Minireview: Transgenerational Inheritance of the Stress Response: A New Frontier in Stress Research

Stephen G. Matthews and David I. W. Phillips

Departments of Physiology, Medicine, and Obstetrics and Gynaecology (S.G.M.), Faculty of Medicine, University of Toronto, Medical Sciences Building, Toronto, Ontario M5S 1A8, Canada; and Medical Research Council Epidemiology Resource Centre (D.I.W.P.), Southampton General Hospital, Southampton SO16 6YD, United Kingdom

It is well established in animal models that the prenatal environment can have a major impact on stress axis function throughout life. These changes can predispose to various metabolic, cardiovascular, and neurobiological pathophysiologies. Emerging evidence indicates that the same programming effects occur in humans. It is now becoming clear that the pathophysiological effects are not confined to the first-generation offspring and that there is transgenerational memory of fetal experience that can extend across multiple generations. The complex mechanisms by which transgenerational transmission of stress responsiveness occur are rapidly becoming a focus of investigation. Understanding these fundamental biological processes will allow for development of intervention strategies that prevent or reverse adverse programming of the stress response. **(*Endocrinology* 151: 7–13, 2010)**

Although alterations in the hypothalamo-pituitary-adrenal (HPA) axis and associated neuroendocrine changes form a key component of the response of the organism to stressful challenges, it is becoming increasingly clear that these neuroendocrine responses to stress do not merely affect a single generation but are transmitted to subsequent generations and that this occurs by means of nongenomic mechanisms. This has been demonstrated experimentally in studies in a variety of different animal species, and in a more limited way in human observational studies, by showing that stressful exposures during pregnancy affect the set-point of HPA responses in the offspring and that these effects may be transmitted through the maternal line affecting subsequent generations. This new frontier in stress research is not only of biological interest but may also have important clinical, economic, and societal consequences because it has the potential to provide one explanation as to how adverse environmental influences affecting one generation can influence the physiology, behavior, and disease risk in subsequent generations. We have confined this short review to the effects of a modified fetal environment on HPA function across multiple generations.

Maternal Programming of HPA Function in First-Generation Offspring

Animal studies

A very large number of animal studies have investigated the effects of manipulating the fetal environment on stress reactivity and behaviors in later life in first-generation (F_1) offspring. These studies have been extensively reviewed (1, 2). As a general consensus, maternal stress during pregnancy leads to increased HPA activity in rat, guinea pig, and primate offspring. However, there has likely been some bias as a result of its being more difficult to publish negative findings or results that do not align with the consensus. One of the major challenges in this field has been the fact that outcomes of these animal studies have been highly variable. Within a given species, effects in the F_1 offspring are highly dependent on the nature of the manipulation (*i.e.* maternal stress, glucocorticoid exposure, undernutrition, or overnutrition) as well as the timing, intensity, and duration of the manipulation in pregnancy. In this regard, we have shown in the guinea pig that although maternal stress in late gestation leads to elevated

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Abbreviations: HPA, Hypothalamo-pituitary-adrenal; 11β-HSD, 11β-hydroxysteroid dehydrogenase; PS, prenatal stress; PTSD, posttraumatic stress disorder.

HPA activity in male offspring, exposure to synthetic glucocorticoid, at very similar times in gestation, results in reduced HPA activity (3, 4). With respect to timing of exposure, Kapoor *et al.* (3) demonstrated that brief exposure to maternal stress at 70% gestation resulted in adult male guinea pig offspring that exhibited elevated basal cortisol levels but normal adrenocortical responses to stress. In contrast, exactly the same stress administered at 90% gestation resulted in adult male offspring that exhibited normal basal cortisol concentrations but increased HPA responsiveness to challenge (3). Outcomes are also dependent on the sex of the offspring, the age at which the outcome is assessed, and in females, the stage in the reproductive cycle when analysis of the given outcome is undertaken. For example, normally cycling adult female guinea pigs, born to mothers exposed to stress in late gestation, exhibited a reduced salivary cortisol response to stress compared with control offspring, but only during the estrous phase of the cycle (5). In general, females are underrepresented in the animal literature, because many of the earlier (and some present) studies are confined to outcome analysis in male offspring, perhaps due to the considerations above. There also appears to be strong interaction between the prenatal and postnatal environments, such that manipulation of the postnatal environment (such as cross-fostering) can reduce or reverse the effects of the prenatal manipulation.

Many of the species differences observed likely arise from differences in the profile of fetal body and brain development that exist between species. In this regard, neuroendocrine development is linked to phases of rapid brain growth (6). The latter occurs during fetal life in the sheep, guinea pig, and many primates. In humans, the rapid phase of brain development is initiated in the last trimester and extends into the postnatal period, whereas in many rodent species (including rats and mice), maximal brain growth is not initiated until postnatal life. As such, a period of maternal stress in the sheep at midgestation would correspond to a very different phase of fetal brain and neuroendocrine development in the rat at the same stage of gestation.

Human studies

Given what we now know from studies in animal models, in which the maternal environment can be tightly controlled, it is perhaps not surprising that human studies show similar effects although as with the animal models, the changes in the offspring are often variable and contradictory in nature. A number of studies have evaluated the effect of stress-provoking experiences during pregnancy (*i.e.* daily hassles, life events, and domestic violence) sometimes in combination with evaluation of the maternal response to stress (perceived stress or anxiety) and assessment of maternal cortisol secretion on offspring neuroendocrine responses. All these approaches have limitations because there is substantial intra-individual variation in the way different mothers respond to various stressors. Furthermore, measures of perceived stress tend to be poorly associated with physiological measurements of HPA or sympathoadrenal activation. Finally, because many studies have been relatively small and have multiple assessments of both maternal stress and outcomes, they risk generating false-positive findings. Nevertheless, there is an emerging consensus that maternal stress is linked with a range of HPA or related neuroendocrine perturbations in the offspring and associated adverse developmental outcomes (1).

In a longitudinal study of mothers and children, self-reported maternal anxiety during late pregnancy was associated with an increased awakening salivary cortisol secretion in the offspring at 10 yr of age, after accounting for obstetric and sociodemographic factors. The effect on awakening cortisol remained significant after controlling for multiple postnatal assessments of maternal anxiety and depression (7). A similar study of mother-child dyads from The Netherlands reported that prenatal anxiety (including daily hassles, fear about pregnancy outcome, or giving birth) at 16 wk gestation was associated with higher cortisol responses in the offspring to vaccination at 5 yr of age. High prenatal maternal cortisol levels also predicted cortisol responses in the offspring (8). In a retrospective study of healthy young adults whose mothers experienced severe stress during pregnancy (*i.e.* death or severe illness in a close relative), cortisol responses to a psychosocial stress test (The Trier Social Stress Test) were higher than observed in the control group. However, baseline pretest cortisol concentrations were lower as were cortisol responses to an ACTH challenge, whereas the home diurnal cortisol concentrations were similar in both groups (9).

Another approach has been to evaluate the effect of famine or other intensely stressful, major disasters on the stress responses of the offspring born to exposed pregnant women, but again because of the diverse nature of these events, the results tend to be highly variable. Several studies show that the offspring of women pregnant at the time of the disaster tend to be smaller and more premature at birth and have a wide range of subsequent behavioral and physiological abnormalities (10). The Dutch famine was a 5-month period of severe food shortage during the last winter of World War II. Previous studies have shown that exposure to famine in early gestation is associated with an increase in coronary artery disease and atherogenic lipid profile and altered clotting in the offspring. This group

had enhanced blood pressure responses to stress; however, they failed to show alterations in HPA function (11).

A study of mothers exposed to the World Trade Center collapse in September 2001 during pregnancy showed that among those who developed posttraumatic stress disorder (PTSD), both the mothers and their 1-yr-old offspring had lower awakening and evening cortisol concentrations than those who did not develop PTSD. Importantly, this effect was most apparent among babies born to mothers with PTSD who were exposed to the trauma in the third trimester (12). A similar effect was reported among the offspring of Jewish Holocaust survivors with PTSD, who had lower mean 24-h cortisol secretion compared with offspring without parental PTSD (13). A further observational study has been carried out comparing the adolescent offspring of women who were pregnant during the Chernobyl disaster of 1986 with the offspring of women who were pregnant after the incident. At the age of 14, they found that cortisol of both sexes and, intriguingly, the testosterone levels in girls were higher after prenatal exposure to the event from the second trimester onward (14).

Maternal Programming of HPA Function in the Second Generation and Beyond

Animal studies

There are very few published reports on transgenerational transmission of the effects of maternal manipulation during pregnancy on offspring phenotype in the F_2 generation and beyond (15). An early study identified that stress during pregnancy led to increased activity in an open field in F_2-generation offspring, although no assessment of HPA function was undertaken (16). Other early studies showed transgenerational influences of maternal diet during pregnancy on birth weight (for review see Ref. 15). However, to the best of our knowledge, no studies have demonstrated transgenerational effects of maternal stress during pregnancy on HPA function in offspring past the F_1 generation. Notwithstanding, in a recent study, we demonstrated that maternal undernutrition modifies basal and activated HPA function as well cardiovascular function for at least two generations in the guinea pig (17). Pregnant guinea pigs were fed 70% of normal intake in the first half (d 1–35; early restriction) or second half (d 36–70; late restriction) of pregnancy. Female offspring (F_1) were mated with control males and fed *ad libitum* to create F_2-generation offspring. Birth weight and growth were most affected by nutrient restriction in late gestation; however, these effects were much greater in the F_2 than in the F_1 offspring despite no manipulation of the F_1 pregnancy. Maternal undernutrition increased basal cortisol and altered HPA responsiveness to challenge in both generations, although the endocrine effects were most pronounced in the F_1 and F_2 offspring of the late restricted mothers (17). With respect to the cardiovascular effects, F_1 offspring born to mothers that had undergone early restriction exhibited increased blood pressure, and increased left ventricular wall thickness. These effects on left ventricular structure were maintained into the F_2 generation. This study clearly illustrates transgenerational programming of HPA and cardiovascular function. However, it also shows, as one might predict, that susceptibility of different organ systems to maternal undernutrition varies as a function of gestational age.

Other studies have reported transgenerational influences of maternal diet composition on aspects of plasma glucose regulation (18). Interestingly, glucose responses to the ip glucose tolerance test were not different between controls and protein-restricted F_1-generation offspring. However, insulin sensitivity was reduced in the female F_2-generation offspring whose grandmothers had been exposed to protein restriction during pregnancy. This effect was not evident in males, indicating sex specificity of the effect. Another single study has reported that exposure of pregnant rats to synthetic glucocorticoid dexamethasone over the last week of gestation results in glucose intolerance in male F_2-generation offspring, and this was associated with increased hepatic phosphoenolpyruvate carboxykinase activity (19). Importantly, this effect passed down the male line, indicating paternal transmission. We reported preliminary evidence of reduced HPA activity in F_2-generation offspring whose grandmothers had been exposed to synthetic glucocorticoid but whose mothers had gone through an undisturbed pregnancy. This effect was investigated only in the context of maternal transmission, however; again, the effects were stronger in the F_2- than the F_1-generation offspring (20).

Human studies

There is still very limited evidence for transgenerational inheritance in humans beyond the first generation, but available data do suggest that fetal nutritional and endocrine insults may persist into subsequent generations. During the Dutch Winter Famine of 1944/1945, pregnant women exposed to famine in late pregnancy gave birth to smaller babies. However, female offspring exposed *in utero* in the first trimester gave birth to children with reduced birth size independently of the effect on maternal birth weight (21). Exposure of pregnant women to diethylstilbestrol, a synthetic estrogen previously used to prevent miscarriage, led to a marked increase in reproductive abnormalities and cancers in their children. Evidence is now emerging that third-generational effects (an increased risk of hypospadias) in boys are transmitted through the

maternal line without further exposure of the intervening generation (22). Suggestive evidence for transgenerational effects involving the HPA axis comes from a study of the offspring of Holocaust survivors with PTSD, who show lower 24-h urinary cortisol excretion than offspring of survivors without PTSD (23). However, there is clearly a need for more information, and it is anticipated that several prospective studies of the long-term consequences of maternal stress, which are in progress, will provide more data on the extent of transgenerational influences on HPA function in humans.

Mechanisms of Programming: F_1 Generation

Prenatal stress (PS) leads to numerous cardiovascular and endocrine changes in the mother, including increases in plasma ACTH, β-endorphin, glucocorticoid, and catecholamine concentrations. The placenta forms a structural and biochemical barrier to many of these maternal factors, although a number will still enter the fetus. There may also be indirect effects on the fetus via modification of placental function. For example, increased maternal catecholamine concentrations will lead to constriction of placental blood vessels and may lead to fetal hypoxia (24). There may also be activation of the fetal sympathetic nervous system, a system that has also been shown to be programmed by the early environment (for review see Ref. 25). Programming of the sympathetic nervous system and neurotransmitter systems in the brain will ultimately lead to altered physiological responses to stress in offspring.

Although a number of factors are doubtless important, glucocorticoids have become a popular candidate for mediating the effects of PS on programming HPA function and behavior into the F_1 generation. Maternal and fetal plasma glucocorticoid concentrations are significantly elevated after maternal stress in rats and guinea pigs. Under normal circumstances, access of maternal endogenous glucocorticoid to the fetus is low. This results from the placental expression of 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2. The efficiency of placental 11β-HSD2 varies among species, however it is generally accepted that placental 11β-HSD2 is of primary importance in excluding maternal endogenous glucocorticoid from the fetus. In this regard, a recent study has shown that PS leads to a reduction in placental 11β-HSD2 expression in the rat (26). A number of approaches have been used to determine the role of maternal glucocorticoid in programming of HPA function during PS. In one elegant study, pregnant rats were adrenalectomized and basal levels of corticosterone replaced. In this group, PS had no effect on HPA function in the adult offspring (27), suggesting that maternal glucocorticoid, or a factor stimulated by glucocorticoids, passes to the fetus to mediate PS-induced changes in HPA function.

Although increased exposure of the fetus to maternal glucocorticoid may represent a mediator of the effects of PS, the question that remains is how these effects are permanent as well as how they can be transmitted across generations. In this regard, it is becoming increasingly evident that the early environment can permanently influence the genome through epigenetic mechanisms and in this way modify endocrine function, metabolism, and behavior of offspring. Importantly, key genes that regulate HPA function (*GR*, *CRH*, *POMC*, and *11β-HSD2*) have been shown to be epigenetically regulated (28–33).

Maternal stress/anxiety and dietary protein restriction during pregnancy (32–34) and altered levels of maternal care (for review see Ref. 35) can leave permanent epigenetic marks in the genome and result in stable lifelong changes in gene expression in offspring. The elegant studies of Meaney and Szyf have elucidated some of the potential mechanisms by which maternal care can influence the epigenome (for review see Ref. 35). Very recent rat and human studies have shown that maternal stress/anxiety during pregnancy leads to altered methylation of the hypothalamic *CRH* promoter (rat offspring) and *GR* promoter in umbilical cord blood mononuclear cells (human infants) (32, 33). The question that remains is what mediates the demethylation? In this connection, glucocorticoids, which are known to be elevated during maternal stress, have been shown to cause permanent demethylation of specific fetal hepatic gene promoters in late gestation (36). This demethylation results in enhanced transcription factor binding, and this is maintained after glucocorticoid withdrawal, indicating stability of the effect. Therefore, there is strong evidence emerging indicating that increased fetal glucocorticoid exposure has profound influences on the fetal epigenome. The route by which fetal exposure to glucocorticoids influences the methylation is not currently known, although it may involve reductions in folate availability. In this regard, patients with Cushing's syndrome exhibit hyperhomocysteinemia (37). Hyperhomocysteinemia inhibits the activity of DNA methyltransferases and induces hypomethylation (38). Therefore, there is strong evidence for epigenetic processes being important for modified HPA function and behaviors in the F_1 generation.

Mechanisms of Programming: Multiple Generations

The question remains as to how these effects could be transmitted across generations. The mechanisms under-

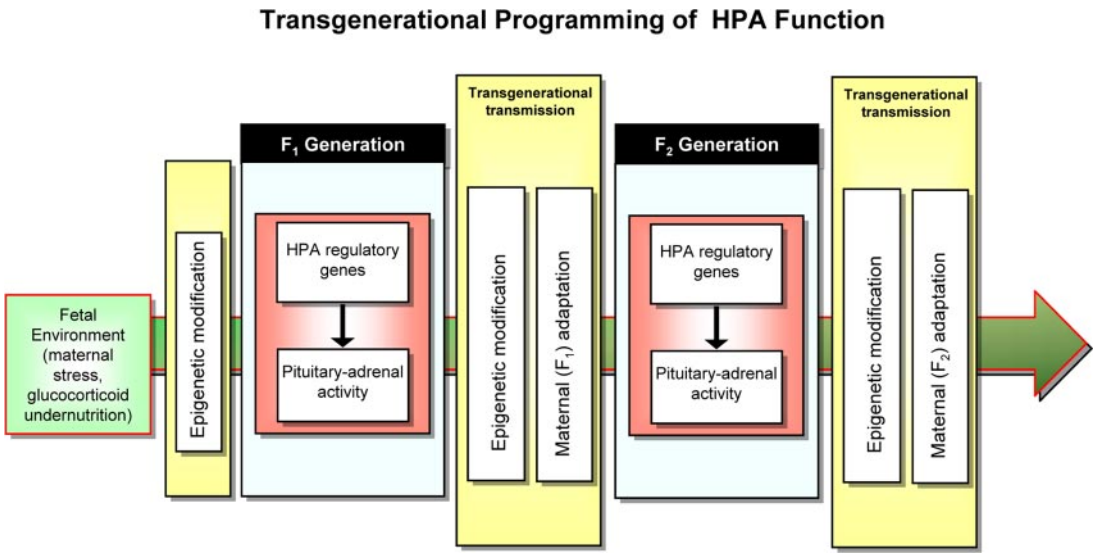

FIG. 1. Schematic illustrating the potential routes by which the fetal environment may lead to transgenerational programming of HPA function. Modified fetal environment will directly affect development of brain and neuroendocrine structures, and this likely involves epigenetic processes. Altered endocrine and cardiovascular function in the first-generation (F_1) offspring will lead to a modification of the normal adaptations that take place during pregnancy, and this may directly program endocrine function of the F_2 offspring. Again, epigenetic mechanisms are likely involved. This process may be repeated for several generations. See text for further details.

lying transgenerational programming likely involve at least two pathways: 1) altered maternal endocrine adaptation to pregnancy and 2) transgenerational transmission of epigenetic modification (Fig. 1).

In pregnancy, there are major adaptations in the regulation of the maternal HPA axis. Maternal HPA activity increases in late gestation (24), but there is a reduction in stress responsiveness (39). If maternal stress during pregnancy (F_0 mothers) results in female offspring (F_1) that exhibit altered pituitary-adrenocortical adaptations to pregnancy, this would modify fetal exposure to maternal endogenous glucocorticoid and result in programming of HPA function in her F_2 offspring with no manipulation of the F_1 pregnancy. Indeed, pharmacological inhibition of placental 11β-HSD2, which represents the primary barrier protecting the fetus from high maternal glucocorticoid concentrations, leads to endocrine and behavioral outcomes in offspring that are analogous to those of excess fetal glucocorticoid exposure.

The potential for transgenerational epigenetic memory remains a little more controversial. Although the majority of DNA methylation in the germline is erased in early embryogenesis, some epigenetic signals (not just those confined to imprinted genes) exhibit meiotic stability and can be transmitted from one generation to the next (40). Transient exposure of pregnant rats to endocrine disruptor vinclozolin or methoxychlor caused decreased spermatogenic capacity in the F_1 generation. These effects were transferred through the male germline to nearly all males up to the F_4 generation. The same group has identified transgenerational transmission of altered methylation patterns through the germline to F_3 (for review see Ref. 41). Although other studies indicating paternal transmission of DNA methylation are emerging, the mechanisms remain to be resolved. It is likely that there will be considerable interaction between glucocorticoid levels (maternal and fetal) and the fetal epigenome during F_1 and F_2 pregnancies. For example, a decrease in maternal endogenous glucocorticoid levels through pregnancy would lead to decreased fetal exposure to glucocorticoid. Alternatively, a reduction in placental *11β-HSD2* gene expression, which is itself heavily epigenetically regulated, would also lead to increased fetal glucocorticoid exposure. Both scenarios could lead to reprogramming of the fetal epigenome.

Conclusions

There is accumulating evidence in a variety of animal species that manipulation of the fetal environment alters the biobehavioral response to stress in the offspring and that these altered responses persist across multiple generations. These observations are generally paralleled in human studies (with as yet few data on F_2 effects), although there are major and largely unexplained differences in outcomes between studies. Despite gaps in our knowledge, these are potentially important findings because they may explain both laboratory and human observations that environmental influences affecting one generation influence the disease risk in subsequent generations. This is because of increasing evidence that subtle changes in the activity of

the HPA axis and related neuroendocrine systems are linked with disease. Hypercortisolemia increases susceptibility to several diseases, including depression, hypertension, and diabetes, with similar associations being identified in animal models (42). In contrast, hypocortisolemia has been linked to chronic fatigue syndrome, chronic pelvic pain, fibromyalgia, PTSD, burnout, and atypical depression (43). In evolutionary terms, these HPA alterations may be part of a strategy by which parents transmit information about their current environment to their progeny, allowing the generation of phenotypes adapted to the environment predicted by the cues available during fetal life, but with associated costs. So, for example, exposure to an adverse environment during pregnancy may lead to increased offspring HPA activity and behavioral or physiological changes that enhance early survival and therefore reproductive potential but at the cost of greater susceptibility to subsequent vascular or metabolic disease with advancing age.

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Address all correspondence and requests for reprints to: Professor S. G. Matthews, Department of Physiology, Faculty of Medicine, University of Toronto, Medical Sciences Building, 1 King's College Circle, Toronto, Ontario, Canada M5S 1A8. E-mail: stephen.matthews@utoronto.ca.

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