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Review Article

Maternal Influences on Epigenetic Programming of the Developing Hypothalamic-Pituitary-Adrenal Axis

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Parental and environmental factors during the prenatal and postnatal periods permanently affect the physiology and metabolism of offspring, potentially increasing disease risk later in life. Underlying mechanisms are being elucidated, and effects on a number of organs and metabolic pathways are likely involved. In this review, we consider effects on the developing hypothalamic-pituitary-adrenal (HPA) axis, which may represent a common pathway for developmental programming. The focus is on prenatal and early postnatal development, during which the HPA axis may be programmed in a manner that affects health for a lifetime. Programming of the HPA axis involves, at least in part, epigenetic remodeling of chromatin, leading to alterations in the expression of genes in many organs and tissues involved in HPA activation and response, including the hippocampus and peripheral tissues. Examples of developmental epigenetic modifications affecting the HPA axis as well as target tissues are provided. *Birth Defects Research (Part A) 91:797–805, 2011.* Published 2011 by Wiley-Liss, Inc.†

Key words: hypothalamus; pituitary; adrenal; epigenetics; programming

INTRODUCTION

In the past two decades, it has become increasingly clear that parental and environmental factors during the preconception to early postnatal periods have influences on the physiology and metabolism of offspring that can manifest as adverse health outcomes at any point later in life (Gluckman et al., 2007; Gluckman et al., 2008). Indeed, such changes may have consequences that extend to subsequent generations. This concept has been called the Developmental Origins of Health and Disease (DOHaD) hypothesis, and the mechanisms through which the developmental environment can alter risks of diseases such as coronary heart disease, diabetes, hypertension, obesity, and cancer later in life are beginning to be elucidated. Parental nutrition is of key importance; maternal undernutrition, overnutrition, and malnutrition have all been associated with elevated morbidity of offspring in humans and animal models. Maternal obesity and diabetes have likewise been associated with such elevated risks, as has maternal smoking. Effects on a number of organs and metabolic pathways are probably involved.

In this chapter, after providing a brief background on the DOHaD concept, we consider how environmental factors affect the developing hippocampus and hypothalamic-pituitary-adrenal (HPA) axis, which may represent a common pathway for developmental programming. The HPA axis, also called the stress axis, is an endocrine system that responds rapidly to changes in the environment throughout life. In this review, we will concentrate on prenatal and early postnatal development, during which the HPA axis may be programmed

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in a much longer-term fashion, one that can affect health throughout life. Long-term programming of the HPA axis involves, at least in part, epigenetic remodeling of the chromatin in such a way as to alter the expression of genes related to HPA activity and target tissue response. Examples of developmental epigenetic modifications affecting the HPA axis are provided.

BACKGROUND

Human Studies

David Barker and colleagues discovered in multiple populations that birth weight in humans correlated inversely with later risk of coronary heart disease, diabetes, and hypertension in adulthood (reviewed in Barker and Martyn, 1992; Hales and Barker, 1992; Osmond and Barker, 2000; Barker, 2004). Developmental programming of adult disease in humans has now been studied widely in the context of diverse adverse exposures. The Dutch famine of 1944–1945 has been studied by several groups. During the famine, some mothers received <1000 calories/day, resulting in low birth weight infants that as adults demonstrated elevated risk of glucose intolerance, altered lipid profile, coronary heart disease, stress sensitivity, and obesity (de Rooij et al., 2006; Painter et al., 2006; Roseboom et al., 2006; Lumey et al., 2009). Obese pregnant women themselves are at increased risk of being hypertensive, hyperinsulinemic, and dyslipidemic (Ramsay et al., 2002). Infants born to obese mothers have increased neonatal fat mass, elevated umbilical cord glucose and insulin concentrations, and evidence of in utero insulin resistance (Catalano et al., 2009). As adults, these children are more likely to be obese (Koupil and Toivanen, 2008) and have an elevated risk of cardiovascular disease (Forsen et al., 1997).

Maternal diabetes has similar effects on programming and is closely associated with maternal obesity (Yogev and Visser, 2009). Glucose intolerance was impaired in adolescents (Silverman et al., 1995), and arterial blood pressure (Silverman et al., 1991) and body mass index (BMI) (Silverman et al., 1995; Silverman et al., 1998) were increased later in life in offspring of diabetic mothers. Children of type 1 diabetic mothers have increased cholesterol levels, increased cholesterol/high-density lipoprotein ratios, and increased inflammatory markers, suggesting an increased risk for metabolic and cardiovascular disease in later life (Manderson et al., 2002). In addition, they have increased BMI, skin-fold thickness, and waist circumference (Lindsay et al., 2010).

Maternal smoking has been shown to reduce birth weight and may be involved in fetal programming (Misra et al., 2005; Rogers, 2008). Children born to mothers who smoke have increased incidence of diabetes (Montgomery and Ekbom, 2002), are overweight, have increased BMI (Somm et al., 2009 for review) and are at an increased risk of hypertension. These children also have an increased heart rate and blood pressure after mild stress during sleep (Cohen et al., 2010). Interestingly, increased umbilical adrenocorticotropic hormone (ACTH), the pituitary factor for releasing cortisol from the adrenal, has also been observed, which may connect maternal smoking to effects on HPA programming (McDonald et al., 2006).

Animal Studies

Since the emergence of the Barker hypothesis, large and small animal models of intrauterine growth retardation (IUGR) have been used to study developmental programming. Experimental treatments include maternal undernutrition (food restriction), maternal malnutrition (restriction of one or more essential nutrients, low protein being the best studied), uterine artery ligation, and glucocorticoid (primarily dexamethasone [DEX]) exposure. Maternal undernutrition (Woodall et al., 1996), protein restriction (Langley and Jackson, 1994), iron restriction (Lewis et al., 2001; Gambling et al., 2003), and uterine ligation (Jansson and Lambert, 1999) increase offspring blood pressure later in life. Other outcomes associated with these maternal treatments are altered insulin sensitivity (Ozanne et al., 1996; Sugden and Holness, 2002; Fernandez-Twinn et al., 2005), increased fat deposition (Bellinger et al., 2006), and impaired renal function (Woods et al., 2004). It is unclear whether fetal programming stems primarily from nutritional status or through endocrine alterations in the mother and fetus (or both) because prenatal glucocorticoid exposure produces metabolic effects similar to those seen in IUGR models (Benediktsson et al., 1993; Nyirenda et al., 1998; Sugden et al., 2001; Tamashiro et al., 2009).

THE HPA AXIS

Glucocorticoid Programming and the HPA Axis

Exposure to stress results in hypothalamic release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which travel through the portal circulation to the anterior pituitary to stimulate release of ACTH (Fig. 1, NORMAL). The cortex of the adrenal gland is stimulated by ACTH to produce glucocorticoids, including cortisol in humans and corticosterone (CORT) in rodents. Negative feedback at the levels of the pituitary, hypothalamus, and hippocampus, which contain glucocorticoid receptors (GR), dampens the stress response and prevents damaging effects of long-term glucocorticoid exposure. The hippocampus contains a high level of GR and has a major role in inhibiting the HPA axis through feedback inhibition by glucocorticoids (Vazquez, 1998 for review). Other components of the limbic system, including the amygdala, also contain GR and play a lesser role in inhibiting the HPA axis. Peripheral tissues including the kidney, liver, and lung contain GR and exhibit metabolic and physiologic responses to changes in circulating glucocorticoids. Variants of the GR exist in a tissue specific manner and are transcribed from a single gene with multiple promoters.

Effects of Maternal Stress

Studies in which laboratory animals were undernourished during pregnancy have demonstrated effects on developmental programming. It is unclear whether this is due to fetal nutrient restriction, excess exposure of the fetus to maternal corticosteroids, or a combination of these, because undernutrition can increase maternal and fetal glucocorticoid levels (Bloomfield et al., 2004; Nunez et al., 2008). Several experiments have used different prenatal stressors to demonstrate programming effects in the absence of dietary manipulation. Maternal stress induced by foot shocks during pregnancy in rats increases both

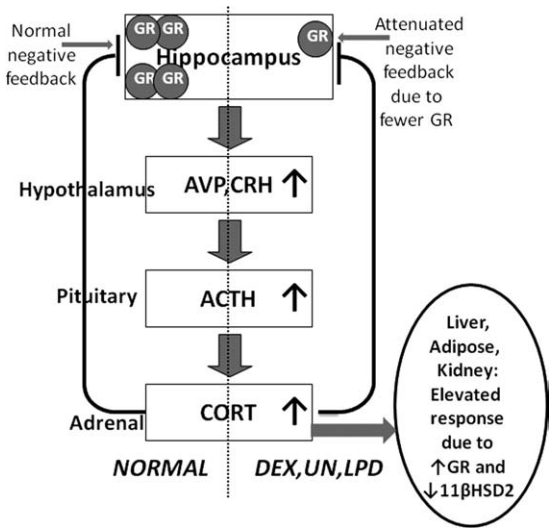

Figure 1. The offspring Hypothalamic-Pituitary-Adrenal (HPA) axis, under normal (left side) and stressed (dexamethasone [DEX] treatment, underfeeding [UN] or low-protein diet [LPD]) (right side) conditions. Under normal conditions, adrenal corticosteroids exert negative feedback on the hippocampus, which inhibits release of arginine vasopressin (AVP) and corticotrophin releasing hormone (CRH), thereby dampening the stress cascade. Abundant glucocorticoid receptors (GR) in the normal hippocampus mediate this negative feedback. In offspring of DEX-, UN-, or LPD-treated dams, GR in the hippocampus are fewer, attenuating the negative feedback response and prolonging the elevated release of and exposure to corticosteroids. The numbers of GR in the liver, kidney, and adipose tissue are increased, and activity of the enzyme 11βHSD2 decreased, in offspring of DEX-, UN-, or LPD-treated dams. Increased circulating CORT, increased GR and decreased 11βHSD2 activity can combine to enhance the glucocorticoid response in these tissues. (Adapted in part from Cottrell and Seckl, 2009).

ACTH and CORT in the fetus (Takahashi and Kalin, 1991). The serum CORT response after restraint stress in adult offspring of dams restrained during pregnancy declines more rapidly than in controls (Maccari et al., 2003), suggesting altered programming of stress reactivity. Animals prenatally exposed to maternal stress, high fat diet, or both were obese and showed impaired glucose tolerance as adults (Tamashiro et al., 2009). Further, induction of a systemic inflammatory response by IL-6 exposure during pregnancy increased maternal CORT and ACTH 4 hours after exposure; offspring were hypertensive and had altered stress reactivity as adults (Samuelsson et al., 2004).

In humans, maternal stressors such as daily hassles, trauma, or exposure to natural disasters are associated with elevated basal cortisol levels or cortisol responses to stress, as well as emotional or behavioral problems, reduced cognition, and risk of diseases such as autism and schizophrenia in their children, although long-term follow-up studies are few (O'Donnell et al., 2009 for review). Prenatal exposure to stress is also associated with lower intellectual ability in children, measured by poorer school grades (Niederhofer and Reiter, 2004) and lower scores on the Mental Scale of the Bayley Scale of Infant Development (Laplante et al., 2004). There is little evidence, however, that alteration of the HPA axis in the child is the cause of the neurobehavioral affects associated with maternal stress.

Deficits in behavior and cortical function have also been demonstrated in animal models. Prenatally stressed rats show depressive-like behaviors including increased immobility in the Porsolt swim test (Alonso et al., 1991; Frye and Wawrzycki, 2003) and increased anxiety in the elevated plus maze (Fride and Weinstock, 1988). Spatial learning deficits are also observed in adolescent mice (Bustamante et al., 2010) and adult rats (Hosseini-Sharifabad and Hadinedoushan, 2007; Wu et al., 2007) of prenatally restrained mothers.

Effects of Prenatal Exogenous Glucocorticoids

Maternal glucocorticoid administration has been used to examine long-term programming effects on offspring. The synthetic glucocorticoid DEX has been shown to reduce birth weight (Nyirenda et al., 1998) and cause adult hypertension in maternally exposed rat offspring (Benediktsson et al., 1993; Sugden et al., 2001). Basal CORT levels are elevated and hippocampal mineralocorticoid receptor (MR) and GR mRNA expression is reduced in adult rats prenatally exposed to DEX, suggesting that these receptors may be key in the programming effects (Levitt et al., 1996). In rhesus monkeys, offspring exposed to DEX prenatally have increased basal and stress-responsive cortisol levels (Uno et al., 1994). Rat dams treated with DEX or CORT early in pregnancy have offspring with reduced nephron endowment (Ortiz et al., 2001; Singh et al., 2007), which is associated with adult hypertension (Ortiz et al., 2003; Singh et al., 2007). Rat fetuses exposed to DEX during the third week of gestation were hyperglycemic, insulin resistant, and showed increased hepatic phosphoenolpyruvate carboxykinase (PEPCK, the enzyme that catalyzes the rate-limiting step in gluconeogenesis) as adults (Nyirenda et al., 1998). These findings were not due to differences in maternal care (Nyirenda et al., 2001). However, DEX-induced reduction in maternal food intake and body weight may also be associated with hypertensive programming effects (Woods and Weeks, 2005; Woods, 2006).

DEX administration in rats reduced social play in juvenile offspring, reduced acoustic startle reflex, increased acoustic startle prepulse inhibition, and increased locomotor activity after amphetamine challenge (Kleinhaus et al., 2010). Spatial learning deficits (Emgard et al., 2007) and anxiolytic behavior (Hossain et al., 2008) are observed in DEX-treated males during adulthood. CORT exposure in mice during the last week of gestation and throughout weaning also caused increased locomotor activity in the open field and depressive-like effects in the Porsolt swim test (Pechnick et al., 2006). Other studies found no DEX-induced reduction in pleasure, depression, or spatial learning deficits in offspring (Hauser et al., 2009), but, regardless of prenatal treatment, rats fostered to DEX-treated mothers had spatial learning deficits, suggesting that maternal care played a key role, because the DEX-treated mothers weighed less, ate more, and were more active outside the nest than controls (Brabham et al., 2000; Hauser et al., 2009).

Role of the Placenta

There are indications that glucocorticoid programming of offspring results from transplacental exposure to

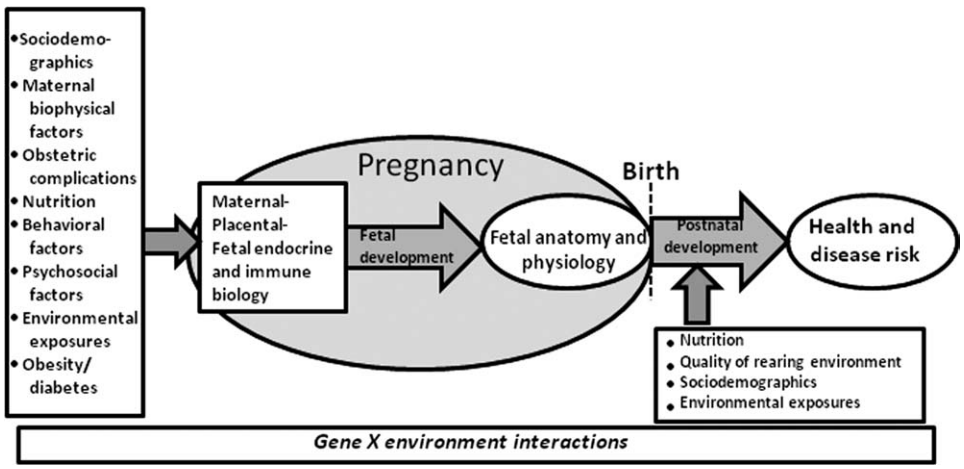

Figure 2. Maternal biologic, behavioral and environmental factors impact the intrauterine milieu, the placenta and fetal physiology. Some conditions including under- or malnutrition and stress can result in elevated maternal circulating glucocorticoids, and may decrease expression or activity of 11βHSD2 in the placenta. Elevated glucocorticods can alter developing organs and tissues, including premature maturation and growth inhibition, leading to altered anatomy and physiology. The birth phenotype, in part, determines response to the postnatal environment, potentially resulting in increased disease risk. The genotype of the offspring also determines its interactions with the environment. (Modified after Entringer et al., 2010).

maternal steroids. Using [^{14}C]-4-corticosterone, it has been demonstrated that maternal CORT crosses the rat placenta and reaches fetal tissues, including the brain (Zarrow et al., 1970). The enzyme 11β-hydroxysteroid dehydrogenase-2 (11βHSD2) is highly expressed in the placenta and is involved in conversion of cortisol and CORT to inactive cortisone and 11-dehydroxycorticosterone (Brown et al., 1996; White et al., 1997). Therefore, under normal conditions, placental 11βHSD2 minimizes fetal exposure to maternal glucocorticoids (Benediktsson et al., 1997). There is high capacity of 11βHSD2 to inactivate glucocorticoids, so an elevated maternal glucocorticoid load does not necessarily translate to increased fetal exposure unless 11βHSD2 is deficient or capacity is exceeded under high levels of maternal stress or disease (Benediktsson et al., 1997). Indeed, stress-induced high levels of maternal glucocorticoids can cross the placenta (Takahashi et al., 1998). DEX readily crosses the placenta and is not inactivated by 11βHSD2, suggesting that bypassing this system may contribute to low birth weight and fetal programming of hypertension (Benediktsson et al., 1993; Nyirenda et al., 1998; Sugden et al., 2001). In further support of this idea, inhibition of 11βHSD2 by carbenoxolone during gestation produces hypertension in adult offspring (Langley-Evans, 1997).

Maternal hormones can also stimulate production of placental CRH, which may enter the fetal circulation and activate the fetal HPA (Majzoub and Karalis, 1999). CORT levels normally rise during late gestation in fetal rats (Dupouy et al., 1975; Boudouresque et al., 1988), likely corresponding with maturation of the fetal HPA. Therefore, stress-induced increases in fetal CORT near term may also involve the fetal HPA.

Developmental programming of physiology and metabolism most likely comprises the contributions of numerous maternal, placental, and embryo-fetal factors that together constitute the developmental environment. Along with the genetic blueprint, these factors sum to shape the phenotype of the offspring (Fig. 2).

Endocrine Signaling Pathways and Mechanisms

There are several targets and mechanisms thought to be involved in glucocorticoid programming, primarily involving GR and MR. The ontogenic timing of hippocampal GR and MR expression is species-specific (Cintra et al., 1993; Diaz et al., 1998; Noorlander et al., 2006), suggesting that windows for glucocorticoid programming differ between species. Prenatal DEX exposure decreases GR and MR expression in the adult hippocampus, which may limit negative feedback and result in increased basal CORT levels in the adult (Levitt et al., 1996).

The disruption in negative HPA feedback may contribute to adult hypertension (Seckl, 2001). Mice that are haplo-insufficient for GR exhibit increased HPA activity and are hypertensive (Michailidou et al., 2008), whereas transgenic mice carrying extra copies of the GR gene have reduced plasma CORT levels and are more resistant to restraint stress (Reichardt et al., 2000). Hypertension associated with prenatal glucocorticoid exposure may be due to reduced numbers of nephrons in the kidney, alterations in the renin-angiotensin system or alterations in baroreceptors (Seckl and Meaney, 2004; Sloboda et al., 2005 for review).

Glucocorticoids regulate key hepatic gluconeogenic enzymes. PEPCK mRNA transcription is upregulated by glucocorticoids, and this upregulation is associated with programming of diabetes-like effects (Nyirenda et al., 1998). Prenatal DEX exposure leads to increased GR expression in the adult liver and kidney, reduced β-cell mass in the pancreas, and glucose intolerance.

Glucocorticoids appear to program anxiety through changes in GR expression in the amygdala. Prenatal exposure to glucocorticoids increases CRH in the amygdala, which is associated with anxiety (Seckl and Meaney, 2004 for review) and GR overexpressing mice have increased anxiety and depressive-like behavior (Wei et al., 2004). Transgenic mice with low GR expression in the brain show reduced anxiety (Tronche et al., 1999).

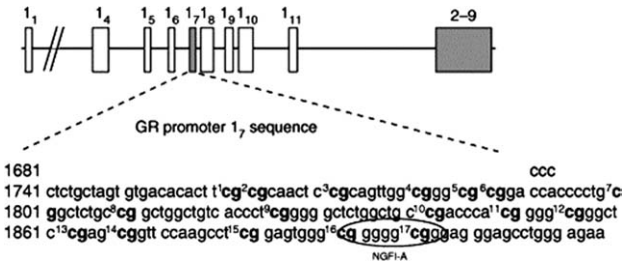

Figure 3. Structure of the rat glucocorticoid gene. The gene contains nine exons, the first of which has numerous promoter sites that are likely specific to different tissue types and glucocorticoid receptor (GR) functions therein. The promoter 1_7 site has a specific binding sequence for nerve growth factor-inducible factor A (NGFI-A, see text). (From Meaney and Szyf, 2005 with permission.)

Although lower levels of GR reduce the negative feedback of the HPA, organs such as the liver and kidney, as well as adipose tissue, exhibit increased GR expression in offspring after exposure to DEX in utero (Seckl, 2001), undernutrition, or low protein diet. Combined with dampened feedback inhibition, this leads to elevation of GR-mediated activities in peripheral tissues (Fig. 2).

Transgenerational Effects

Programming effects of maternal nutrition, stress or glucocorticoid exposure can span multiple generations (reviewed in Drake and Walker, 2004; Matthews and Phillips, 2010), and the transgenerational nature of these findings suggests that epigenetic changes may be involved. Female rats born small-for-gestational age (SGA) were more likely to have SGA infants than mothers that were not born SGA (Klebanoff et al., 1997). In guinea pigs, both the F1 and F2 generations of undernourished F0 mothers showed increased thickness of septal and left ventricular walls of the heart (Bertram et al., 2008). In addition, both F1 and F2 animals had increased basal cortisol and altered HPA stress reactivity. The F1 generation of F0 dams fed a low protein diet during pregnancy and/or lactation produced an F2 generation with effects on growth and metabolism, even though the F1 mothers were fed a normal diet (Pinheiro et al., 2008). F2 offspring were hyperglycemic, hyperinsulinemic, and insulin resistant. These effects on glucose and insulin metabolism appear to be sex- and exposure period-specific (Zambrano et al., 2005). Protein restriction of F0 dams was also associated with reduced nephron number and increased blood pressure in F2 animals, but these effects were not present in the F3 generation (Harrison and Langley-Evans, 2009). DEX administration to F0 dams resulted in low birth weight, glucose intolerance, and increased liver PEPCK in the F2 generation, suggesting that excess glucocorticoid action in the F1 fetus may account for some transgenerational effects (Drake et al., 2005).

Epigenetic Mechanisms of Effects on Offspring HPA axes

Physiologic and metabolic responses of the conceptus to maternal stress have been viewed as ''predictive adaptive responses'' (Gluckman et al., 2005) that prepare the offspring for a postnatal environment of adversity and limited food availability. Alterations such as increased insulin sensitivity, increased adipocyte glucose transporters, reduced pancreatic β-cell mass, reduced muscle mass, and changes in arterial structure could confer an advantage in a nutritionally sparse environment. However, such adjustments are decidedly maladaptive if the postnatal environment is one of readily available, high calorie nutrition. Epigenetic adjustment of the expression of genes contributing to these adaptations during development is clearly a plausible mechanism.

Mechanisms of epigenetic regulation of gene expression include DNA methylation, changes in chromatin structure through histone modifications, and the actions of small noncoding RNAs (microRNAs, not discussed in this review) (for review of epigenetic regulation, Ellis-Hutchings and Rogers, 2008). These mechanisms work together to affect the structure of chromatin and the accessibility of gene promoter sequences, response elements, and binding domains to their binding proteins and cofactors. Importantly, there are specific stages of development during which the epigenetic landscape is more labile than it is during adulthood.

DNA Methylation

DNA methylation is a covalent modification, primarily of cytosine residues at CpG dinucleotides, resulting in the formation of 5-methylcytosine (5MC). This reaction is catalyzed by DNA methyltransferases (DNMTs) a family of proteins that use S-adenosylmethionine (SAM) as the methyl donor. The enzyme DNMT-1 is a maintenance methyltransferase that preferentially uses hemimethylated DNA as a substrate and serves to maintain fidelity of the methylation pattern during DNA replication. In general, methylation in the promoter region of a gene is associated with inhibition of transcription. Methylation of the promoter serves to block access of transcription factors and other DNA binding proteins and to attract specific 5MCpG binding proteins that induce chromatin condensation by recruiting corepressor proteins and enzymes involved in histone modifications. Demethylation of parental DNA occurs at several points during gametogenesis, fertilization, and embryonic development. Reestablishment of DNA methylation then proceeds in the embryo, accomplished by the de novo methyltransferases, DNMT3A, DNMT3B, and DNMT3L. The availability of sufficient methyl donors is critical for the remethylation process.

Histone Modifications

Histones consist of octamers of the histone proteins H2A, H2B, H3, and H4. The octamer is wrapped by 147 base pairs (bp) of DNA to form the nucleosome. The tails of the histone proteins protrude from the nucleosomes and are subject to an array of modifications that affect the charge and conformation of the histones and availability of the DNA for transcription. Histone modifications include acetylation, methylation, poly-ADP-ribosylation, glycosylation, phosphorylation, sumoylation, and ubiquitination. The combination of histone modifications within a given cell type constitutes what has been termed the ''histone code'' that, in part, determines the cell-specific pattern of gene expression. Acetylation is one of the

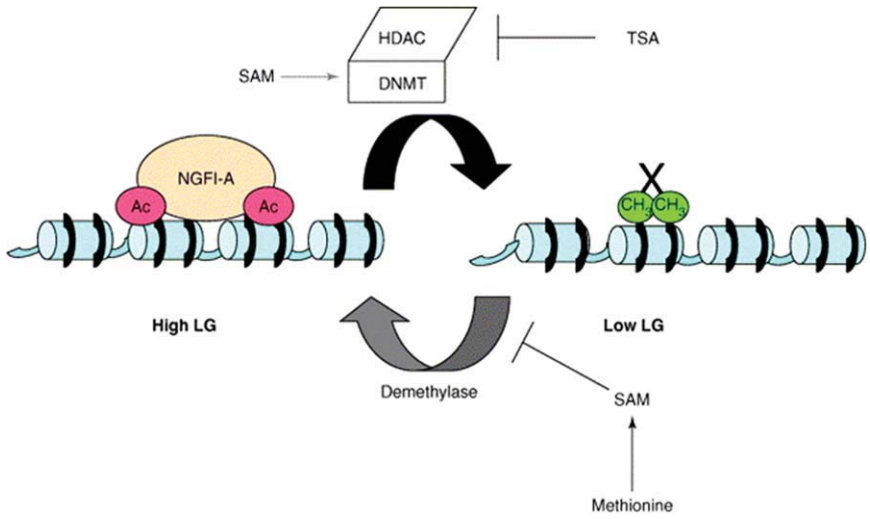

Figure 4. Maternally programmed stress responses in rat offspring are reversible and depend on glucocorticoid receptor (GR) expression. Epigenetic status of the GR promoter region is determined in part by maternal nurturing behavior in the postnatal period and is then maintained. However treatment with the histone deacetylase inhibitor, trichostatin A (TSA), increases histone acetylation and decreases methylation of the GR promoter, upregulating expression of the gene. Conversely, treatment with the methyl donor, methionine, results in hypermethylation of the GR promoter and decreased GR expression. (From Meaney and Szyf, 2005, with permission.)

common histone modifications, and acetylation of lysine 9 on histone protein H3 (denoted as H3K9Ac) is associated with promoter activation. Histone acetylation results from the activity of histone acetyltransferases and histone deacetylases.

Epigenetic Programming

Offspring of pregnant rats fed a diet low in methyl donors exhibited lower levels of DNA methylation and increased H3K9Ac in promoters of genes including those for the GR and the peroxisome proliferator activator-α (PPAR-α). These changes were associated with increased hepatic expression of these genes in juvenile (Lillycrop et al., 2005) and adult offspring (Lillycrop et al., 2007). Folic acid supplementation during pregnancy (Lillycrop et al., 2005; Lillycrop et al., 2007; Lillycrop et al., 2008) or in the postnatal period (Burdge et al., 2009) ameliorated these effects.

One of the best examples of epigenetic programming of offspring is the relationship between maternal care and programming of the HPA axis in offspring of Long Evans rats, elucidated by Meaney, Weaver, Szyf and colleagues (for reviews, Meaney, 2001; Weaver, 2009; Meaney, 2010). Lactating Long Evans mothers display considerable variation in the degree of maternal care given to their offspring. By segregating dams into high licking and grooming (high LG) and low licking and grooming (low LG) categories, Meaney and coworkers have studied the role of early maternal care in the ontogeny of the stress response and other behaviors in offspring. Adult male offspring of high LG mothers have lower plasma ACTH and CORT concentrations in response to stress, elevated hippocampal GR mRNA, and elevated hypothalamic CRH mRNA than do male offspring of low LG dams. Variations in maternal LG are transmitted across generations, such that female offspring of high LG mothers become high LG mothers themselves, and daughters of low LG dams likewise become low LG mothers.

The GR is the central focus of the epigenetic programming of the offspring stress response by the level of maternal care. The GR is a ligand-activated transcription factor that is found in the cytoplasm and the nucleus. In the cytoplasm, the GR exists as a multiprotein complex that contains chaperone (HSP90) and cochaperone (p23) proteins. On binding to CORT, the GR undergoes a conformational change, homodimerizes and translocates to the nucleus. The activated GR binds to specific elements in the DNA, and also binds other cofactors in a cell type-specific manner. Different cofactors present in different cell types lead to cell type-specific actions induced by the GR. For example, activation of the GR in the fetal lung leads to surfactant production, whereas GR activation in the forebrain leads to decreased neurogenesis and decreased synaptic plasticity. The structure of the GR gene is similar in humans and rats. The rat GR gene consists of nine exons (Fig. 3). Exons 2–9 encode multiple variants of the GR. Exon 1 contains a number of promoters that are used in a cell type-specific manner. For example, the exon 1_7 promoter binds the transcription factor nerve growth factor-inducible factor A (NGFI-A) (Crosby et al., 1991).

Hippocampal GR regulates the HPA axis through a negative feedback loop. Higher levels of GR in the hippocampus are associated with a dampened stress response (Fig. 2). Expression of the GR gene in the hippocampus is inversely related to the degree of methylation in the GR 1_7 promoter region. The binding site for NGFI-A within the 1_7 promoter, is methylated to a greater extent in hippocampi from low LG offspring than it is in hippocampi from high LG offspring. Lower methylation of the NGFI-A binding site allows for more binding of NGFI-A, and hence higher levels of GR transcription. Differences in degree of promoter methylation between high LG offspring and low LG offspring appear after birth and

persist through weaning into adulthood. The epigenome of high LG and low LG offspring can be altered by treatment with trichostatin-A (TSA), a histone deacetylase inhibitor that also promotes demethylation of DNA. Adult offspring of low LG mothers lose the low LG phenotype when treated with TSA (Weaver et al., 2004; Weaver et al., 2006). This treatment specifically targets the methylation of the GR 1_7 promoter region. Conversely, administration of the methyl donor methionine, which promotes methylation, causes offspring of high LG mothers to become more stress reactive and have lower levels of hippocampal GR mRNA (Weaver et al., 2005). Aspects of the control of GR gene expression are depicted in Figure 4.

Interestingly, female offspring of high LG and low LG mothers diverge at the level of ER-α gene expression in the median preoptic area of the brain, with long-term suppression of ER-α gene expression in low LG female offspring. Similar to the GR promoter, increased levels of DNA methylation of the ER-α promoter region of low LG female offspring leads to lower expression of the ER-α gene.

Another model of epigenetic shaping of the stress response uses repeated isolation of mouse pups from their mother during the first 10 days of life (Murgatroyd et al., 2009). In this case the epigenetic changes observed were at another level of the HPA axis, namely the *AVP* gene, which codes for arginine vasopressin in the paraventricular nucleus of the hypothalamus. Maternal deprivation was associated with hypomethylation of a binding site for MeCP2. Hypomethylation of this region was associated with persistent upregulation of *AVP* gene expression and hyperactivation of the HPA axis for at least 1 year. These offspring also exhibited reduced stress-coping ability and memory deficits. The hypomethylation of the MeCP2 binding site develops gradually. The first stage is the phosphorylation of MeCP2, which eliminates its binding affinity for the *AVP* binding site. In the absence of MeCP2 binding, methylation of the *AVP* binding site is inadequately maintained, leading to enhanced transcription of the gene. Once MeCP2 is dephosphorylated, the decreased methylation of the binding site results in decreased binding of MeCP2, so increased transcription is maintained despite reversion of MeCP2 to the dephosphorylated form.

Epigenetic Control of 11βHSD2

Earlier in this review, we discussed glucocorticoid metabolism by 11βHSD2 in the placenta and peripheral tissues. CpG islands covering the promoter and exon 1 of the gene *HSD11B2*, which encodes 11βHSD2, are heavily methylated in tissues with low expression but not those exhibiting high expression of *HSD11B2* (Alikhani-Koopaei et al., 2004). In the kidney, where the gene is highly expressed, reduced activity of the enzyme can cause hypertension through overactivation of the MR by CORT, leading to renal sodium retention and a salt-sensitive increase in blood pressure (Ferrari and Krozowski, 2000). Indeed, in humans elevated *HSD11B2* promoter methylation is associated with hypertension (Friso et al., 2008). In an IUGR rat model of hypertension, persistently decreased renal 11βHSD2 mRNA and protein levels were associated with decreased binding of the transcription factors SP1, NF-κB p65, NF-κB p50, and Egr-1 (Baserga et al., 2010). Also observed were increased DNA methylation and modified patterns of methylation in the promoter and decreased trimethylation of H3K36 in exon 5 of the *HSD11B2* gene. These changes were associated with decreased transcription of the gene, possibly contributing to the elevated blood pressure observed in these offspring.

CONCLUSIONS

The stress response is an essential endocrine mechanism for survival and is controlled by the HPA axis. Elevated responses to stress are adaptive, increasing the availability of energy substrates and heightening the ''fight or flight response.'' Although this may have obvious benefits in times of crisis, chronically elevated stress response can predispose individuals to chronic diseases including metabolic derangements and psychologic illnesses. The HPA axis, as well as the hippocampus and the responsiveness of peripheral tissues to glucocorticoids, appear to be tuned in response to the developmental environment (pre- and postnatal) as a predictive adaptive response, but this may be maladaptive if the environment later in life is dissonant with that experienced during development. Functioning of the HPA and set points for the stress response are, in part, determined by the epigenome, as exemplified here by the epigenetic determination of the expression of the genes for the GR, 11βHSD2, and AVP. Although epigenetic remodeling of the chromatin is not the only means to achieving developmental programming, these examples show the elegant way in which the epigenome can define physiologic and metabolic responses for a lifetime.

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