



Minireview

Developmental Programming by Perinatal Glucocorticoids

Jun Young Hong*

Department of Systems Biology, College of Life Science and Biotechnology, Yonsei University, Seoul 03722, Korea

*Correspondence: junyoung.hong@yonsei.ac.kr

<https://doi.org/10.14348/molcells.2022.0042>www.molcells.org

Early-life environmental factors can have persistent effects on physiological functions by altering developmental procedures in various organisms. Recent experimental and epidemiological studies now further support the idea that developmental programming is also present in mammals, including humans, influencing long-term health. Although the mechanism of programming is still largely under investigation, the role of endocrine glucocorticoids in developmental programming is gaining interest. Studies found that perinatal glucocorticoids have a persistent effect on multiple functions of the body, including metabolic, behavioral, and immune functions, in adulthood. Several mechanisms have been proposed to play a role in long-term programming. In this review, recent findings on this topic are summarized and the potential biological rationale behind this phenomenon is discussed.

Keywords: adaptation, developmental endocrine, developmental programming, glucocorticoids, perinatal period, stress

INTRODUCTION

Adaptation to the environment is an essential feature for living organisms. Organisms sense environmental changes and induce adaptive responses to survive. In most cases, these adaptive programs are not initiated in the default state and are only induced by specific challenges. The adaptations are

usually transient and revert to the normal basal state. For example, activation of the sympathetic nervous system in the fight-or-flight response can be an example of this transient adaptive program. This system is activated only under acute stress and is not maintained for a long time. Once the stressful condition disappears, the system returns to its basal state.

However, when environmental challenges become chronic, different strategies are implemented. In this case, environmental challenges are continuously encountered and a more stable adaptive program is induced. This type of program can generally be regarded as acclimatization. Increased red blood cell production in a hypoxic environment or the induction of beige adipose tissue differentiation is a good example of acclimatization. As in the case of transient adaptation, the induced programs in acclimatization may return to a normal basal state once the challenge vanishes. However, compared with transient adaptation, restoration of the basal state may take longer in acclimatization because of its stability.

Organisms with a short lifespan or living in seasonal environments may face environmental challenges throughout their lifetime. Under these chronic environmental changes, organisms may induce adaptive programs with irreversible changes. The best-known cases of this type of adaptation are developmental plasticity or polyphenism, which have been reported in various species. For example, the wing pigmentation of the butterfly *Araschnia* is differentially generated based on seasonal fluctuations in temperature and photoperiod (Gilbert, 2005). The crustacean *Daphnia* recognizes the chemical traces of a predator and produces offspring

Received 18 March, 2022; revised 29 May, 2022; accepted 15 June, 2022; published online 23 September, 2022

eISSN: 0219-1032

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with a defensive “helmet” structure (Bateson et al., 2004). The desert locust *Schistocerca gregaria* is hidden, shy, and sedentary under low density, but becomes conspicuous, gregarious, and migrative under crowded conditions (Bateson et al., 2004). Although the lifespan of vertebrates is generally longer than that of invertebrates, similar long-term adaptive programming of phenotypes has been observed. For example, the temperature during embryonic development in zebrafish has a perpetual effect on thermal acclimatization and swimming activity during the adult life of the larvae (Scott and Johnston, 2012). In mammals, such as rats, protein intake (low, medium, or high) during the gestation and lactation periods of dams persistently affects the weight gain rate and longevity of offspring, which show a higher survival rate when their post-weaning diet matches the diet consumed by their dams (Sasaki et al., 1982). Studies utilizing experimental animal models have shown long-term alterations in phenotypes on exposure to specific environmental factors in early life (McMullen and Mostyn, 2009). Such adaptations can be generally termed “developmental programming,” as the long-term phenotype is programmed by the modification of developmental processes due to early-life environmental exposure.

This program is similar to changing the blueprint of a house to meet specific needs before construction is completed (Fig. 1A). Since this process is irreversible, a match and mismatch relationship with the actual environment can also occur (Fig. 1). This idea is the basis for the developmental origin of the health and disease (DOHaD) hypothesis in humans (Barker, 2007; Bateson et al., 2004; Gluckman and Hanson, 2004). Accumulated epidemiological studies on DOHaD strongly support the notion that developmental programming is conserved among humans. Pioneering studies on this subject have linked intrauterine fetal growth retardation with an increased risk of cardiovascular diseases, hypertension, and type 2 diabetes mellitus (Barker, 2002; Gluckman and Hanson, 2004). In addition to metabolic and cardiovascular diseases, early-life adversity is also linked to various immunological diseases, such as allergies, asthma, infectious diseases, and cancer (Flanigan et al., 2018; Kelly-Irving et al., 2013; Moore et al., 2006; van de Loo et al., 2016). Despite a number of accumulated cases supporting DOHaD, mechanistic insight on this subject is still elusive.

STRESS, GLUCOCORTICIDS, AND ADAPTATION

In mammals, one of the major factors induced by environmental stressors is glucocorticoids (GCs). GCs are a class of steroid hormones that increase in response to various environmental challenges, including starvation, cold exposure, predators, infection, and psychological stress. Pleiotropic effects are exhibited by GCs on multiple cells and tissues; however, such responses should have an adaptive value to increase the chances of survival. For example, GCs have a significant impact on whole-body metabolism. GCs promote protein catabolism, amino acid mobilization, and glucose sparing by increasing glycogenolysis and gluconeogenesis (Kuo et al., 2013; 2015). Also, GCs induce lipolysis, at least following acute exposure (Macfarlane et al., 2008; Peckett et al., 2011). These metabolic changes are essential for survival under stressful conditions such as starvation. Moreover, GCs have a significant impact on brain function and behavior (Lupien et al., 2009; McEwen et al., 2012), which can also enhance the chance of survival in harsh environments.

Another important change caused by GCs is immune regulation. They suppress inflammation by inhibiting nuclear factor-kappa B (NF- κ B) activation (Padgett and Glaser, 2003). This is partly via sequestration of NF- κ B in the cytosol with the induction of inhibitory kappa B ($I\kappa$ B) synthesis or through competition for a binding partner between GC receptor (GR) and NF- κ B (Padgett and Glaser, 2003). Furthermore, activated GR binds to important gene loci to suppress gene expression and immune activation (Surjit et al., 2011). However, stimulation of GR signaling does not always cause immune suppression. T cells with GR deficiency show reduced activation and survival, particularly in the circadian range of GC concentrations, suggesting the immune-enhancing role of GC (Hong et al., 2020; Shimba et al., 2018). Since the hypothalamus, where GC is regulated, is an integration and allocation center, it is conceivable that immune suppression by GC has evolved to reallocate energy and resources for more essential functions in stressful environments (Wang et

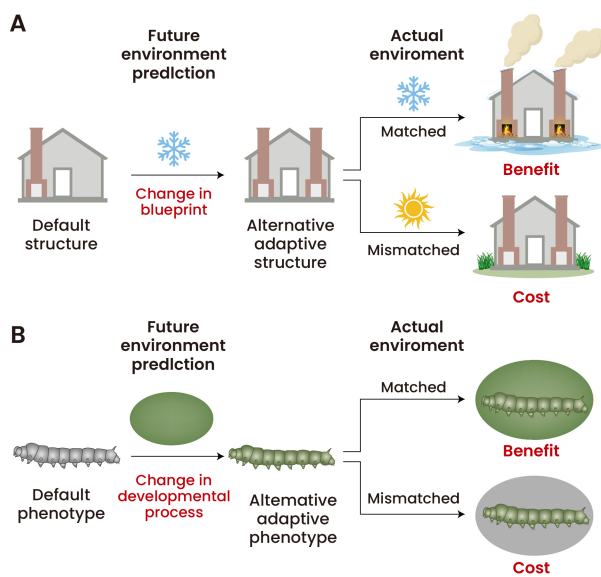


Fig. 1. Developmental programming and match/mismatch-prompted benefit/cost. (A) An analogy for developmental programming. Two fireplaces are built with a modification in the blueprint in expectation of cold weather. When the actual temperature matches the predicted value (cold), then there is a benefit (top). In case of a mismatch, there is a cost (bottom). (B) Example of developmental programming. Alternative adaptive phenotype (green skin color) is generated by modifying developmental processes with the expectation of a green environment. The benefit of being camouflaged will occur when the actual environment matches the expectation (top). In case of a mismatch, there will be a cost and will lead to maladaptation (bottom).

al., 2019). However, the exact biological rationale behind energy allocation between immunity and other functions of the body is yet to be elucidated.

GLUCOCORTICOIDS AND DEVELOPMENTAL PROGRAMMING

Endocrine signals govern organismal adaptation to external environmental changes. The role of various endocrine hormones in transient physiological changes or acclimatization has been well described. However, the role of endocrine signals in developmental programming for long-term adaptation remains relatively unknown, particularly in mammals. Studies in invertebrates have shown that endocrine hormones such as juvenile hormones and ecdysteroids mediate phenotypic changes in adaptive developmental programming (Gilbert, 2005). Moreover, thyroid hormones are known to be involved in the phenotypic plasticity of amphibians (Ruthsatz et al., 2020). Therefore, the significance of endocrine signals in mammalian developmental programming is highly conceivable.

In cases that support DOHaD, early environmental factors associated with long-term disease risks, such as malnutrition, infection, immune activation, and psychosocial stress, can induce GCs. Therefore, GCs may mediate the long-term developmental programming of phenotypes and affect disease risk. Epidemiological studies have shown that one of the strongest perinatal factors associated with long-term disease risk is intrauterine growth retardation (IUGR) (Bateson et al., 2004; Gluckman and Hanson, 2004). Since prenatal GC can directly elicit IUGR, GC may play a central role in disease development through IUGR by mediating developmental programming (French et al., 1999; Gluckman and Hanson, 2004). For example, maternal GC may directly inhibit fetal development. Maternal GC was hypothesized to be incapable of crossing the placenta and thus affecting offspring owing to the activity of hydroxysteroid dehydrogenase 11 β type 2 (HSD11b2), which inactivates GCs by degradation. However, studies have found that maternal GC can enter the fetus at a circadian peak or under stress (Barbazanges et al., 1996; Venihaki et al., 2000). Moreover, the expression level of Hsd11b2 is reduced under chronic stress, which allows maternal GC to affect the fetus (Mairesse et al., 2007). Other studies have also found that behavior and hypothalamic-pituitary-adrenal (HPA) axis activity are persistently affected by maternal GC exposure during lactation (Catalani et al., 1993; 2011). However, whether this programming by lactational GCs is a direct effect of GCs or an indirect effect caused by the change in maternal care, which has been reported to have a strong influence on HPA axis development, is uncertain. Overall, these results suggest that GC acts as an endocrine signal for long-term developmental programming.

Consistent with this hypothesis, perinatal GC exposure has been reported to induce long-term metabolic alterations. For example, prenatal GC exposure leads to persistent postnatal glucose intolerance in experimental rodent models (Nyirenda et al., 1998; 2001). Prenatal treatment with dexamethasone (DEX), a GR agonist, significantly enhances hepatic phosphoenolpyruvate carboxykinase (PEPCK) gene expres-

sion and activity, thereby enhancing gluconeogenesis (Nyirenda et al., 1998; 2001). This leads to hyperglycemia and hyperinsulinemia during fasting in adult offspring exposed to prenatal DEX during late pregnancy (Nyirenda et al., 1998). Another study found that hepatic hepatocyte nuclear factor 4 α (HNF4 α) is also significantly enhanced by prenatal DEX exposure, which can also contribute to altered glucose levels (Nyirenda et al., 2006). Moreover, a study on non-human primates found that prenatal GC administration leads to glucose intolerance and hyperinsulinemia, with decreased pancreatic β cell numbers (de Vries et al., 2007). Studies in humans have also shown that prenatal GC treatment is associated with altered glucose metabolism in adulthood (Dalziel et al., 2005; Kelly et al., 2012). However, a more extensive and controlled study is required to decipher the programming effect of GC on human metabolism.

Perinatal GC also affects the long-term risk of hypertension. Late-pregnancy DEX exposure causes increased blood pressure in old offspring rats (Levitt et al., 1996; Sugden et al., 2001) and is also associated with decreased GR and mineralocorticoid receptor (MR) expression in the hippocampus (Levitt et al., 1996). Consistent with these findings, gestational GC exposure also leads to increased blood pressure in adult sheep (Figueroa et al., 2005). In this study, IUGR was not identified; however, the number of glomeruli decreased with prenatal GC (Figueroa et al., 2005). A study on primates found that prenatal GC treatment increased blood pressure in offspring (de Vries et al., 2007), while another study found no differences (Bramlage et al., 2009). This discrepancy could be attributed to the differences between the model species and duration of GC treatment. In humans, antenatal GC treatment is associated with higher blood pressure at 14 years of age (Bramlage et al., 2009). However, another study found no difference in blood pressure in adults exposed to antenatal GC treatment (Dalziel et al., 2005). These retrospective studies have limitations, and a controlled clinical study is required to determine the exact role of perinatal GC exposure on blood pressure in adult life in humans.

Perinatal GC can also affect long-term behavior. Prenatal GC treatment leads to anxiety during adulthood in rats (Nagano et al., 2008; Welberg et al., 2001). Together with other studies, the development of anxiety due to perinatal GC treatment has been associated with alterations in the amygdala region of the brain (Nagano et al., 2008; Welberg et al., 2000; 2001). In other studies, postnatal GC exposure also led to increased anxiety-like behavior, particularly in threatening environments (Neal et al., 2004). Moreover, cortisol levels in mother's milk are linked to the altered temperament of infant rhesus macaques (Hinde et al., 2015). In humans, a prenatal increase in maternal cortisol levels also affects an infant's temperament (Davis et al., 2007). Moreover, children exposed to prenatal GC show enhanced psychological stress responses (Erni et al., 2012). Although changes in perinatal exposure to GC are often regarded as a disease, these altered behaviors may also be adaptive responses that increase the chances of survival. For example, heightened anxiety may lead to a vigilant phenotype, which would be beneficial for survival in harsh environments (Hanson and Gluckman, 2014).

Perinatal GC exposure can also cause long-term immune

alterations. In an experimental rodent model, prenatal maternal psychological stress suppressed the immune function in the offspring (Kay et al., 1998). In a direct GC-exposure model, neonatal DEX treatment leads to enhanced susceptibility to experimental autoimmune encephalomyelitis (EAE) in adult rats (Bakker et al., 2000). In this study, neonatal DEX treatment reduced HPA axis activity, but the exact contribution of the HPA axis to the pathogenesis of EAE is unclear. More direct evidence of the role of HPA axis programming on immune regulation has been provided recently; perinatal GC programs the HPA axis, and reduced HPA axis activity is responsible for immune suppression (Hong et al., 2020). In this study, perinatal GC exposure resulted in diminished CD8⁺ T-cell responses in adulthood and impaired control of tumor growth and bacterial infection. Using T-cell-specific GR-deficient mice and an adrenalectomy model, decreased corticosterone (CORT) levels are found to be responsible for diminished CD8⁺ T-cell function (Hong et al., 2020). Considering the general immune-suppressive function of GC, it is somewhat unexpected that diminished CORT hormone level leads to reduced T cell function. While the immunosuppressive function of GC is still valid, especially with the GC level under various stressors, the circadian level of GC can enhance immune function with its permissive role in other settings. For example, GC increases the expression of cytokine and chemokine receptors, such as the IL-7 receptor and CXCR4, in T cells, allowing T cells to survive and migrate (Hong et al., 2020; Shimba et al., 2018). In adrenalectomy and genetic GR-deficient models, the activation and survival of CD8⁺ T cells reduce with the reduction in CD25 and Bcl2 signaling (Hong et al., 2020; Shimba et al., 2018). Whether this immunostimulatory role of GC at the circadian level can be applied to immune cells other than T cells is unknown. Moreover, the molecular mechanisms underlying the differential dosage effects of GC on T cells are yet to be elucidated. Overall, peri-

natal GC has a persistent effect on immune function.

MECHANISM OF DEVELOPMENTAL PROGRAMMING BY PERINATAL GC

Persistent HPA axis threshold change

Long-term phenotypic changes observed with GC exposure during development is generally related to the normal function of GC hormone. For example, the metabolic alteration, behavioral changes, and immune modification discussed above are all associated with changes that occur due to either hyperactive or hypoactive HPA axis activity and increased or decreased GC levels. Therefore, developmental programming could be mediated by persistent changes in the HPA axis. Supporting this hypothesis, a recent extensive review found that either hyperactive or hypoactive HPA axis activity is identified with exposure to diverse perinatal stressors (van Bodegom et al., 2017). Mild to moderate stress causes hyperactivity in the HPA axis, whereas extreme stress causes hypoactivity in the HPA axis (van Bodegom et al., 2017). The exact mechanisms underlying these phenomena are yet unknown; nevertheless, changes in HPA axis activity do not appear to be random but may be programmed to adapt to predicted environments after birth, as some studies have suggested (Braun et al., 2013). According to the match/mismatch stress theory (Schmidt, 2011), a heightened HPA axis could be beneficial in stressful situations (Fig. 2, top). When environmental stress is excessive, the organism may benefit from a reduction in stress sensitivity (Fig. 2, middle), and in extremely stressful conditions, being insensitive to the consistently active stress axis is beneficial for survival and reproduction (Fig. 2, bottom). This HPA axis programming is like 'calibration' for the range of phenotype expression of an organism for survival and long-term adaptation. This calibration is made by the interaction with the perinatal environment and is established by the modification of the set point of the GC hormone level.

Modifications in GC levels due to early-life stresses have been observed in other species, such as birds and fish (Henriksen et al., 2011; Reyes-Contreras et al., 2019). Consistent with animals, the early-life environment appears to program the human HPA axis as well. Children and adults with low birth weights have higher plasma and urine adrenocorticotropic hormone or GC levels (Clark et al., 1996; Phillips et al., 1998; Reynolds et al., 2001). Importantly, perinatal GC can persistently affect CORT levels later in life. Two studies on HPA function in 4-month-old newborns and 30-year-old individuals have shown a positive relationship between intrauterine GC exposure and basal (morning) CORT concentrations (Dalziel et al., 2005; Glover et al., 2005). Overall, these studies in various species, including humans, support the notion of evolutionarily conserved long-term HPA-axis programming.

The hyperactive or hypoactive HPA axis can be programmed by modifying the negative-feedback threshold. MR and GR are two receptors that form a negative feedback loop upon binding to CORT (De Kloet et al., 1998). The hippocampus and paraventricular nucleus of the hypothalamus (PVH) are the sites for the regulation of the HPA axis by expressing these receptors. Particularly in the hippocampus, GR- or

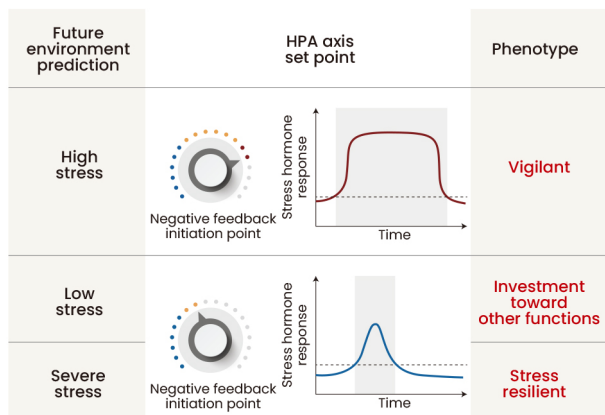


Fig. 2. Adaptation to a predicted future environment via HPA axis 'calibration'. The set point for HPA axis threshold of negative feedback can be differentially established by the interaction with the perinatal environment. This perinatal calibration leads to the difference in stress response and phenotype expression which can promote survival in the target environment.

MR-expressing neurons relay negative neuronal signaling toward corticotropin-releasing hormone (CRH)-producing neurons in the hypothalamus. The MR has a higher binding affinity for CORT than that of GR and is suggested to be a key regulator of the HPA axis when CORT oscillations are in the lower circadian range (De Kloet et al., 1998). As CORT levels rise with stress, CORT binding to GR also increases, and both GR and MR work together to provide negative feedback, bringing HPA axis activity back to a normal state (Bradbury et al., 1994; De Kloet et al., 1998).

Recent single-cell biology studies have provided a clearer elucidation of GR and MR expression and HPA axis regulation. Hippocampal MR increases the expression of FK506-binding protein 51 (FKBP5), a negative regulator of GR function, decreasing ligand-binding activity (Hartmann et al., 2021). This regulation is particularly important for emotional and behavioral changes associated with CORT (Hartmann et al., 2021). These results along with other single-cell studies show that hippocampal neuronal composition and regulation of GR and MR are generally conserved between mice and humans (Hartmann et al., 2021; Hodge et al., 2019).

Stable alteration of the HPA axis threshold can be programmed by modifying the expression of MR and GR in the hippocampus. One of the most prominent factors that can stably alter the HPA axis is maternal care. The offspring of rats with low maternal licking and grooming show heightened anxiety with a hyperactive HPA axis. These rats express low levels of GR in the hippocampus, thereby decreasing the threshold for negative feedback of the HPA axis and increasing systemic CORT levels (Weaver et al., 2004; Zhang et al., 2013). This is accompanied by the epigenetic modification of GR expression. Tactile stimulation from maternal licking increases hippocampal serotonin (5-HT) and expression of nerve growth factor-inducible factor A (NGFI-A). This factor binds to exon 1 of the GR gene with epigenetic modifications, which increases GR expression in the hippocampus (Weaver et al., 2004; Zhang et al., 2013).

MR expression is altered by various early life stresses. In particular, MR expression levels increased in various regions of the hippocampus following perinatal GC exposure (Hong et al., 2020). Although the specific mechanism of this induction has not been determined, epigenetic modifications in MR gene loci could have been responsible.

In addition to epigenetic changes in the expression of GR and MR, neuronal network development can significantly influence persistent changes in the HPA axis activity. For example, hippocampal neurogenesis in the dentate gyrus region alters the HPA axis threshold (Eliwa et al., 2021; Schloesser et al., 2009). While neurogenesis can occur in adulthood in this region, perinatal GC probably affects long-term neuronal network development in this region. The role of perinatal GC in general hippocampal development has been previously reviewed (Matthews, 2000).

Direct epigenetic programming by GC in the target cells and tissues

Another possible mechanism for long-term programming is direct epigenetic programming. For example, antenatal

GC treatment in guinea pigs alters DNA methylation patterns and gene expression in multiple fetal and neonatal tissues such as the liver, adrenal gland, and kidney (Crudo et al., 2012). These changes are maintained in adulthood and even transmitted to the next generation (Crudo et al., 2012). In a mouse model, epigenetic modification of CD8⁺ T cells has been associated with perinatal GC exposure (Hong et al., 2020). Naïve CD8⁺ T cells in mice with perinatal GC treatment showed reduced T-bet expression and decreased chromatin accessibility in T-bet regulating loci, including IFN- γ (Hong et al., 2020). Further, perinatal GC reduces T-bet expression since chromatin accessibility in T-bet loci is reduced where the consensus GR-binding motif is present (Hong et al., 2020). These results support the notion of direct epigenetic programming of target cells and tissues by perinatal GC.

CONCLUSION

GCs are one of the major pathways involved in adaptation to multiple stressful environments. In addition to the role of GCs in acute physiological adaptation, studies have suggested that GC may mediate adaptation via developmental programming. The accumulated cases strongly support the notion of long-term physiological programming by perinatal GC. The precise biological rule behind this phenomenon is still unclear, but it does not appear to be random and may foster future adaptations to environmental changes after birth. Long-term programming by GC is, at least in part, mediated by HPA axis threshold programming; however, direct epigenetic programming is also possible. Further studies on this topic are needed to overcome the fundamental gaps in our current understanding.

ACKNOWLEDGMENTS

I apologize for not being able to cite all seminal papers on this subject due to limited space. This work was supported by the Yonsei Research Fund (2021-22-0049), Yonsei Signature Research Cluster Program of 2022 (2022-22-0013), and the National Research Foundation of Korea (NRF), Ministry of Science, ICT, and Future Planning NRF-2022R1C1C1007283.

CONFLICT OF INTEREST

The author has no potential conflicts of interest to disclose.

ORCID

Jun Young Hong <https://orcid.org/0000-0002-4963-7147>

REFERENCES

- Bakker, J.M., Kavelaars, A., Kamphuis, P.J., Cobelens, P.M., van Vugt, H.H., van Bel, F., and Heijnen, C.J. (2000). Neonatal dexamethasone treatment increases susceptibility to experimental autoimmune disease in adult rats. *J. Immunol.* *165*, 5932-5937.
- Barbazanges, A., Piazza, P.V., Le Moal, M., and Maccari, S. (1996). Maternal glucocorticoid secretion mediates long-term effects of prenatal stress. *J. Neurosci.* *16*, 3943-3949.
- Barker, D.J. (2007). The origins of the developmental origins theory. *J. Intern. Med.* *261*, 412-417.
- Barker, D.J.P. (2002). Fetal programming of coronary heart disease. *Trends Endocrinol. Metab.* *13*, 364-368.

- Bateson, P., Barker, D., Clutton-Brock, T., Deb, D., D'Udine, B., Foley, R.A., Gluckman, P., Godfrey, K., Kirkwood, T., Lahr, M.M., et al. (2004). Developmental plasticity and human health. *Nature* *430*, 419-421.
- Bradbury, M.J., Akana, S.F., and Dallman, M.F. (1994). Roles of type I and II corticosteroid receptors in regulation of basal activity in the hypothalamo-pituitary-adrenal axis during the diurnal trough and the peak: evidence for a nonadditive effect of combined receptor occupation. *Endocrinology* *134*, 1286-1296.
- Bramlage, C.P., Schlumbohm, C., Pryce, C.R., Mirza, S., Schnell, C., Amann, K., Armstrong, V.W., Eitner, F., Zapf, A., Feldon, J., et al. (2009). Prenatal dexamethasone exposure does not alter blood pressure and nephron number in the young adult marmoset monkey. *Hypertension* *54*, 1115-1122.
- Braun, T., Challis, J.R., Newnham, J.P., and Sloboda, D.M. (2013). Early-life glucocorticoid exposure: the hypothalamic-pituitary-adrenal axis, placental function, and long-term disease risk. *Endocr. Rev.* *34*, 885-916.
- Catalani, A., Alema, G.S., Cinque, C., Zuena, A.R., and Casolini, P. (2011). Maternal corticosterone effects on hypothalamus-pituitary-adrenal axis regulation and behavior of the offspring in rodents. *Neurosci. Biobehav. Rev.* *35*, 1502-1517.
- Catalani, A., Marinelli, M., Scaccianoce, S., Nicolai, R., Muscolo, L.A., Porcu, A., Koranyi, L., Piazza, P.V., and Angelucci, L. (1993). Progeny of mothers drinking corticosterone during lactation has lower stress-induced corticosterone secretion and better cognitive performance. *Brain Res.* *624*, 209-215.
- Clark, P.M., Hindmarsh, P.C., Shiell, A.W., Law, C.M., Honour, J.W., and Barker, D.J.P. (1996). Size at birth and adrenocortical function in childhood. *Clin. Endocrinol. (Oxf.)* *45*, 721-726.
- Crudo, A., Petropoulos, S., Moisiadis, V.G., Iqbal, M., Kostaki, A., Machnes, Z., Szyf, M., and Matthews, S.G. (2012). Prenatal synthetic glucocorticoid treatment changes DNA methylation states in male organ systems: multigenerational effects. *Endocrinology* *153*, 3269-3283.
- Dalziel, S.R., Walker, N.K., Parag, V., Mantell, C., Rea, H.H., Rodgers, A., and Harding, J.E. (2005). Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. *Lancet* *365*, 1856-1862.
- Davis, E.P., Glynn, L.M., Schetter, C.D., Hobel, C., Chicx-Demet, A., and Sandman, C.A. (2007). Prenatal exposure to maternal depression and cortisol influences infant temperament. *J. Am. Acad. Child Adolesc. Psychiatry* *46*, 737-746.
- De Kloet, E.R., Vreugdenhil, E., Oitzl, M.S., and Joels, M. (1998). Brain corticosteroid receptor balance in health and disease. *Endocr. Rev.* *19*, 269-301.
- de Vries, A., Holmes, M.C., Heijnis, A., Seier, J.V., Heerden, J., Louw, J., Wolfe-Coote, S., Meaney, M.J., Levitt, N.S., and Seckl, J.R. (2007). Prenatal dexamethasone exposure induces changes in nonhuman primate offspring cardiometabolic and hypothalamic-pituitary-adrenal axis function. *J. Clin. Invest.* *117*, 1058-1067.
- Eliwa, H., Brizard, B., Le Guisquet, A.M., Hen, R., Belzung, C., and Surget, A. (2021). Adult neurogenesis augmentation attenuates anhedonia and HPA axis dysregulation in a mouse model of chronic stress and depression. *Psychoneuroendocrinology* *124*, 105097.
- Erni, K., Shaqiri-Emini, L., La Marca, R., Zimmermann, R., and Ehlert, U. (2012). Psychobiological effects of prenatal glucocorticoid exposure in 10-year-old-children. *Front. Psychiatry* *3*, 104.
- Figuerola, J.P., Rose, J.C., Massmann, G.A., Zhang, J., and Acuña, G. (2005). Alterations in fetal kidney development and elevations in arterial blood pressure in young adult sheep after clinical doses of antenatal glucocorticoids. *Pediatr. Res.* *58*, 510-515.
- Flanigan, C., Sheikh, A., Dunn Galvin, A., Brew, B.K., Almqvist, C., and Nwaru, B.I. (2018). Prenatal maternal psychosocial stress and offspring asthma and allergic diseases: a systematic review and meta-analysis. *Clin. Exp. Allergy* *48*, 403-414.
- French, N.P., Hagan, R., Evans, S.F., Godfrey, M., and Newnham, J.P. (1999). Repeated antenatal corticosteroids: size at birth and subsequent development. *Am. J. Obstet. Gynecol.* *180*, 114-121.
- Gilbert, S.F. (2005). Mechanisms for environmental regulation of gene expression: ecological aspects of animal development. *J. Biosci.* *30*, 65-74.
- Glover, V., Miles, R., Matta, S., Modi, N., and Stevenson, J. (2005). Glucocorticoid exposure in preterm babies predicts a salivary cortisol response to immunization at four months. *Pediatr. Res.* *58*, 1233-1237.
- Gluckman, P.D. and Hanson, M. (2004). Living with the past: evolution, development, and patterns of disease. *Science* *305*, 1733-1736.
- Hanson, M.A. and Gluckman, P.D. (2014). Early developmental conditioning of later health and disease: physiology and pathophysiology? *Physiol. Rev.* *94*, 1027-1076.
- Hartmann, J., Bajaj, T., Klengel, C., Chatzinakos, C., Ebert, T., Dedic, N., McCullough, K.M., Lardenoije, R., Joëls, M., Meijer, O.C., et al. (2021). Mineralocorticoid receptors dampen glucocorticoid receptor sensitivity to stress via regulation of FKBP5. *Cell Rep.* *35*, 109185.
- Henriksen, R., Rettenbacher, S., and Groothuis, T.G. (2011). Prenatal stress in birds: pathways, effects, functions, and perspectives. *Neurosci. Biobehav. Rev.* *35*, 1484-1501.
- Hinde, K., Skibiël, A.L., Foster, A.B., Del Rosso, L., Mendoza, S.P., and Capitanio, J.P. (2015). Cortisol in the mother's milk during lactation reflects maternal life history and predicts infant temperament. *Behav. Ecol.* *26*, 269-281.
- Hodge, R.D., Bakken, T.E., Miller, J.A., Smith, K.A., Barkan, E.R., Graybuck, L.T., Close, J.L., Long, B., Johansen, N., Penn, O., et al. (2019). Conserved cell types with divergent features in human versus mouse cortex. *Nature* *573*, 61-68.
- Hong, J.Y., Lim, J., Carvalho, F., Cho, J.Y., Vaidyanathan, B., Yu, S., Annicelli, C., Ip, W.K.E., and Medzhitov, R. (2020). Long-term programming of CD8 T cell immunity by perinatal exposure to glucocorticoids. *Cell* *180*, 847-861. e15.
- Kay, G., Tarcic, N., Poltyrev, T., and Weinstock, M. (1998). Prenatal stress suppresses immune function in rats. *Physiol. Behav.* *63*, 397-402.
- Kelly-Irving, M., Lepage, B., Dedieu, D., Lacey, R., Cable, N., Bartley, M., Blane, D., Grosclaude, P., Lang, T., and Delpierre, C. (2013). Childhood adversity as a risk factor for cancer: findings from the 1958 British Birth Cohort Study. *BMC Public Health* *13*, 767.
- Kelly, B.A., Lewandowski, A.J., Worton, S.A., Davis, E.F., Lazdam, M., Francis, J., Neubauer, S., Lucas, A., Singhal, A., and Leeson, P. (2012). Antenatal glucocorticoid exposure and long-term alterations in aortic function and glucose metabolism. *Pediatrics* *129*, e1282-e1290.
- Kuo, T., Harris, C.A., and Wang, J.C. (2013). Metabolic function of glucocorticoid receptors in skeletal muscle. *Mol. Cell. Endocrinol.* *380*, 79-88.
- Kuo, T., McQueen, A., Chen, T.C., and Wang, J.C. (2015). Regulation of glucose homeostasis by glucocorticoids. *Adv. Exp. Med. Biol.* *872*, 99-126.
- Levitt, N.S., Lindsay, R.S., Holmes, M.C., and Seckl, J. (1996). Dexamethasone in the last week of pregnancy attenuated hippocampal glucocorticoid receptor gene expression and elevated blood pressure in adult offspring of rats. *Neuroendocrinology* *64*, 412-418.
- Lupien, S.J., McEwen, B.S., Gunnar, M.R., and Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat. Rev. Neurosci.* *10*, 434-445.
- Macfarlane, D.P., Forbes, S., and Walker, B.R. (2008). Glucocorticoids and fatty acid metabolism in humans: fuelling fat redistribution in metabolic syndrome. *J. Endocrinol.* *197*, 189-204.
- Mairesse, J., Lesage, J., Breton, C., Breant, B., Hahn, T., Darnaudery, M., Dickson, S.L., Seckl, J., Blondeau, B., Vieau, D., et al. (2007). Maternal stress alters endocrine function of the feto-placental unit in rats. *Am. J. Physiol.*

- Endocrinol. Metab. 292, E1526-E1533.
- Matthews, S.G. (2000). Antenatal glucocorticoids and programming of the developing CNS. *Pediatr. Res.* 47, 291-300.
- McEwen, B.S., Eiland, L., Hunter, R.G., and Miller, M.M. (2012). Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress. *Neuropharmacology* 62, 3-12.
- McMullen, S. and Mostyn, A. (2009). Animal models for the study of the developmental origins of health and disease: workshop on nutritional models of the developmental origins of adult health and disease. *Proc. Nutr. Soc.* 68, 306-320.
- Moore, S.E., Collinson, A.C., Tamba N'Gom, P., Aspinall, R., and Prentice, A.M. (2006). Early immunological development and mortality from infectious diseases later in life. *Proc. Nutr. Soc.* 65, 311-318.
- Nagano, M., Ozawa, H., and Suzuki, H. (2008). Prenatal dexamethasone exposure affects anxiety-like behavior and the neuroendocrine system in an age-dependent manner. *Neurosci. Res.* 60, 364-371.
- Neal, C.R., Jr., Weidemann, G., Kabbaj, M., and Vázquez, D.M. (2004). Effects of neonatal dexamethasone exposure on growth and neurological development in adult rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 287, R375-R385.
- Nyirenda, M.J., Dean, S., Lyons, V., Chapman, K.E., and Seckl, J.R. (2006). Prenatal programming of hepatocyte nuclear factor 4 α in rats: a key mechanism in the fetal origins of hyperglycemia? *Diabetologia* 49, 1412-1420.
- Nyirenda, M.J., Lindsay, R.S., Kenyon, C.J., Burchell, A., and Seckl, J.R. (1998). Glucocorticoid exposure during late gestation permanently programs rat hepatic phosphoenolpyruvate carboxykinase and glucocorticoid receptor expression and causes glucose intolerance in adult offspring. *J. Clin. Invest.* 101, 2174-2181.
- Nyirenda, M.J., Welberg, L.A., and Seckl, J.R. (2001). Programming hyperglycemia in rats through prenatal exposure to glucocorticoid-fetal effects or maternal influence? *J. Endocrinol.* 170, 653-660.
- Padgett, D.A. and Glaser, R. (2003). How stress influences the immune response. *Trends Immunol.* 24, 444-448.
- Peckett, A.J., Wright, D.C., and Riddell, M.C. (2011). The effects of glucocorticoids on adipose tissue lipid metabolism. *Metabolism* 60, 1500-1510.
- Phillips, D.I., Barker, D.J., Fall, C.H., Seckl, J.R., Whorwood, C.B., Wood, P.J., and Walker, B.R. (1998). Elevated plasma cortisol concentrations: a link between low birth weight and insulin resistance syndrome? *J. Clin. Endocrinol. Metab.* 83, 757-760.
- Reyes-Contreras, M., Glauser, G., Rennison, D.J., and Taborsky, B. (2019). Early life manipulation of cortisol and its receptors alters stress axis programming and social competence. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 374, 20180119.
- Reynolds, R.M., Walker, B.R., Syddall, H.E., Andrew, R., Wood, P.J., Whorwood, C.B., and Phillips, D.I. (2001). Altered control of cortisol secretion in adult men with low birth weight and cardiovascular risk factors. *J. Clin. Endocrinol. Metab.* 86, 245-250.
- Ruthsatz, K., Dausmann, K.H., Drees, C., Becker, L.I., Hartmann, L., Reese, J., Reinhardt, S., Robinson, T., Sabatino, N.M., Peck, M.A., et al. (2020). Altered thyroid hormone levels affect the capacity for temperature-induced developmental plasticity in larvae of *Rana temporaria* and *Xenopus laevis*. *J. Therm. Biol.* 90, 102599.
- Sasaki, A., Nakagawa, I., and Kajimoto, M. (1982). Effect of protein nutrition throughout gestation and lactation on the growth, morbidity, and life span of rat progeny. *J. Nutr. Sci. Vitaminol. (Tokyo)* 28, 543-555.
- Schloesser, R.J., Manji, H.K., and Martinowich, K. (2009). Suppression of adult neurogenesis leads to an increased hypothalamic-pituitary-adrenal axis response. *Neuroreport* 20, 553-557.
- Schmidt, M.V. (2011). Animal models of depression and mismatch hypothesis of disease. *Psychoneuroendocrinology* 36, 330-338.
- Scott, G.R. and Johnston, I.A. (2012). The temperature during embryonic development has persistent effects on the thermal acclimation capacity of zebrafish. *Proc. Natl. Acad. Sci. U. S. A.* 109, 14247-14252.
- Shimba, A., Cui, G., Tani-Ichi, S., Ogawa, M., Abe, S., Okazaki, F., Kitano, S., Miyachi, H., Yamada, H., Hara, T., et al. (2018). Glucocorticoids drive diurnal oscillations in T cell distribution and response by inducing the Interleukin-7 receptor and CXCR4. *Immunity* 48, 286-298.e6.
- Sugden, M.C., Langdown, M.L., Munns, M.J., and Holness, M. (2001). Maternal glucocorticoid treatment modulates placental leptin and leptin receptor expression and materno-fetal leptin physiology during late pregnancy and elicits hypertension associated with hyperleptinemia in early growth-retarded adult offspring. *Eur. J. Endocrinol.* 145, 529-539.
- Surjit, M., Ganti, K.P., Mukherji, A., Ye, T., Hua, G., Metzger, D., Li, M., and Chambon, P. (2011). Widespread negative response elements mediate direct repression by agonist-ligand glucocorticoid receptor. *Cell* 145, 224-241.
- van Bodegom, M., Homberg, J.R., and Henckens, M. (2017). Modulation of the hypothalamic-pituitary-adrenal axis by early life stress exposure. *Front. Cell. Neurosci.* 11, 87.
- van de Loo, K.F., van Gelder, M.M., Roukema, J., Roeleveld, N., Merkus, P.J., and Verhaak, C.M. (2016). Prenatal maternal psychological stress, childhood asthma, and wheezing: a meta-analysis. *Eur. Respir. J.* 47, 133-146.
- Venihaki, M., Carrigan, A., Dikkes, P., and Majzoub, J.A. (2000). Circadian rise in maternal glucocorticoids prevents pulmonary dysplasia in fetal mice with adrenal insufficiency. *Proc. Natl. Acad. Sci. U. S. A.* 97, 7336-7341.
- Wang, A., Luan, H.H., and Medzhitov, R. (2019). An evolutionary perspective on immunometabolism. *Science* 363, eaar3932.
- Weaver, I.C., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., and Meaney, M.J. (2004). Epigenetic programming by maternal behavior. *Nat. Neurosci.* 7, 847-854.
- Welberg, L.A., Seckl, J.R., and Holmes, M.C. (2000). Inhibition of 11 β -hydroxysteroid dehydrogenase, the feto-placental barrier to maternal glucocorticoids, permanently programs amygdala GR mRNA expression and anxiety-like behavior in offspring. *Eur. J. Neurosci.* 12, 1047-1054.
- Welberg, L.A., Seckl, J.R., and Holmes, M.C. (2001). Prenatal glucocorticoid programming of brain corticosteroid receptors and corticotrophin-releasing hormone: possible implications for behavior. *Neuroscience* 104, 71-79.
- Zhang, T.Y., Labonté, B., Wen, X.L., Turecki, G., and Meaney, M.J. (2013). Epigenetic mechanisms for early environmental regulation of hippocampal glucocorticoid receptor gene expression in rodents and humans. *Neuropsychopharmacology* 38, 111-123.