001). On the one hand, glucocorticoids may inhibit key nutrients such as glucose uptake, modulate both excitatory and inhibitory neurotransmission, increase intracellular calcium concentrations, enhance excitotoxicity and induce perturbation of 11β-HSD, which may retard fetal brain growth, delay myelination, promote synapse degeneration and enhance neuronal vulnerability to hypoxic/ischemic insults (Abraham *et al.*, 1996; Doyle *et al.*, 1993; Joels and de Kloet, 1994; Moghaddam *et al.*, 1994; Seckl and Walker, 2001). On the other hand, some studies indicate *via* modulating calcium currents, increasing synthesis of neurotrophic factors, such as lipocortin-1, basic fibroblast growth factor (bFGF), nerve growth factor (NGF), and decreasing lipid peroxidation, glucocorticoids may be neuroprotective (Flower and Rothwell, 1994; Joels and de Kloet, 1994; Mocchetti *et al.*, 1996; Young and Flamm, 1982). There are experimental findings suggesting that glucocorticoids affect the vulnerability of fetal and neonatal brain to

hypoxiaischemia challenge. However, the results were inconsistent, contradictory, and dependent on experimental protocol, dosage, time, animal age, strains and species (Flavin, 1996; Kauffman *et al.*, 1994; Tombaugh *et al.*, 1992; Tuor, 1995, 1997; Whitelaw and Thoresen, 2000). It appears that the concentration and duration of glucocorticoids treatment are the two key factors determining the detrimental or beneficial effects of glucocorticoids in the brain. Exposure to long-term and high levels of glucocorticoids enhances neurotoxic effects in brain injury, such as in HIE, whereas physiological or slightly higher (slightly supraphysiological elevated levels in a narrow concentration window) levels of glucocorticoids may confer on the brain protective potential to challenges (Abraham *et al.*, 2001). Although there are some controversial reports in the literature, the notion has been widely accepted that overexposure to glucocorticoids enhances neuronal degeneration (Abraham *et al.*, 2001). Given that most prenatal stress increases both basal and stressful glucocorticoids levels in offspring mainly *via* reprogramming of the HPA axis, which may contribute to enhanced vulnerability of neonatal HIE and other challenges, it is plausible that glucocorticoid itself may be a pivotal mediator in such pathophysiological processes. However, such effects may be variable depending on the duration, timing, severity and types of prenatal stresses.

Fetal stress may also reprogram expression patterns of matrix metalloproteinases (MMPs) in the neonatal brain, which contribute to the enhanced vulnerability of HIE. MMPs belong to a family of zinc-dependent proteases that exert pronounced effects in the ECM turnover. These enzymes remodel almost all components of the matrix and play an essential role in cell signaling regulation, cell survival and cell death. MMPs, especially MMP-2, MMP-3 and MMP-9, may target the extracellular matrix of blood vessels, basal lamina, and tight junctions in endothelial cells, increase the permeability of the blood-brain barrier in neuroinflammation due to hypoxiaischemia, multiple sclerosis and CNS infection, which can result in cytotoxic and vasogenic edema, promote hemorrhagic transformation, induce apoptosis of neurons and oligodendrocytes (Cunningham *et al.*, 2005; Rosenberg, 2009). However, in later stage of such pathology, MMPs play critical roles in tissue repair and remodeling process *via* inducing angiogenesis and neurogenesis. Growing evidence suggests that overly upregulated activity/expression of MMPs, particularly MMP-2 and MMP-9, are deleterious in the acute phase of stroke. Inhibition of MMPs in the acute phase may reduce the damage to BBB (Gasche *et al.*, 2001). There is a report indicating decreased damage to BBB and reduced infarct size in a focal ischemic MMP-9 knockout model (Asahi *et al.*, 2001). More importantly, a recent study in a neonatal rat HIE model revealed that early inhibition of MMPs conferred acute and long term beneficial effects *via* reducing tight junction proteins degradation, attenuating the permeability of BBB, improving brain edema, and preventing brain atrophy (Chen *et al.*, 2009a). Fetal hypoxia reprograms expression patterns of MMPs in the heart and brain and increases activities/expressions of both MMP-2 and MMP-9 in the neonatal brain (Tong *et al.*, 2010, 2011; Tong and Zhang, 2011). Considering the evident detrimental effects of MMPs in the acute stroke models and other neurological pathophysiologies, it is plausible that altered expression patterns of MMPs by prenatal stress is another important mediator in programming of ischemic-sensitive phenotype and increased susceptibility of HIE in the neonatal brain.

Hypoxia inducible factor-1 (HIF-1), a key regulator in response to cellular hypoxia and oxygen homeostasis (Wang *et al.*, 1995), may be profoundly involved in the programming effects of prenatal stress on the vulnerability to neonatal HIE. Being a heterodimeric transcription factor, HIF-1 consists of an oxygen-sensitive HIF-1α and a constitutively expressed HIF-1β. The normal oxygen level results in a rapid degradation of HIF-1α, but hypoxia can enhance the stability of HIF-1α and promote the transactivation of its target genes. More than 100 HIF-1α targeted genes have been identified up to now, including erythropoiesis (EPO), angiogenesis (VEGF), cell proliferation (IGF-2), glucose metabolism

(Glut-1,3), inflammation (COX-2), cell apoptosis (BNIP3, P53), vascular tone and matrix metabolism, etc. (Ke and Costa, 2006). Based on its regulation of a wide spectrum of genes in diverse contexts, the effects of HIF-1α activation may be very complex and variable, to some extent similar to those of glucocorticoids. During brain challenges, such as in hypoxia-ischemia, HIF-1α may be both anti-apoptotic *via* enhancing the transcription of EPO, VEGF, IGF-2 and GLUT-1, etc., but it also can be pro-apoptotic by upregulation of factors such as COX-2, BNIP3 and P53 that contribute to cell death (Chen *et al.*, 2009b; Fan *et al.*, 2009). Notably, VEGF promotes the permeability of BBB and enhances brain edema in the acute phase of HI, which is different from its later beneficial effects such as neovascularization (Chen *et al.*, 2009b). The bidirectional effects of HIF-1α in hypoxia may be affected by some factors, such as the duration and severity of hypoxia, and the type of pathological stimuli. Mild hypoxia may predominantly induce anti-apoptotic gene expression, but more sustained and severe hypoxia promotes pro-apoptotic gene expression (Chen *et al.*, 2009b; Fan *et al.*, 2009). In addition, effects of HIF-1α in HI may be cell type specific. In vitro studies suggest that functional loss of HIF-1α may be neuroprotective for astrocyte but enhances neuronal vulnerability to HI injury (Vangeison *et al.*, 2008). Under normal conditions, HIF-1α is essential for normal fetal brain development *via* the activation of genes such as VEGF because of the relatively lower physiological oxygen level in uterus (Fan *et al.*, 2009; Lee *et al.*, 2001; Trollmann and Gassmann, 2009). In addition to maternal hypoxia, some other prenatal stresses, such as nicotine, cocaine, and ethanol exposure, may also trigger the release of catecholamines, resulting in various degrees of ischemia/hypoxia insult to the fetus and leading to a sustained or episodic upregulation of HIF-1α. Long-term and supraphysiological high levels of HIF-1α in the fetus, combined with its adverse impacts on the developing brain, may persist into the postnatal developmental stage and enhance the vulnerability of neonatal HIE injury.

There are some studies indicating that aberrant development of the monoaminergic system in specific brain regions and/or peripheral organs such as the heart and adrenals also weakens the tolerance to hypoxia/ischemia insults in neonates. It is well recognized that prenatal nicotine exposure is a major risk factor for SIDS in which defective arousal and cardiorespiratory response adjustment are considered to be the potential mechanisms (Milerad and Sundell, 1993; Slotkin, 1998; Wickstrom, 2007). Prenatal nicotine exposure exerts negative effects on the development of central and peripheral catecholaminergic system by decreasing synthesizing enzymes and reducing synthesis and release of catecholamines in brainstem nucleus, adrenals and heart, which may particularly impact the crucial defensive response to acute stress including hypoxia/ischemia and enhance the vulnerability of neonatal HIE (Slotkin *et al.*, 1987; Wickstrom *et al.*, 2002). These detrimental effects in defensive responses appear to correlate with functional loss of some subtypes of nAChRs *via* activity-dependent desensitization (Cohen *et al.*, 2002). A recent study in rhesus monkey also reported that prenatal nicotine exposure compromises the brainstem serotonergic pathways, another important neural structure implicated in autonomic function, arousal and cardiorespiratory responses to acute hypoxic/ischemic challenge (Slotkin *et al.*, 2011).

Evidently, the impacts of prenatal stress on fetal and neonatal brain development are very complicated, dynamic, variable and multifaceted, which may also be subtle or drastic, and are profoundly affected by exposure age, duration, protocol, severity and nature of stress stimuli, and genetic traits. The underlying mechanisms of neonatal HIE remain to be further elucidated. In addition to the common potential mediators mentioned above, there are other possible factors that may be involved in programming of the vulnerability of neonatal HIE under different types of prenatal stressor. For example, the decreased expression of some neurotrophic factors, such as BDNF; perturbation of neurotransmitters and their receptors, such as glutamate, GABA and NMDA; enhanced oxidative stress; dysfunction of

mitochondria; and inflammatory factors, may all act as potential mediators to alter the vulnerability of HIE in the neonatal brain (Archer, 2011; Levitt, 1998; Warner and Ozanne, 2010).

Another factor deserving consideration is the methodologies employed to assess the vulnerability of neonatal HIE. As discussed above, the effects may be varied greatly depending on the methods used. Some changes may be significant enough so that some preliminary methods can reveal the underlying differences, such as quantification of infarction size by TTC staining, brain water content measurement and BBB permeability detection. However, some changes may be so subtle that we may readily deny their existence. In such conditions, more sensitive and challenging methods must be explored and employed, such as histological techniques; neurobehavioral, psychological and psychiatric assessments; and long-term structural and functional evaluations, to reveal or reject the distinction.

5. Potential intervention targets

Trying to avoid potential stress stimuli during pregnancy is essential for effectively preventing or ameliorating the adverse programming effects on fetal development. Quitting use of ethanol, cocaine and nicotine should be encouraged, which can be further supported by behavioral modifications and counseling strategies. Owing to the lack of solid evidence of its efficacy and safety, NRT should not be readily recommended to pregnant women until carefully weighing its potentially adverse effects on the fetus (Pauly and Slotkin, 2008; Slotkin, 1998). For pregnant women who are strongly indicated for glucocorticoids therapy, the selection of glucocorticoids and administration protocol are vital. Normally, 11β-HSD2 sensitive glucocorticoids should be favored and betamethasone may be preferred to dexamethasone, and low dosage administration and fewer times of injection may be more beneficial to the fetus based on available clinical studies (Gulino *et al.*, 2009; Heine and Rowitch, 2009; Whitelaw and Thoresen, 2000). It is also important to treat underlying systemic diseases to prevent or attenuate possible placental insufficiency and fetal ischemia/hypoxia and to improve maternal nutrition status with an optimal balanced diet supplying nutrients including various macro and/or micro nutrients when necessary.

A wide variety of emerging evidence has suggested that epigenetic modifications of gene expression patterns exhibit a central role in fetal stress-mediated programming of neurological and cardiometabolic disorders in later life. Predictably, pharmacological manipulations of epigenetic mechanisms present a promising interventional strategy. Indeed, several experimental studies offered exciting results. As mentioned above, programming of the HPA axis provides an important common pathway for the alteration of vulnerability to various pathophysiologies in later life in which epigenetic modification of GR gene expression patterns in hippocampus plays a critical role. Animal studies conducted in high or low maternal LG offspring have revealed that central infusion of a HDAC inhibitor, trichostatin A (TSA) or methyl donor S-adenosylmethionine (SAM), can reverse the epigenetic modification status in GR promoter region, rescue the binding capacity of NGFI-A to exon 1_7 region, recover GR expression in hippocampus, restore the HPA axis activity, and reverse the increased vulnerability of neurological dysfunction in later life (Weaver *et al.*, 2004; Weaver *et al.*, 2005). More importantly, these studies imply that it is still reversible for some gene expression controlled by lasting epigenetic modifications, and enriching postnatal environment, or providing pharmacological interventions may restore long-term aberrant programming effects. In addition to HDAC inhibitors and DNA methylation inhibitors, other agents, such as plant-derived isoflavone genistein, leptin, folate, fish oil, omega-3 and vitamin D, can alter the corresponding abnormal epigenetic modification status and improve the adverse programming effects caused by prenatal stress

(Gregorio *et al.*, 2008; Hypponen *et al.*, 2007; Torrens *et al.*, 2006; Vickers *et al.*, 2008; Wyrwoll *et al.*, 2007). However, up to now, most of epigenetic therapy compounds exert nonspecific modifications on genes and transposable elements, and thus their adverse effects should not be neglected, including inducing or inhibiting other non-responsible genes expression, the potential tumorigenesis and mutagenesis properties, as well as promoting cell-cycle arrest and apoptosis (Karpf *et al.*, 2001; Laird *et al.*, 1995). In general, current epigenetic therapy is still in its infancy.

For the neonates at risk of HIE or already harmed by HIE, prevention and therapy are complex and somewhat frustrating. Timely diagnosis and therapy are crucial but are also very challenging, which greatly affects the final outcomes. If possible, various available clinical techniques, such as advanced neuroimaging, EEG, some reliable biomarkers of brain damage (e.g., S-100, NSE), should be employed to identify and monitor HIE injury in a timely manner (Perlman, 2006; Rees *et al.*, 2011). Despite apparent limitations, moderate hypothermia is the only currently established available therapy for full-term newborns with mild to moderate HIE. A wealth of animal studies have conferred some promising interventional strategies, such as NMDA receptor blockade, NOS inhibition, prevention of apoptosis and free radical formation, administration of neurotrophic factors and growth factors, AT_2 receptor stimulation, as well as early inhibition of MMPs and HIF-1α, all of which should enrich our understanding of HIE pathophysiology and provide us with more potentially promising therapeutic options (Chen *et al.*, 2009a; Chen *et al.*, 2009b; Perlman, 2006; Rees *et al.*, 2011).

6. Conclusions and perspectives

Both human and animal studies have supported the notion of developmental origins of adult health and disease. Prenatal stress including hypoxia, malnutrition, nicotine, cocaine, ethanol and glucocorticords exerts great impacts on the fetus during the vulnerable developmental stage at multifaceted levels, resulting in adverse programming of ischemic-sensitive phenotype in the developing brain and heightened vulnerability of neonatal hypoxicischemic encephalopathy and long-term neurodevelopmental disorders, in addition to cardiovascular and metabolic diseases in later life. All of these fetal stress insults, individually and/or combined, act at cellular and molecular levels to alter normal brain cell behavior and specific cerebral structure, reconstruct the HPA axis, and disturb vital neurotransmissions, which in the end, to various extents, change normal brain development trajectory and enhance the susceptibility of neonatal HIE and long-term neurological disorders. Although there are diverse stress stimuli, strong evidence has suggested that reprogramming of the HPA axis by glucocorticoids may at least in part represent a common underlying pathway, and epigenetic modifications of GR gene expression patterns play a key role in such a process. This provides us with the promising interventional targets although epigenetic pharmacological manipulation is just at the beginning and is mainly tested in animal studies. To protect pregnant mothers from harmful stress exposure is still a critical interventional strategy, which may at least prevent or attenuate the brain injury of HIE in some cases. Because of current deficiency in potent and effective therapy, the prognosis and outcome for most neonatal HIE are less than optimal at the best, which makes further exploration and investigation of pathophysiology and underlying mechanisms for the heightened neonatal HIE in various species of animals and humans particularly urgent. The combination of limited successful diagnostic and therapeutic techniques currently available, plus newly emerged knowledge of fetal programming and potential epigenetic manipulations, as well as improved maternal care and active perinatal intervention strategies, may confer us a further hopeful future in the management of such a catastrophic disease of neonatal HIE.

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List of Abbreviations

ABC	ATP-binding cassette
ACC	anterior cingulated cortex
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotropic hormone
ADHD	attention-deficit/hyperactivity disorder
Ang II	angiotensin II
AP-1	activator protein 1
AP2B1	adaptor-related protein complex 2, beta 1 subunit
Arp1,2,3	actin-related protein 1,2,3 homolog B
AT_1R	angiotensin II type 1 receptor
AT_2R	angiotensin II type 2 receptor
Bax	Bcl-2–associated X protein
BBB	blood brain barrier
Bcl-2	B-cell lymphoma 2
Bcs1L	cytochrome b-c1 complex subunit Rieske
BDNF	brain derived neurotrophic factor
bFGF	basic fibroblast growth factor
BNIP3	Bcl-2/adenovirus E1B 19-kDa protein-interacting protein 3
BPA	Bisphenol A
CA1,2,3,4	Cornu Ammonis 1,2,3,4
CAH	congenital adrenal hyperplasia
CAT	catalase
CBF	cerebral blood flow
CBG	corticosteroid-binding globulin
CD	conduct disorder
CHN1	chimerin 1
CLTB	clathrin light polypeptide
CNS	central nervous system
COX-2	cyclooxygenase 2
CpG	cyotsinephosphodiester bond-guanine
CRH	corticotropin-releasing hormone

CX3CL1	chemokine (CX3-C motif) ligand 1
CYP2E1	cytochrome P450 2E1
DA	dopamine
DG	dentate gyrus
DHA	decosahexaenoic acid
DNCIC1	dynein cytoplasmic intermediate chain 1
DNCLC1	dynein cytoplasmic light chain 1
DNMT	DNA methyl transferase
ECM	extracellular matrix
ED	embryonic day
EEG	electroencephalograph
E2f	E2F transcription factor
Egr 1	early growth response protein 1
EPO	erythropoietin
FAS	fetal alcohol syndrome
FASD	fetal alcohol spectrum disorders
FIRS	fetal inflammatory response syndrome
GABA	gamma amino butyric acid
Glut1,3	glucose transporter 1, 3
GPM6A	glycoprotein M6A
GR	glucocorticoids receptor
GREs	glucocorticoids response elements
GSH	glutathione
GSSG	glutathione disulfide
HAFP	human alpha-fetoprotein
HDAC	histone deacetylase
HIE	hypoxic-ischemic encephalopathy
HIF-1	hypoxia inducible factor 1
HIF-1α	hypoxia inducible factor 1 α subunit
HIF-1β	hypoxia inducible factor 1 β subunit
HPA	hypothalamic-pituitary-adrenal
HPTM	histone posttranslational modifications
11β-HSD1	11-beta-hydroxysteroid dehydrogenase type-1
11β-HSD2	11-beta-hydroxysteroid dehydrogenase type-2
ICAM5	intercellular adhesion molecule 5
IGF-2	insulin-like growth factor 2

IL-6	interlukin-6
IUGR	intrauterine growth restriction
KIF5C	kinesin family member 5C
LAMP	limbic system-associated membrane protein
LG	licking and grooming
LIFE	the losartan intervention for endpoint reduction in hypertension study
LIMK1	LIM domain kinase 1
LIS1	lissencephaly
MAO-A	monoamine oxidase A
MAP1B	microtubule-associated protein 1B
MAP2	microtubule-associated protein 2
MAPKK1	mitogen-activated protein kinase kinase 1
MDD	methyl donor diet
MDR P-glycoproteins	multidrug-resistant P-glycoproteins
miRNA	microRNA
MMPs	matrix metalloproteinases
MOSES	the morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention study
MPF	medial prefrontal cortex
MPR	Maternal protein restriction
MR	mineralocorticoid receptor
nAChR	nicotinic acetylcholine receptor
Nduf8	NADH dehydrogenase ubiquinol iron-sulphur protein
NEFL	neurofilament light polypeptide
NGF	nerve growth factor
NGFI-A	nerve growth factor-induced protein A
NMDA	n-methyl-d-aspartic acid
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NRT	nicotine replacement therapy
NRXN3	neurexin 3
NSE	neuron specific enolase
OBCAM	opioid binding protein/cell adhesion molecule-like
P53	protein 53 or tumor protein 53
PAE	prenatal alcohol exposure

PCLO	piccolo (presynaptic cytomatrix protein)
Pdx1	pancreatic and duodenal homeobox 1
PKC$_\varepsilon$	protein kinase C epsilon
PLA$_2$	Phospholipase A2
POMC	proopiomelanocortin
Prdx3	thioredoxin-dependent peroxide reductase
PTSD	post-traumatic stress disorder
PVN	paraventricular nucleus
RAS	renin-angiotensin system
ROS	reactive oxygen species
S-100	s-100 protein
SAM	S-adenosyl-methionine
SC1 (=ALCAM)	activated leukocyte cell adhesion molecule
SIDS	sudden infant death syndrome
SNAP25	synaptosomal-associated protein 25
SOD	superoxide dismutase
SP1	specificity protein 1
SYT1	synaptotagmin 1
SYT4	synaptotagmin 4
TCP1	T-complex protein 1
T2DM	type 2 diabetes mellitus
TNF-α	tumor necrosis factor alpha
TSA	trichostatin A
TTC	triphenyltetrazolium chloride
TUBB2	beta-tubulin 2
USF1	upstream stimulatory factor 1
VEGF	vascular endothelial growth factor

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Highlights

- Fetal stress reprograms vulnerability to disease later in life.
- Fetal stress acts at cellular and molecular levels to impact brain development.
- Glucocorticoids programming is one of common pathways in such process.
- Epigenetic modification plays crucial roles in programming actions.
- Fetal stress enhances vulnerability to neonatal hypoxic-ischemic encephalopathy.

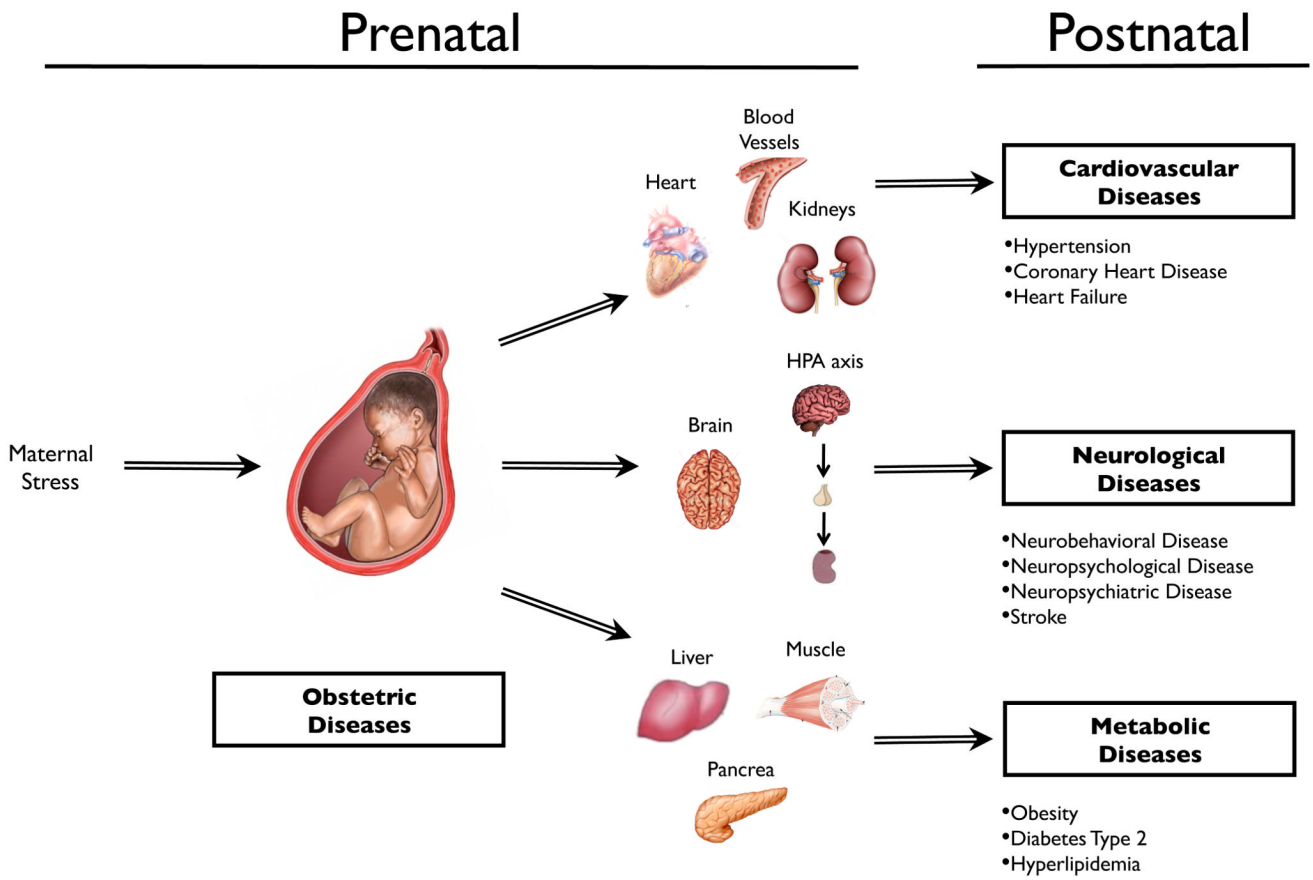

Figure 1. Developmental programming of health and disease

Maternal stress impacts normal fetal tissues/organs development and increases the risk of development of cardiovascular, metabolic syndrome, stroke and various neurobehavioral, neuropsychological, neuropsychiatric diseases later in life. HPA, hypothalamic-pituitary-adrenal

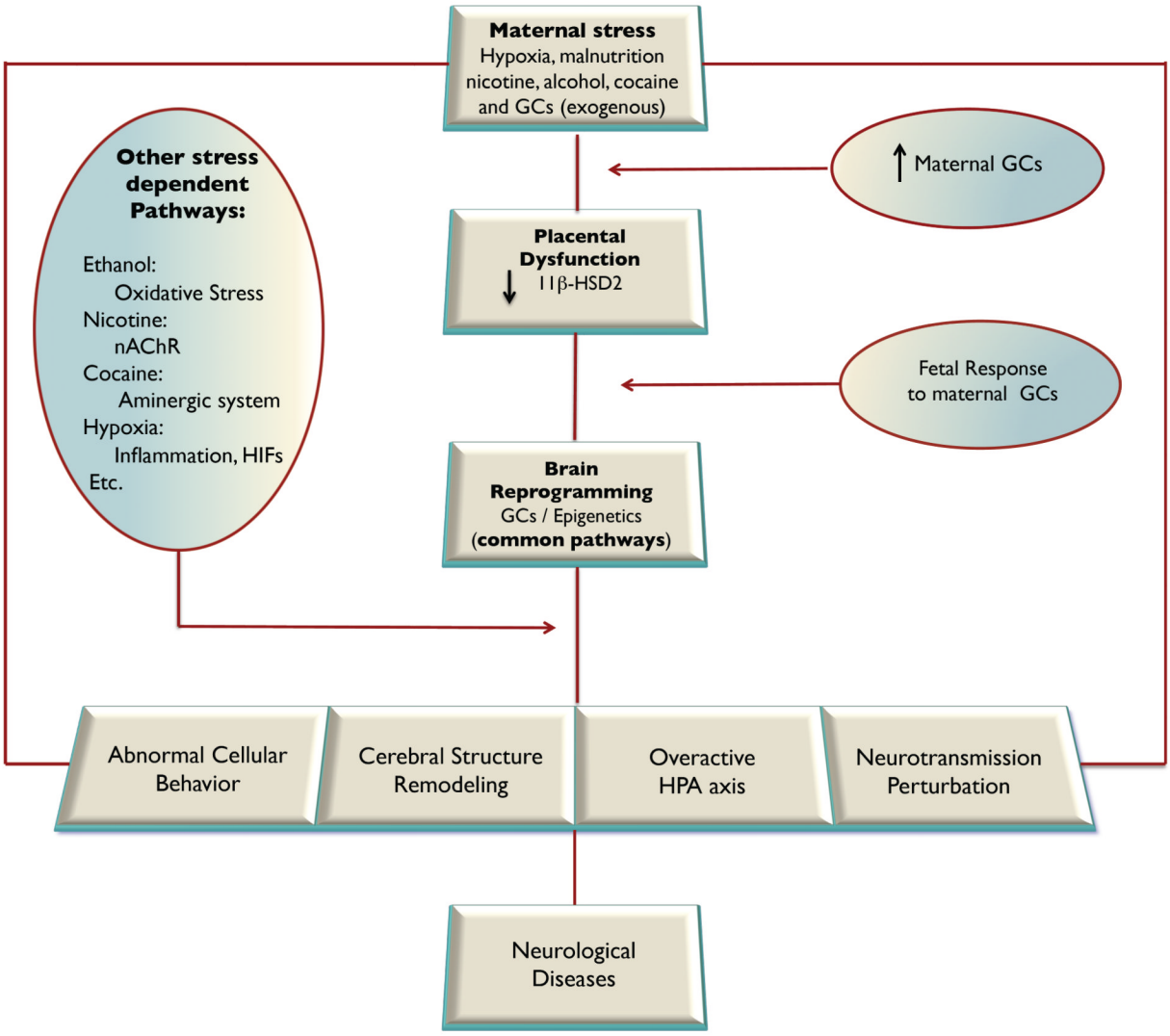

Figure 2. Mechanisms of developmental programming of neurological diseases

Prenatal stress changes normal brain developmental trajectory, alters brain cellular behavior, remodels cerebral structure and morphology, reconstructs the HPA axis activity, disturbs neurotransmission, and reprograms the vulnerability or resiliency to neurological diseases in later life, of which epigenetic modifications of glucocorticoid receptors (GCs) gene expression patterns may represent as a common pathway in response to different adverse intrauterine stimuli. 11β-HSD2, 11-beta-hydroxysteroid dehydrogenase type-2; HIFs, hypoxia inducible factors; HPA, hypothalamic-pituitary-adrenal; nAChR, nicotinic acetylcholine receptor.

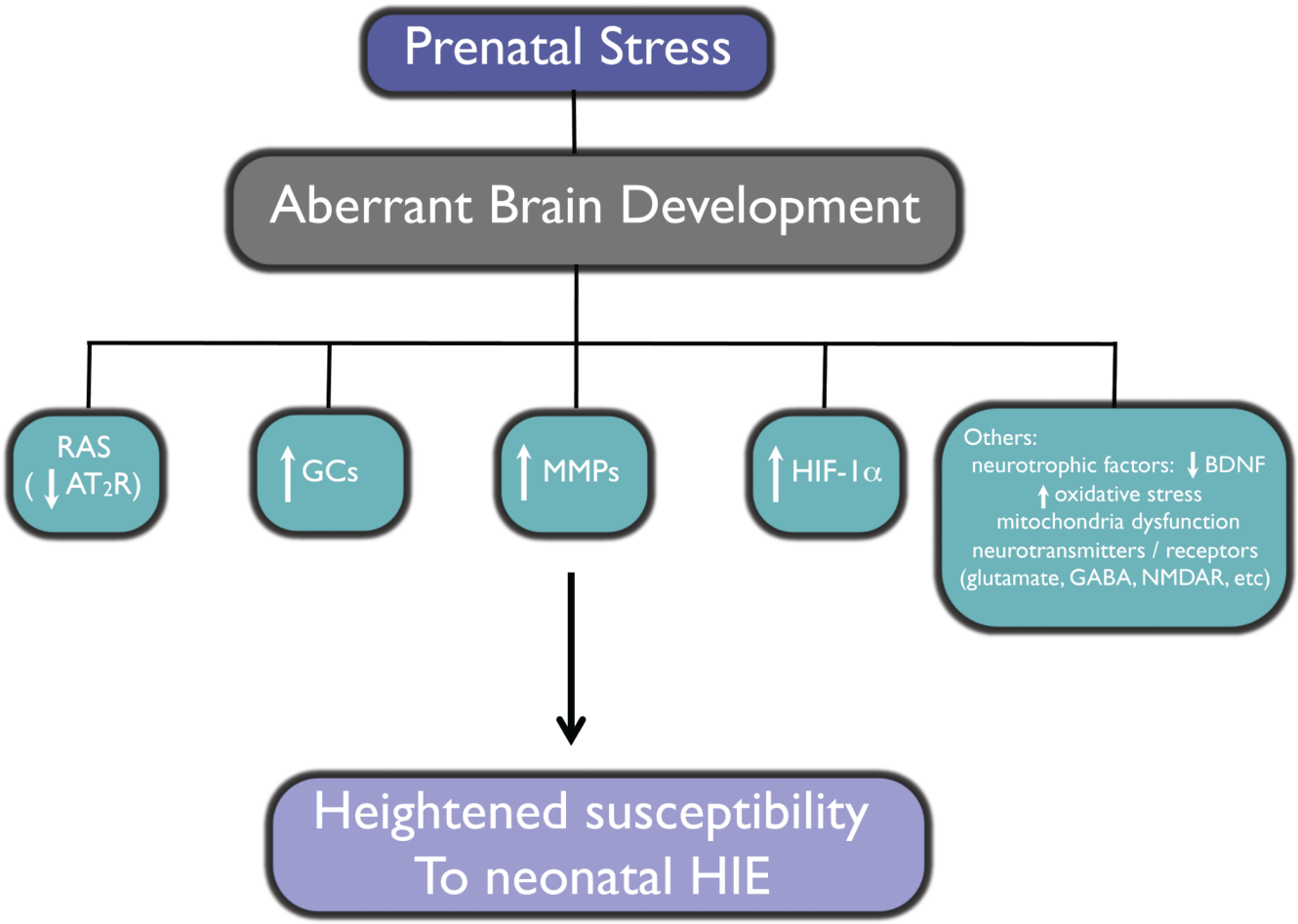

Figure 3. Potential mechanisms in programming of neonatal HIE phenotype

Prenatal stress induces aberrant brain development, reprograms expression patterns of key functional mediators associated with pathophysiology of neonatal HIE, including RAS (AT_2R), GCs, MMPs, HIF-1α, BDNF, glutamate, GABA, NMDA-R, etc., which contribute to the heightened susceptibility of neonatal HIE. The response of these mediators may be stress-specific. AT_2R, angiotensin II type 2 receptor; BDNF, brain derived neurotrophic factor; GABA, gamma amino butyric acid; GCs, glucocorticoid receptors; HIE, hypoxic-ischemic encephalopathy; HIF-1α, hypoxia inducible factor 1α subunit; MMPs, matrix metalloproteinases; NMDAR, n-methyl-d-aspartic acid receptor; RAS, renin-angiotensin system.