CHAPTER

25

The Effects of Stress on Early Brain and Behavioral Development

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OUTLINE

25.1 INTRODUCTION

Over a half century of research using animal models has documented the impact of early-life stress on neurobehavioral development (Sanchez et al., 2001). Both stress to the mother or more directly to the fetus during prenatal development and stressors that affect mother and infant during postnatal development have been shown to impact circuits that are developing during the period of stressor exposure, including the development of stress-mediating systems. Alterations in stress-mediating systems, in turn, influence how the organism responds to stressors throughout development, producing cascading effects that may result in significant physical and mental health problems later in life. Research on the neurobiological sequelae of stress during human pre- and postnatal development has a much shorter history. However, inroads are being made in understanding how exposure to stress early in life influences neurobehavioral development and lifelong health (Shonkoff et al., 2009).

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Activity of the hypothalamic–pituitary–adrenocortical (HPA) axis, a stress-sensitive neuroendocrine system, has figured prominently in animal studies of early-life stress ever since it was noted in the 1950s that early experiences permanently altered its reactivity and regulation (Levine, 1957). Because the HPA axis produces hormones that function as gene transcription factors in numerous organs and tissues and because experience alters its activity as well as the activity of its receptors, research on early-life stress has continued to include a focus on the HPA axis. Attention to activity of this system in studies of human development has been promoted by the availability of assays that allow noninvasive measurement of cortisol, its end hormone, in small samples of saliva (Gunnar and Donzella, 2002). Consistent with the history of research in this area, a focus is maintained, although not exclusively, on the HPA axis in reviewing the research on early-life stress and human neurobehavioral development.

This chapter consists of four parts. First, it contains a brief review of the anatomy and physiology of the mature HPA axis and related stress-mediating systems and second, a discussion of prenatal stress and fetal programming. Third, there is a discussion on the postnatal development of the HPA system, the importance of social regulation of the HPA axis in early human development, and what is currently known about long-term impacts of early-life stress on later physical and mental health. Finally, issues that need to be addressed are considered as this field moves forward.

25.2 THE ANATOMY AND PHYSIOLOGY OF STRESS

Stressors are real or perceived threats to psychological or physical viability that are responded to by stressor-specific release of molecules termed stress mediators. These molecules bind to their receptor targets and orchestrate integrated responses that have evolved to increase survival in the immediate face of threat (Joels and Baram, 2009). Glucocorticoids (cortisol in humans) are steroid hormones that serve as a major mediator of the mammalian stress response. Glucocorticoids are produced by the cortex of the adrenal glands; the medulla of the adrenals produces adrenaline, a hormone that is central to the fight/flight response. Glucocorticoids serve multiple roles in defensive responding (Sapolsky et al., 2000). At basal levels they are permissive, in the sense that they maintain organs and tissues in a state that permits rapid and sustained mobilization by other neurotransmitters or hormones. At elevated levels they suppress the actions of other stress-mediating systems and, through negative feedback, return the HPA system to basal levels of activity. Via effects on gene transcription, glucocorticoids also can have long-term effects on neural systems mediating perception and response to threat, both up- and down-regulating reactions to subsequent stressors. Critically, the effects of acute activations of the HPA system and those of chronic activation are markedly different, with chronic activation resulting in progressive changes in the expression of stress-mediating genes, alteration in neuronal systems that process signals of threat, and changes in neuronal firing patterns throughout the brain.

The cascade of events that produce changes in cortisol release by the adrenals begins with the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) by cells in the paraventricular nuclei of the hypothalamus (see Figure 25.1, reviewed in Gunnar and Vazquez (2006)). CRH and AVP are released through small blood vessels to the anterior pituitary where they stimulate the release of adrenocorticotropic hormone (ACTH) into the bloodstream. Cells on the cortex of the adrenal glands respond to ACTH and start a cascade of enzymatic actions that convert cholesterol to cortisol (corticosterone in rodents). Activation of the adrenal cortex by ACTH also results in the production of dehydroepiandrosterone (DHEA), an adrenal androgen that because of its anabolic effects has antistress properties. Once released into the circulation, because of its lipid solubility, cortisol enters the cytoplasm of cells throughout the body and brain where it interacts with its receptors if they are present.

Cortisol has affinity to two receptors, mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). Its affinity with MRs is many times greater than to GRs; hence, if both are present MRs will be occupied and activated first, followed by GRs. In most areas of the body, however, cortisol cannot access MRs because an enzyme is present (11 beta hydroxysteroid dehydrogenase or 11β-HSD) that converts cortisol to a form with low MR affinity. As discussed later, this enzyme is also present in the placenta where it serves to regulate impacts of maternal cortisol on the placenta and fetus. In the brain, however, the enzyme is not present, allowing the levels of cortisol in circulation to determine the balance between MR and GR activation. Under basal levels MRs tend to be almost wholly occupied; while when cortisol rises to stress levels and also at the peak of the diurnal rhythm, GRs become occupied as well. MRs tend to mediate many of the permissive effects of cortisol, while GRs mediate many of the more catabolic stress effects. GRs are also involved in negative feedback of the axis, functioning at the level of the pituitary, hypothalamus, hippocampus, and likely also the medial frontal cortex, to contain the HPA response and help return the axis to basal levels of activity.

While there is increasing evidence that under conditions of stress, rapid cell-membrane-mediated effects

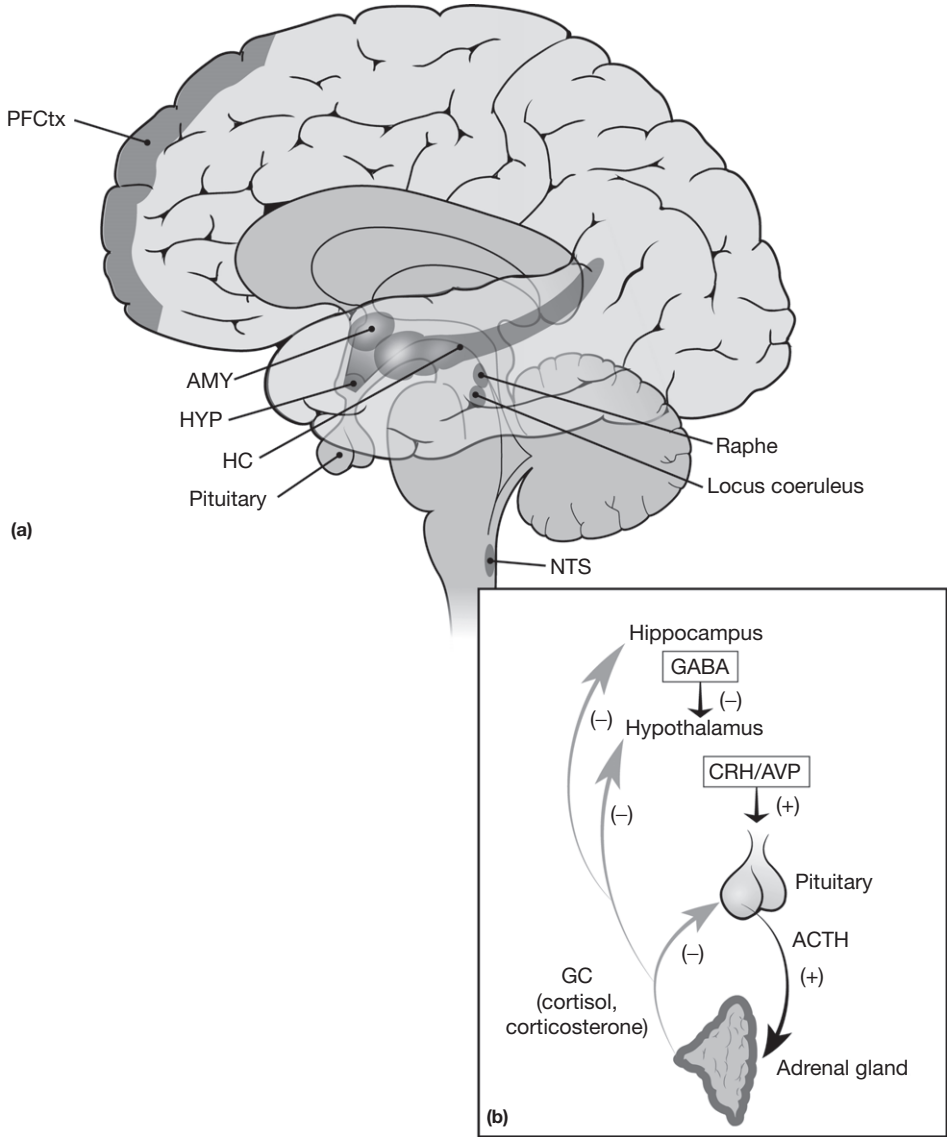

FIGURE 25.1 The HPA system. (a) depicts the anatomy of the HPA system and structures important in its regulation. PFCtx, prefrontal cortex; AMY, amygdala; HYP, hypothalamus; HC, hippocampus; NTS, nucleus of the tractus solitarius. (b) depicts the activation (+) and negative feedback inhibition (−) pathways of the HPA system. Increases in GCs are initiated by the release of CRH/AVP from the medial parvocellular region of the paraventricular nucleus (mpPVN) in the hypothalamus. Negative feedback inhibition operates through GCs acting at the level of the pituitary, hypothalamus, and hippocampus. GABA, gamma animobutyric acid; CRH, corticotropin releasing hormone; AVP, arginine vasopressin; ACTH, adrenocorticotropic hormone. *Reproduced from Gunnar MR and Vazquez D (2006) Stress neurobiology and developmental psychopathology. In: Cicchetti D and Cohen D (eds.)* Developmental Psychopathology:Developmental Neuroscience, *2nd edn., vol. 2, pp. 533–577. New York: Wiley, with permission.*

of cortisol occur, most effects of cortisol involve translocation of the cortisol–receptor complex from the cytoplasm to the cell nucleus where cortisol interacts with glucocorticoid receptive elements (GREs) in the promotor region of many genes. Activation of GREs increases or decreases gene transcription in interaction with other gene transcription factors. Because many of cortisol's effects are produced via gene transcription, they take minutes to hours to be produced. This means that while acute threat may stimulate increases in cortisol production, cortisol itself is not a major factor in fight/flight responses that proceed on the basis of seconds to minutes.

Activation of the HPA axis is regulated by complex signals derived across a number of pathways that carry information about the state of the internal and external milieu (see Figure 25.2). Activation of the system in response to threats to internal homeostasis (e.g., blood volume loss), travel to the CRH-producing cells in the hypothalamus through brainstem pathways. Psychological threats that require integration of information about

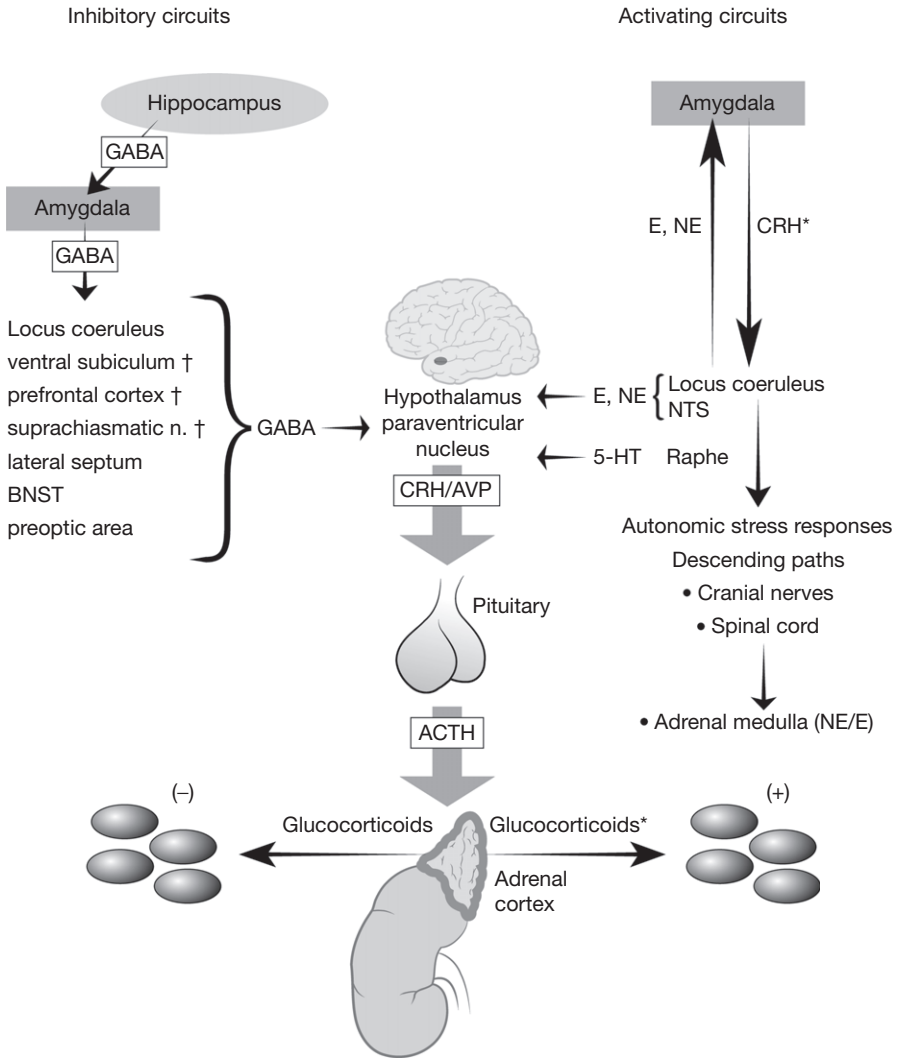

FIGURE 25.2 Schematic representation of the activating (right side) and inhibiting (left side) circuits that contribute to the regulation of the HPA system. Catecholamines, *norepinephrine* (*NE*), *and epinephrine* (*E*) arising from medullary nuclei of the brainstem are the primary neurotransmitters providing activation of CRH synthesis and release from the mpPVN. *Serotonin* originating from dorsal raphe is weakly activating; it acts both directly on mpPVN and indirectly through *excitatory glutamate neurons* or *inhibitory gamma aminobutyric acid* (*GABA*) inputs. Paradoxically, the inhibitory GABA neurotransmitter activates the mpPVN to secrete CRH, as two GABA neurons activated in series leads to excitation and not inhibition. *Extrahypothalamic CRH also acts as a neurotransmitter to initiate autonomic and behavioral responses to stress.* The activation of the extrahypothalamic CRH system is initiated by *rising* glucocorticoid levels that operate on the amygdala to secrete CRH that, in turn, impacts on the locus cerouleus (LC). Through the activation of catecholaminergic brainstem nuclei there is also stimulation of descending pathways leading to NE/E release from the adrenal medulla that facilitates cardiovascular autonomic responses to stress. Inhibition of the HPA axis seen in the left side is provided by *glucocorticoids* acting on glucocorticoid receptors (GR) in the hypothalamus and pituitary where CRH and ACTH release is halted. The hippocampus serves to inhibit the stress response via multiple circuits, some of which are direct inhibitory GABA inputs; others are indirect through glutamate excitatory inputs to GABA neurons converging in the mpPVN. GABA neurons located in each of the structures further modify the stress reactivity and inhibition from other brain regions such as the thalamus, association cortex, cortical and limbic afferents. *Glucocorticoids provide positive stimulation to the amygdala for the synthesis and release of CRH, but negative to the pituitary, hypothalamus, and hippocampus. †Interaction is through glutamate outflow from these regions that synapse on local GABAergic neurons, producing inhibition of mpPVN. *Reproduced from Gunnar MR and Vazquez D (2006) Stress neurobiology and developmental psychopathology. In: Cicchetti D and Cohen D (eds.)* Developmental Psychopathology: Developmental Neuroscience*, 2nd edn., vol. 2, pp. 533–577. New York: Wiley, with permission.*

external events are mediated through pathways involving the amygdala and bed nucleus of the stria terminalis (BNST). Notably, neural systems involved in activating the axis in response to psychosocial threats either produce CRH or have receptors for CRH. The central nucleus of the amygdala is one region rich in CRH-producing neurons, activation of which plays a role not only on activating the HPA axis but also in stimulating increases in central norepinephrine and peripheral activation of the sympathetic nervous system. The extrahypothalamic CRH system is part of the fight/flight system and a key orchestrator of fear behavior (Rosen and Schulkin, 1998).

The expression of CRH and its receptors in the various brain regions involved in emotion and cognition is age-dependent and regulated by stress throughout the life span. Recent evidence indicates that effects of stress on neurodevelopment are mediated by CRH, as well as cortisol (Korosi and Baram, 2008).

25.3 PRENATAL STRESS AND NEUROBEHAVIORAL DEVELOPMENT

25.3.1 Fetal Programming

Fetal development proceeds at a more rapid pace than any later developmental stage (Barker, 1998a,b). For this reason, the human fetus is particularly vulnerable to both organizing and disorganizing influences, which have been described as programming. Programming is the process by which a stimulus or insult during a vulnerable developmental period has a long-lasting or permanent effect (Barker, 1998a,b; Kuzawa, 2005). The effects of programming are dependent on the timing (i.e., the developmental stage of organ systems and the changes in maternal and placental physiology) and the duration of exposure (Davis and Sandman, 2010; Nathanielsz, 1999). There is convincing support for fetal programming of adult health outcomes including heart disease, diabetes, and obesity; however, the evidence comes primarily from retrospective studies that rely on birth phenotype (e.g., small size at birth or preterm delivery) as an index of fetal development (e.g., Barker, 1998a,b). It is unlikely that birth phenotype alone is the cause of subsequent health outcomes. Birth phenotype, instead, reflects fetal adaptation to exposures that shape the structure and function of physiological systems that underlie health and disease risk (Gluckman and Hanson, 2004). Prenatal exposure to maternal stress signals is one of the primary pathways for prenatal programming of later health and development. In the first section, the role that prenatal maternal stress signals might play in preparing the fetus for adaptation to the postnatal world is discussed.

25.3.2 Stress Regulation and Pregnancy

During the prenatal period, signals from the maternal host environment influence the fetal developmental trajectory. Some of these effects may have evolved to help prepare the infant for the postnatal environment. The HPA axis participates in a surveillance and response system that is present in many species, from the desert-dwelling Western Spadefoot tadpole to the human fetus, and allows for the detection of threat so that development can be adjusted accordingly. For instance, rapidly evaporating pools of desert water result in the elevation of CRH in the tadpole, accelerating metamorphosis, and increasing the likelihood of survival. If the CRH response is blocked during environmental desiccation, then development is not accelerated and the tadpole's survival is compromised. There are long-term consequences for the tadpole that survives this early-life stress because its growth is stunted and it is at a disadvantage in the competition for food and reproduction (Denver, 1997). It has been argued that a similar signaling pathway participates in the regulation of human fetal development. Detection by the fetal/placental unit of stress signals from the maternal environment (e.g., cortisol) informs the fetus that there may be a threat to survival. This information may prime or advance the placental clock (McLean et al., 1995) by activating the promoter region of the CRH gene and increasing the placental synthesis of CRH (Sandman et al., 2006). The rapid increase in circulating CRH begins the cascade of events resulting in myometrial activation and in extreme cases, preterm birth. Early departure (i.e., preterm birth) from the inhospitable host environment may be essential for survival, but it also may have long-term consequences for the human fetus just as it does for the tadpole. The developmental trajectory of the fetus, whether born early or at term, is influenced by the maternal environment and adaptation of the developmental program to maternal stress signals may prepare the fetus for postnatal survival.

25.3.2.1 Changes in the Maternal HPA and Placental Axis Over the Course of Pregnancy

Regulation of the HPA axis is altered dramatically during pregnancy because the placenta expresses the genes for CRH (hCRHmRNA) and the precursor for ACTH and betaendorphin (proopiomelanocortin; see Figure 25.3). All of these stress-responsive hormones increase as pregnancy advances, but the exponential increase in placental CRH (pCRH) over the course of gestation in maternal plasma is remarkable, as by the latter half of gestation it reaches levels observed only in the hypothalamic portal system during physiological stress. pCRH is identical to hypothalamic CRH in structure, immunoreactivity, and bioactivity. There is, however, one crucial difference in its regulation. In contrast to the negative feedback regulation of hypothalamic CRH, cortisol stimulates the expression of hCRHmRNA in the placenta, establishing a positive feedback loop that allows for the simultaneous increase of pCRH, ACTH, and cortisol over the course of gestation (see for review, Sandman and Davis, 2010). The normative increase in stress-responsive hormones such as cortisol and pCRH plays an important role in the regulation of pregnancy as well as facilitating maturation of the fetus. However, because of the positive feedback between cortisol and pCRH, the effects of maternal stress on the fetus may

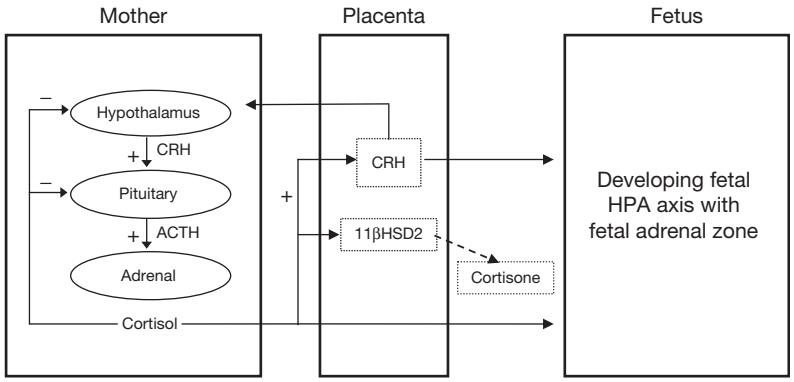

FIGURE 25.3 The regulation of the maternal HPA axis changes dramatically over the course of gestation with profound implications for the mother and the fetus. One of the most significant changes during pregnancy is the development of the placenta, a fetal organ with significant endocrine properties. In nonpregnant women, exposure to stress activates a cascade of events including the release of CRH, ACTH, and cortisol. This stress system is regulated by a negative feedback loop in which cortisol 'turns off' the HPA axis. During pregnancy, CRH is released from the placenta into both the maternal and fetal compartments. In contrast to the negative feedback regulation of hypothalamic CRH, cortisol *increases* the production of CRH from the placenta. Placental CRH (pCRH) concentrations rise exponentially over the course of gestation. Because of the positive feedback between cortisol and pCRH, the effects of maternal stress on the fetus may be amplified representing one pathway by which stress may exert influences on the fetus. In addition to its effects on pCRH, maternal cortisol passes through the placenta. However, the effects of maternal cortisol on the fetus are modulated by the presence of a placental enzyme 11βHSD2 which oxidizes it into an inactive form, cortisone. Activity of this enzyme increases as pregnancy advances, and then drops precipitously so that maternal cortisol is available to promote maturation of the fetal lungs and central nervous system as well as other organ systems. Structures of the HPA axis begin their development early in gestation and become increasingly functional with the progression toward term. See the text for description.

be amplified with potentially negative consequences for the developing fetus.

The effects of CRH and cortisol are modulated by the activities of binding proteins and enzymes. For example, in conjunction with the rapid acceleration of pCRH, CRH-binding protein levels decline sharply toward the end of gestation, increasing the availability of bioactive pCRH (McLean et al., 1995). Levels of binding protein have been associated with birth outcome (Hobel et al., 1999) and may moderate the activity and the effects of pCRH on the fetal nervous system. Maternal production of cortisol binding globulin (CBG) is stimulated by estrogen and thus levels increase progressively with advancing gestation, but then decline before term increasing fetal exposure to maternal cortisol in late gestation (Ho et al., 2007). Variations in CBG may contribute to individual differences in developmental outcomes because levels have been shown to be lower in women with growth-restricted fetuses (Ho et al., 2007). Another gestational timing effect may relate to the activity of the placental enzyme 11β-HSD2. This enzyme oxidizes maternal cortisol into cortisone, inactivating it and protecting the fetus from its direct and sometimes harmful effects during critical periods of development. The levels of placental 11β-HSD2 rise as gestation progresses before falling precipitously near term ensuring maturation of the fetal lungs, CNS and other organ systems in full-term births (Murphy and Clifton, 2003). Despite the presence of this protective enzyme early in gestation, maternal cortisol does reach the fetus and the amount varies with circulating maternal levels (Gitau et al., 1998). In addition, maternal stress down-regulates 11β-HSD2 activity in the placenta allowing a greater proportion of maternal cortisol to cross the placenta to reach the fetus (Mairesse et al., 2007; O'Donnell et al., 2011) with negative consequences for fetal growth and development (Kajantie et al., 2003). This is another mechanism whereby the consequences of maternal stress for the developing fetus may be amplified. Because of the timetable of fetal development and the changes in maternal and placental physiology, the consequences of stress exposures will vary on the basis of the gestational period of exposure.

It is critical to acknowledge that the differences in reproductive and stress physiology, even in very closely related species such as humans and nonhuman primates, limit the validity of generalizing from animal models (Power et al., 2006). For these reasons, this review focuses on studies of gestational stress in humans.

25.3.3 Fetal Adrenal Development

The fetal adrenals make unique contributions to both the regulation of fetal development and the timing of parturition. Cortisol is thought to play critical roles in the promotion of fetal maturation in preparation for extrauterine life. Further, DHEA sulfate produced by the fetal adrenal is an obligate precursor for placental estrogen and is thought to contribute to the initiation of parturition.

Morphologically, the fetal adrenal gland is comprised of two zones: the outer, definitive zone, and the large, inner fetal zone. Between these two zones is the transitional zone. The fetal and definitive zones can be recognized after the eighth gestational week. The fetal adrenals grow rapidly until the third trimester so that at term the fetal adrenals are significantly larger, relative to body weight, than the adult adrenals. At the end of human pregnancy, the fetal zone begins to atrophy. The human fetal adrenal has steroidogenic enzymes as early as the seventh gestational week and cortisol secretion can be detected as early as the eighth week. Cortisol production from the fetal adrenal is regulated by ACTH and ACTH-containing cells can be seen in the pituitary by eight gestational weeks (Jaffe et al., 1998; Kempna and Fluck, 2008). There is evidence that the fetus responds to pain with an increase in cortisol during the latter half of gestation (Gitau et al., 2001).

25.3.3.1 Fetal Brain Development and Susceptibility to Stress and Stress Hormones

The rapid changes in the developing fetal brain render it particularly susceptible to organizing and disorganizing influences of stress-responsive hormones such as cortisol and pCRH. Between 8 and 16 gestational weeks migrating neurons form the subplate zone, awaiting connections from afferent neurons originating in the thalamus, basal forebrain, and brainstem. Once neurons reach their final destination, they arborize and branch in an attempt to establish appropriate connections (Sidman and Rakic, 1973). Cessation of neuronal proliferation and migration to the cortical plate occurs around 20–24 weeks. However, dramatic changes in the organization of the cerebral cortex continue through term (Bourgeois, 1997; Volpe, 2008). During the last third of human pregnancy the fetal brain is forming secondary and tertiary gyri, and exhibiting neuronal differentiation, dendritic arborization, axonal elongation, synapse formation and collateralization, and myelination (Bourgeois, 1997; Volpe, 2008). Synapse formation during this period accelerates to a rate of approximately 40 000 synapses per minute (Bourgeois, 1997). Linear increases in total gray matter volume of 1.4% per week are seen from 29 to 41 gestational weeks and approximately 50% of the increase in cortical volume occurs between 34 and 40 gestational weeks (Kinney, 2006).

Regions of the brain that are both integral to the regulation of stress responses and vulnerable to exposure to stress hormones, including the hippocampus and amygdala, develop rapidly throughout gestation. Both are identifiable between 6 and 8 gestational weeks and by term the basic neuroanatomical architecture of these regions is present. Limited information exists regarding the time course of prenatal development of cortisol receptors in humans. There is evidence that both types of cortisol receptors are present in the human hippocampus by 24 gestational weeks (Noorlander et al., 2006).

Data from animal models have documented that exposure to prenatal maternal biological and psychosocial stress influences the developing fetal brain and endocrine systems producing long-term effects on cognition, emotion, and physiology in the offspring (Kapoor et al., 2006). Evidence for persistent organizational changes or programming influences on the nervous system has been growing and may include changes in neurotransmitter levels, cell growth and survival, and adult neurogenesis. For instance, at high concentrations, the CRH and cortisol may inhibit growth and differentiation of the developing nervous system. Considerable evidence indicates that glucocorticoids, such as cortisol, are neurotoxic to hippocampal CA3 pyramidal cells, and fetal exposure to high levels of glucocorticoids produces irreversible damage to the hippocampus. Similar neurotoxic effects are observed with exposure to high levels of CRH. Exogenously administered CRH increases neuronal excitation leading to seizures in limbic areas associated with learning and memory and may participate in the mechanisms of neuronal injury. These data from animal models suggest mechanisms by which early-life stress may provoke long-term effects on stress, emotional regulation, and cognition (see Joels and Baram, 2009; Seckl, 2008 for reviews).

25.3.4 Gestational Stress Influences the Human Fetus

In humans, a compelling body of work has documented that both maternal report of elevated maternal stress or anxiety and exposure to traumatic events during pregnancy are associated with increased risk for preterm birth. These associations are independent of sociodemographic and obstetric risk factors. There are several pathways by which maternal stress may lead to preterm birth including accelerated production of pCRH and altered vascular and immune functioning (see Dunkel Schetter and Glynn, 2011 for review). Preterm birth is associated with pervasive developmental delays (Aarnoudse-Moens et al., 2009). It is believed, however, that intrauterine exposures, including stress, contribute to these impairments independently from birth outcomes. The study of human fetal development is important because it provides a direct test of the fetal programming hypothesis with the opportunity to assess the effects of gestational stress on development before the effects of external forces, such as birth outcome, parenting, and socialization, are exerted.

The idea that the fetus is responsive to maternal distress is not new and there are a number of reports suggesting that maternal exposure to trauma (e.g., earthquake)

during pregnancy has direct and profound implications for fetal physiology and behavior (Ianniruberto and Tajani, 1981). More direct tests of the effect of maternal psychological state on the fetus come from studies manipulating maternal stress or anxiety and evaluating the consequences for fetal behavior. Fetuses display a consistent response profile in response to maternal exposures to moderate laboratory challenges such as the Stroop color-word test or viewing videos of labor and delivery (DiPietro, 2004). The nature of these responses appears to be moderated by maternal psychological state (Kinsella and Monk, 2009). These laboratory studies provide compelling evidence that fetuses are responsive to maternal stress and anxiety and they raise the possibility that repeated exposures over the course of gestation may influence the developing fetal nervous system.

Direct measures of fetal responses to external stimulation provide an index of fetal nervous system development and have been used to assess the developmental consequences of exposure to physical or maternal psychological stress. The response to a vibroacoustic stimulus (VAS) is an indication of fetal maturity reflecting maturation and integrity of neural pathways through the cerebral cortex, midbrain, brainstem, vagus nerve, and the cardiac conduction system. Using the fetal response to VAS, it has been shown that stress signals, most clearly pCRH trajectories, influence the developing fetal nervous system. Low pCRH is associated with more mature or earlier development of the fetus' ability to mount a response to the VAS and with a more mature profile to a classic habituation/dishabituation paradigm (Class et al., 2008; Sandman et al., 1999). Other maternal stress signals including overexpression of beta-endorphin and underexpression of ACTH have additionally been linked to the fetal response to VAS (Sandman et al., 2003).

These studies provide evidence that signals of maternal stress during gestation exert programming influences on the nervous system that cannot be explained by postnatal experiences. Continuity between the fetal and infant periods in assessments of movement and heart rate indicate that maternal influences that shape developmental trajectories during the prenatal period will continue to influence functioning postnatally (DiPietro, 2004). It is additionally clear that consideration of sexually dimorphic profiles of fetal development is necessary, as discussed later in this chapter.

25.3.5 Prenatal Maternal Psychosocial Stress and Infant and Child Development

25.3.5.1 Socioemotional Development

A growing literature indicates that prenatal exposure to elevated levels of maternal psychosocial stress is associated with behavioral and emotional disturbances during infancy and childhood among healthy full-term infants that is independent of postpartum maternal psychosocial stress (Bergman et al., 2007; Blair et al., 2011; Davis et al., 2004, 2007). Both maternal report of psychosocial stress and report of stressful life events are associated with more fearful and reactive behaviors during infancy and toddlerhood. Effects on social and emotional development continue to be observed during childhood and adolescence. Maternal antenatal anxiety and depression predict reports of childhood behavioral and emotional problems, including attention deficit hyperactivity disorder and anxiety problems (Davis and Sandman, 2012; O'Connor et al., 2002; Van den Bergh and Marcoen, 2004). These associations remain significant after controlling for birth outcomes and postnatal maternal psychological state. This suggests that signals of maternal psychosocial stress influence the fetal developmental trajectory with implications for children's functioning after birth.

25.3.5.2 HPA Axis Functioning

Alterations to the fetal HPA axis are frequently proposed as the primary biological pathway underlying fetal programming of later health and development. Animal studies suggest that the fetal HPA axis may be particularly vulnerable to prenatal exposure to maternal stress (Kapoor et al., 2006); however, relatively little is known about the consequences of prenatal maternal stress for HPA axis functioning in humans. There is evidence for higher cortisol levels, during a laboratory challenge among infants and toddlers exposed prenatally to elevated maternal cortisol (Grant et al., 2009). Several studies have suggested that prenatal maternal psychosocial stress is associated with altered circadian regulation during childhood and adolescence, both on typical days (O'Connor et al., 2005; Van den Bergh et al., 2007) and on days when stressors such as the first day of school are experienced (Gutteling et al., 2005). These studies suggest that prenatal exposure to maternal psychosocial stress may influence the developing fetal HPA axis and that this has implications for the regulation of cortisol production during infancy, childhood, and adolescence.

The mechanism by which maternal psychosocial stress is communicated to the fetus is unknown. It is unlikely that maternal cortisol mediates the effect of maternal report of psychosocial stress on child outcomes, as the majority of published studies find that during gestation maternal cortisol and psychosocial distress are not correlated and they exert independent effects on child outcomes (e.g., Davis and Sandman, 2010; de Weerth and Buitelaar, 2005; Harville et al., 2009). Data from human and animal models indicate that an epigenetic mechanism may underlie both the maternal communication of adversity to the fetus and the persistent

influence of the exposure (Champagne and Curley, 2009; Oberlander et al., 2008; Szyf, 2011). Further, maternal psychosocial stress exerts widespread influences on a number of stress-sensitive systems other than the HPA axis including the immune and vascular systems (Dunkel Schetter and Glynn, 2011) indicating alternative pathways by which maternal psychological distress signals may impact the developing fetus.

25.3.5.3 *Neurodevelopment*

The influence of gestational exposure to maternal psychosocial stress on cognitive and motor development is less clear. There is evidence that maternal self-report of elevated stress and anxiety as well as exposure to traumatic life events, such as severe ice storms, during pregnancy are associated with delayed infant and child cognitive, language, and neuromotor development, and that these deficits may persist into adolescence. However, not all studies have demonstrated such associations and there is evidence that modest elevations in psychosocial stress during late gestation may actually increase cognitive maturation (Davis and Sandman, 2010; DiPietro et al., 2006).

Inconsistencies across studies may suggest that moderate exposure to prenatal maternal psychosocial stress does not negatively affect neurodevelopment. It is plausible, however, that generalized self-report measures of psychological distress do not adequately characterize stress that is unique during pregnancy. As reviewed in Davis and Sandman (2010), evidence is emerging that measures of pregnancy-specific stress (e.g., "I am fearful regarding the health of my baby," "I am concerned or worried about losing my baby") are better than measures of generalized psychological distress for predicting neurodevelopmental outcomes including fetal behavior, infant neurodevelopment, infant and toddler cognitive and motor development, and child brain development. It is important to note that these associations are not explained by actual medical risk associated with pregnancy and birth outcome. Support for the importance of pregnancy-specific stress for developmental outcomes comes from a recent study documenting associations between elevated pregnancy-specific anxiety and decreased gray matter density at 6–10 years of age (Buss et al., 2010). Elevations in pregnancy-specific anxiety, particularly early in gestation, are associated with gray matter volume reductions in the prefrontal cortex, the premotor cortex, the medial temporal lobe, the lateral temporal cortex, the postcentral gyrus as well as the cerebellum, extending to the middle occipital gyrus and the fusiform gyrus. These brain regions are associated with a variety of cognitive processes including reasoning, planning, attention, memory, and language, and raise the possibility that developmental alterations to these regions may underlie associations between elevated pregnancy-specific anxiety and cognitive performance observed in prior studies (Buss et al., 2011).

25.3.6 Prenatal Maternal Biological Stress Signals and Infant and Child Development

Alterations to the maternal HPA and placental axis are most frequently cited as the mechanisms that underly fetal programming of later health and developmental outcomes. Although robust evidence exists from animal models, there are only a handful of studies that have evaluated the influence of biological stress signals during gestation on human development.

25.3.6.1 *Social/emotional Development*

Prenatal exposure to elevated maternal cortisol predicts increased fussiness, negative behavior, and fearfulness during infancy (Blair et al., 2011; Davis et al., 2007; de Weerth et al., 2003) and toddlerhood (Bergman et al., 2007). Further, there is evidence that elevations in pCRH contribute to the increased fearfulness observed during infancy (Davis et al., 2005). These studies suggest that maternal HPA and placental axis hormones contribute to the development of a fearful or reactive temperament. These data indicate that maternal and placental hormones contribute to the development of fearful temperament. New data from our prospective cohort suggest that this effect persists. Elevated gestational cortisol levels are associated with an increase in anxiety risk among preadolescent children (Davis and Sandman, 2012).

25.3.6.2 *HPA Axis Functioning*

Few studies have evaluated the consequences of prenatal maternal cortisol on HPA axis regulation in the offspring. In a prospective study with multiple prenatal assessments, it was documented that prenatal exposure to elevated levels of maternal cortisol is associated with a larger and more prolonged infant response to stress (Davis et al., 2011b). There is emerging, but as yet limited, evidence that this effect persists. In samples of 24 and 29 children, respectively, Gutteling et al. (2004) found that elevated maternal cortisol stress measured at one time during gestation (15–17 gestational weeks) independently predicted children's higher cortisol levels on the day of an inoculation and on the first day of a new school year. These studies provide evidence for effects of prenatal maternal cortisol on HPA axis functioning. Further prospective studies with multiple prenatal and postnatal measures are needed to address this question.

25.3.6.3 *Neurodevelopment*

Although little is known about the role of biological stress signals in shaping infant and child cognitive development, it is apparent that timing of exposure will be critical to understanding the developmental effects on outcome. Evidence suggests that the trajectory of maternal cortisol across gestation is the strongest predictor of child neurodevelopment. Elevated maternal cortisol during early and mid gestation has been associated with decreased neuromuscular maturity in the newborn (Ellman et al., 2008) and delayed cognitive development during toddlerhood (Bergman et al., 2010; Davis and Sandman, 2010). Conversely, elevated maternal cortisol late in gestation has been associated with significantly higher scores on measures of mental development at 1 year (Davis and Sandman, 2010).

These findings linking cortisol to neurodevelopment are remarkably consistent with its function in the maturation of the human fetus. Early in pregnancy, the fetus is protected from the naturally occurring increases in maternal cortisol by 11β-HSD2 (see Figure 25.3). However, because 11β-HSD2 is only a partial barrier, excessive increases in maternal cortisol early in gestation will expose the fetus to toxic levels with potentially detrimental consequences. In contrast, as pregnancy advances toward term, exposure to cortisol is necessary and beneficial for fetal maturation and exposure to increased cortisol is facilitated by the sharp drop in 11β-HSD2 activity, allowing a greater proportion of maternal cortisol to cross the placental barrier (Murphy and Clifton, 2003). The beneficial effects of modestly elevated cortisol during late gestation are consistent with animal models demonstrating that modest cortisol increases during the early postnatal period are associated with persisting beneficial effects for the developing brain (Catalani et al., 2000).

25.3.7 Is This Fetal Programming?

One concern that challenges research with humans is whether associations between maternal stress and anxiety and fetal outcomes should be interpreted as fetal programming, or alternatively, as a reflection of shared genetic factors. In the studies of naturally occurring variations in maternal cortisol or maternal self-reported stress, it is difficult to differentiate between these alternative explanations. The programming findings reported here, however, are consistent with animal models where random assignment is possible (Kapoor et al., 2006) and with human studies that evaluated the consequences of randomly occurring traumatic events, such as natural disasters (LaPlante et al., 2004; Yehuda et al., 2005) and with prenatal exposure to synthetic glucocorticoids (Davis et al., 2006, 2011a; French et al., 1999). More convincingly, in a recent human study, similar effects of prenatal stress on child outcomes were documented among children conceived by *in vitro* fertilization in a model where mother and fetus were genetically unrelated (Rice et al., 2009). Thus, while in most human studies of prenatal stress, genetic mechanisms cannot be ruled out as a possible explanation, there is reasonable evidence to warrant the conclusion that maternal stress has effects on the neurodevelopment of the fetus.

25.3.8 Summary

Both psychosocial and biological maternal stress signals are associated with developmental consequences for the fetus. Further, these effects cannot be accounted for by birth outcome or postnatal maternal psychological distress. However, it is important to acknowledge that biological and psychosocial stress signals tend not to be correlated during pregnancy and have been shown to exert independent influences on developmental outcomes (Sandman and Davis, 2012). Future research will have to examine vascular or immune pathways that could be mechanisms by which increases in maternal psychosocial stress might also affect the fetus.

These studies emphasize the importance of performing prospective longitudinal studies in order to evaluate the trajectory of maternal stress signals across gestation and its association with infant and child developmental outcomes. Data indicate that the trajectory or profile biological and psychosocial stress signals may be more critical for determining developmental outcomes as compared to level at a given gestational interval (Davis and Sandman, 2010; Glynn et al., 2008). Both severity and timing of exposure must be considered in order to evaluate associations between prenatal stress measures and infant outcomes. The adaptive significance of these associations is yet to be determined and requires long-term follow-up evaluating the interaction between the prenatal and the postnatal environments.

25.4 POSTNATAL DEVELOPMENT

25.4.1 Postnatal Development of the HPA Axis

At birth, the HPA axis is not morphologically mature (Gunnar and Vazquez, 2006). The adrenal cortex still includes the fetal zone that involutes over the first six postnatal months. As the fetal zone involutes, the structure of the mature gland becomes more distinct. CBG is low in the neonate, increasing gradually over the initial postnatal months. As a result, small increases in total (bound and unbound) plasma cortisol concentrations in response to stressors in the neonatal period may index large increases in the biologically active unbound

fraction of the hormone. There is also some indication that adrenal sensitivity to ACTH decreases over the first postnatal months (Forest, 1978), being higher in months 1–4 than later in development. Thus for several months following birth, the human HPA axis is more highly reactive to stimulation than it is later in development. This is consistent with evidence that during the first 3 or 4 months even mild stimulation (e.g., being undressed, weighed, and measured) provokes significant elevations in cortisol, while by 4 months of age the same stimulation no longer elevates cortisol in most typically developing infants.

The pattern of diurnal cortisol production also changes over the first few years of life (Gunnar and Vazquez, 2006). At birth, basal levels of cortisol bear no relation to time-of-day, although they are associated with levels of behavioral arousal. By as early as 6 weeks of age, an early morning peak and evening nadir can be observed; however, because of marked day-to-day variability, observing these aspects of the diurnal rhythm requires analytical methods that isolate average patterns from variability. In the next months, the peak and nadir become more distinct; but, it is not until about 4 years of age as children give up their daily naps that a more fully mature pattern is noted from mid-morning to late afternoon. Throughout the first few years of life, napping is associated with decreases in cortisol over the nap periods and rebounds to prenap levels by about 30–45 min after the child awakens. Other normal daily events have also been associated with decreases and then rebounds in cortisol levels; the rebounds can be misinterpreted as a stress response. Such normal events include the car trip the child takes on the way to the laboratory for testing. Thus accurate assessment of HPA activity during infancy requires control of more than time-of-day.

Following infancy, there is little developmental change in cortisol levels or reactivity until puberty. Over the pubertal transition, basal cortisol levels increase, with the sharpest increase around Tanner stage 3 (Netherton et al., 2004). Reactivity of the axis to psychosocial stressors also appears to increase with puberty (Stroud et al., 2009). As there is evidence that pubertal maturation is associated with increased reactivity of emotion systems, researchers have speculated that increased HPA activity at puberty may contribute to the psychiatric vulnerability associated with this period of development (Spear, 2000). It may also be that the impacts of early experience on the development of HPA reactivity and regulation are not fully realized until the neurobiological changes associated with puberty and adolescent development have occurred.

Because the HPA axis is under multifactorial regulation (Ulrich-Lai and Herman, 2009), developmental changes in HPA reactivity and regulation are also dependent on the development of the many systems whose activity ultimately impinges on CRH-producing neurons in the hypothalamus. With regard to psychological stressors, the amygdala and BNST are critical in activation of the axis, while the hippocampus and medial prefrontal cortex (mPFC) are involved in constraining and terminating its response (see Figure 25.2). There is no information on how development of these extrahypothalamic structures affects reactivity and regulation of the human HPA response to stressors during childhood and adolescence. Furthermore, there is little information on the developmental changes in GRs in extrahypothalamic regions in humans. There is evidence that, unlike in the rodent, there is no developmental increase in GR in the hippocampus over development, suggesting that the capacity of the hippocampus to contain and terminate HPA responses to stressors is relatively mature at birth (Pryce, 2008). In contrast, GR mRNA expression levels do increase into adolescence in regions of the prefrontal cortex, consistent with evidence that GR expression is as high or higher in the neocortex in humans as it is in the hippocampus (Pryce, 2008). This latter finding suggests that in human development, activity of the HPA axis both impacts and is importantly affected by the ontogeny of prefrontal circuits. The protracted development of neural systems involved in and affected by activity of the HPA axis further suggests that postnatal experiences will shape the complex circuitry of what Joels and Baram (2009) termed the 'neurosymphony of stress.'

25.4.2 Social Regulation of the HPA Axis in Human Development

In rodents and nonhuman primates, there is considerable evidence that proximity and contact with the caregiver is critical to regulation of the HPA axis (Sanchez et al., 2001). This is also true in human development. As early as the first months of life, infants cared for by more sensitive and responsive caregivers show a more rapid return to baseline following activation of the axis (Blair et al., 2006), while those receiving insensitive care exhibit increases in cortisol during parent–infant play sessions (Spangler et al., 1994). The role of sensitive and responsive care in regulating the axis extends to infants' experiences with surrogate caregivers, including child care providers (Vermeer and van IJzendoorn, 2006). Indeed, throughout the preschool period there is evidence that, for children in out-of-home child care, elevations in cortisol over the child care day are larger for those who receive less sensitive and/or more intrusive/overcontrolling care than for those who are receiving more sensitive care.

Sensitive responsive caregiving is an important feature in the development of secure attachment

relationships. Attachment security is not a trait of the child but characterizes the relationship between a child and their adult caregiver. Children can be securely attached to one parent and insecurely attached to the other. Notably, all studies of the relations between attachment security and regulation of the HPA axis have been done examining mother–child relationships. Overall, children are able to use the presence and availability of their mother more effectively to regulate reactivity of the HPA axis if their relationship is secure rather than insecure (Gunnar and Donzella, 2002). This has been shown in studies using brief separations followed by reunions as the stressor, as well as in studies using physical stressors (i.e., inoculations). In studies of psychosocial threat (e.g., approach by strange objects, individuals), whether or not the effect is observed depends on whether the child exhibits fear behavior or not. For those exhibiting fear, the presence and availability of the attachment figure in secure relationships blocks elevations in cortisol, while in insecure relationships elevations are observed. What this suggests is that access to the mother in secure attachment relationships prevents fear and other negative emotions from stimulating elevations in cortisol. However, this is not the case when the mother is present but the attachment relationship is insecure. There is no understanding of the neurobiological processes underlying maternal buffering of the axis for frightened/distressed infants. One possibility is that secure relationships stimulate larger increases in oxytocin, a presumed antistress neuropeptide (Gouin et al., 2010). Among adults, intranasal infusions of oxytocin increase the stress-buffering effects of social support (Heinrichs et al., 2003). Thus greater productions of oxytocin among fearful infants when the mother is present in secure relationships may help to buffer or block cortisol increases.

While sensitive, responsive care and secure attachment relationships are expected to shape more regulated anxiety and stress responses over time, it is clear that early in life the actual presence of the attachment figure is needed to buffer activity of the HPA axis. A study of toddlers entering a new child care arrangement has shown that while toddlers in secure attachment relationships had lower cortisol levels during days when their mother accompanied them to child care (adaptation), as soon as she was no longer present, no differences in cortisol levels were observed as a function of attachment security (Ahnert et al., 2004). Furthermore, marked elevations in cortisol, relative to home levels, were noted for the first several weeks of child care, with these elevations decreasing but not eliminated after 5 months of experience in the care setting. Thus, however the buffering effect of attachment security is operating early in life, it is a characteristic of the relationship and requires the presence of the adult figure with whom the child is securely attached.

25.4.3 Early Care and HPA Axis Functioning

Given the powerful role of social relationships in regulating reactivity of the HPA axis early in life, one might expect that a child's early care history will shape the development of behavioral and HPA reactivity and regulation. That is, as in the animal literature, programming of threat reactive systems will extend into the postnatal period (Sanchez et al., 2001). While there is no question that early pathogenic care increases the risk of a variety of poor outcomes in human development, in every domain studied individual differences in susceptibility are substantial and numerous factors beyond early exposure to adverse care appear to be involved in predicting whether significant early experience effects are observed or not (Cicchetti and Rogosch, 1996).

The range of early care conditions examined in human studies is large, including not only normal variations in parental sensitivity and responsiveness but also neglect, physical and sexual abuse, exposure to interparental conflict and violence, global deprivation (as in orphanages/institutional care), parental loss, and conditions that often interfere with adequate caregiving (e.g., maternal depression, extreme poverty, homelessness). Some of the conditions involve repeated, acute experiences of threat (i.e., physical abuse), others more chronic experiences of the absence of supportive care (e.g., institutional rearing, neglect). Typically, these experiences do not occur in isolation from one another, and often their effects appear to be cumulative (Brown et al., 2009). With rare exceptions (e.g., children adopted from orphanages), care conditions early in life are more or less predictive of care conditions throughout childhood. Thus it is often challenging to isolate the impacts of early versus later experiences on activity of the HPA axis. Adding to the challenge of understanding the role of early care qualities is the fact that few studies of vulnerable children have examined reactivity and regulation of the HPA axis under conditions known to elicit stress responses. Most studies have either examined patterns of diurnal cortisol production and/or exposed children to mild challenges that do not activate the axis in most individuals (i.e., cognitive testing without feedback; Dickerson and Kemeny, 2004).

25.4.3.1 Diurnal Cortisol Patterns

As noted, the diurnal rhythm of the HPA axis is still maturing during the first years of life. It appears to be sensitive to adverse care, although alterations in diurnal patterns do not appear to be permanent, but rather associated with the more immediate contexts of early care. Effects of care context on diurnal patterns were first noted in research on 2- and 3-year-olds living in a Romanian institution. Of the 46 children studied, not one exhibited a typical diurnal pattern as sampled soon after wakeup,

at noon, and in the early evening. Compared to home-reared Romanian children, average levels were significantly lower in the early morning and tended to be higher, but not significantly so, in the early evening hours (Carlson and Earls, 1997). Similar results have been obtained in studies of preschool-aged children recently removed from maltreating homes and placed in foster homes (Bruce et al., 2009). It is not clear whether the child's age or type of adverse care influences associations with diurnal patterns. There is some evidence that among preschool-aged children emotional maltreatment may be associated with elevated early morning cortisol levels, while neglect is associated with abnormally low levels (Bruce et al., 2009). Studies of children adopted from institutions have noted similar low early morning levels, and hence a relatively flat pattern of cortisol production over the daytime hours. Nonetheless, when post-institutionalized children are studied several years after adoption they all exhibit the typical pattern of high morning and low evening cortisol production (e.g., Kertes et al., 2008). In addition, for children studied monthly for a year in foster care, increasingly flat diurnal patterns have been observed in the absence of interventions designed to help foster parents provide more supportive care, with lower early morning levels being associated with the degree of parenting stress reported by the foster parent (Fisher and Stoolmiller, 2008). Thus, it seems likely that the degree, and possibly the type of alteration in the diurnal rhythm in young children indexes stress in relation to the current context and is not a reflection of permanent alterations in the set point or regulation of the diurnal rhythm.

There are several caveats worth noting. First, although the results have focused on average patterns in cortisol production over the day, day-to-day variability may be just as important. Indeed, one of the impacts of providing support and training to foster parents is that over the course of a year, evening cortisol levels in the children become increasingly stable and low from day to day, while this is not the case for children in regular foster care. Second, in most studies, early morning samples were taken 30 or more minutes after awakening, and thus it is not clear whether the magnitude of the cortisol awakening response is what is reflected in the findings and not wakeup cortisol, which reflects the diurnal rhythm. Thus far, to our knowledge, there are no published studies of the cortisol awakening response during early childhood in children experiencing early adverse care.

25.4.4 Effects of Early Care on Cortisol Set Points and Reactivity

Animal models of early care lead to the prediction of unidirectional effects. That is, poorer quality care early in life shapes the set point of the HPA axis and increases behavioral and physiological reactivity to threat. Recently, Boyce and Ellis (2005) have argued for a U-shaped pattern whereby moderate parental support early in life reduces, while both extremely high and low supportive care results in heightened behavioral and physiological reactivity. Thus far, there have been few tests of the argument that extremely supportive care is associated with heightened behavioral and physiological reactivity to threat. There is more support for the argument that poorer care and/or conditions associated with poorer early-life care predict increases in HPA set points and reactivity or lability. Thus, children whose mothers reported significant economic stress and depressive symptoms during the children's infancy exhibited higher afternoon cortisol levels at age four if the family was still under economic stress at that time, and levels of cortisol at this age predicted heightened internalizing problems in first and second grade (Essex et al., 2002; Smider et al., 2002). Among extremely poor families in rural Mexico, a cash-transfer program instituted during the children's infancy was associated with lower cortisol levels, but not less HPA reactivity, when the children were 2 to 6 years old (Fernald and Gunnar, 2009). Likewise, after controlling for later depressive symptoms in the mother, offspring of women who suffered postnatal depression were found to exhibit higher and more labile early morning cortisol concentrations at age 13, which mediated the expression of depression in the children by age 16 (Halligan et al., 2007).

In contrast to these findings, studies of internationally adopted children who experienced severe neglect before adoption challenge the expectation of elevated set points and reactivity following lack of supportive care early in life. Among a small sample of preschool-aged children studied 3 years post adoption, severe preadoption neglect was associated with higher basal urinary cortisol levels and poorer cortisol regulation following a mother–child, but not stranger–child stressor task (Wismer Fries et al., 2008). Among a larger group of children studied in middle childhood, higher early morning levels were noted, but only as a function of physical growth delay at adoption (Kertes et al., 2008). Consistent with the possibility of continued programming of the axis during the postnatal period, this latter finding is very reminiscent of programming effects that have associated poorer intrauterine growth with activity of the HPA axis later in life (Phillips et al., 2000).

Thus far, work on postinstitutionalized children has not revealed evidence of hyperresponsivity of the axis to psychosocial stress in the form of the Trier Social Stress Test (TSST), a public speaking stressor (Gunnar et al., 2009), although only one study has been reported thus far and the children were largely prepubertal. Notably, a recent study of teenage girls in child protective service examined cortisol and cardiac reactivity to the TSST and

noted blunted cortisol but not cardiac responses in these maltreated girls relative to nonmaltreated controls (MacMillan et al., 2009). It is not clear whether the difference between findings for postinstitutionalized and maltreated children reflect differences in the type and timing of early adversity, the timing of assessment (pre- versus postpubertal) or the concurrent life circumstances of the children (stable families versus foster care).

Adult studies of individuals maltreated as children have shown that patterns of HPA reactivity to psychosocial stressors depend on psychiatric diagnosis. For those suffering major depression, childhood maltreatment is associated with hyperreactivity and poor regulation of the axis, a pattern not seen among depressed adults without an early history of maltreatment (Heim et al., 2008). Conversely, among emotionally healthy adults, histories of more adverse family life conditions in childhood (i.e., maltreatment, interparental conflict, rejection) have been associated with a lower set point of the HPA axis and smaller cortisol responses to psychosocial stressor tasks (Carpenter et al., 2007). It has also been noted that among school-aged children, whether those who were sexually abused before age 5 exhibited altered cortisol production during a 5-day camp for maltreated children depended on whether the child exhibited internalizing behavior problems or not (Cicchetti et al., 2010). The confluence of internalizing problems and early sexual abuse predicted altered cortisol production, while neither factor alone appeared to have any association with cortisol levels (although for contradictory findings, see MacMillan et al., 2009).

The effects of trauma on the HPA axis also appear to depend on whether the individual develops posttraumatic stress disorder (PTSD) or not. Studied among adults, individuals with PTSD exhibit normal to low basal levels of cortisol; with varying evidence of hyper- or hyporeactivity to stressors, perhaps related to the extent that the stressor is reminicient of the original traumatizing experience (Yehuda, 2000). Among prepubertal children, PTSD appears to be associated with elevated levels of cortisol production (see review, Tarullo and Gunnar, 2006). Among sexually abused girls with PTSD assessed over time, elevated cortisol levels have been noted in childhood, with decreasing levels beginning in adolescence and levels lower than normal by adulthood (Trickett et al., 2010). It is still not clear whether puberty shifts the relation between PTSD and set points of the axis from hyper to hypo, or whether it is the time since trauma, which gradually alters the axis from hyper- to hypofunctioning.

25.4.5 Individual Differences

Numerous factors likely influence susceptibility to both pre- and postnatal programming of fear- and stress-response systems. Three factors are briefly mentioned here: sex differences, temperamental fearfulness or inhibition, and genes.

There is a developing literature suggesting that there are sexually dimorphic profiles of fetal development (Clifton, 2010). Compelling data from animal models document sex-specific consequences of stress hormone exposure (Goel and Bale, 2009). Further, there is growing appreciation that human fetal neurological development is different for males and females (Bernardes et al., 2008; Buss et al., 2009; DiPietro et al., 1998) and that gestational influences on fetal neurodevelopment may be associated with sex-specific postnatal developmental trajectories including risk for psychiatric disorders (Costello et al., 2007; Goel and Bale, 2009). The role of sex as a moderator of the effects of early postnatal care on fear- and stress-response systems is not clear (Gunnar and Vazquez, 2006). While there are some studies that indicate larger impacts of early parental care for boys than girls, many other studies have not indicated differential sensitivity by sex to variations in supportive early care.

Behavioral inhibition describes a temperament dimension defined by greater behavioral reactivity and inhibition of approach to novel, arousing, or unpredictable stimulation. Behaviorally inhibited infants often develop into children who are shy and prone to social anxiety (Chronis-Tuscano et al., 2009). While there is some evidence that extremely inhibited children have higher cortisol levels and reactivity (Kagan et al., 1987; Schmidt et al., 1997), this is not always found and likely depends on contextual factors, such as the degree of support the child has from attachment figures and whether inhibiting approach is an effective option for regulating stress (Gunnar, 2001; Gunnar and Donzella, 2002). The larger cortisol responses that fearful, inhibited children experience in the context of less supportive care may help mediate the greater vulnerability of these children to adverse early-life care (Phillips et al., 2011). However, their sensitivity may also allow them to excel in higher-quality care environments; a possibility proposed by Boyce and Ellis in their biological sensitivity to context theory (Boyce and Ellis, 2005).

As suggested by the work on behavioral inhibition, sensitivity to variations in the quality of early-life care may be influenced by genetic inheritance. For example, the type 1 CRH receptor mediates behavioral and physiological reactions to threat-provoking stimuli and there is now evidence that variants in the CRHR1 gene interact with early abuse histories to increase the risk of depression (Gillespie et al., 2009). A number of genetic polymorphisms have also been noted in genes that play key roles in the regulation of GR and thus the expression of glucocorticoid-responsive genes (Derijk and de Kloet, 2008). These too may influence risk and resilience to trauma and variations in the quality of early care environments (Derijk and de Kloet, 2008; Gillespie et al., 2009).

In the studies of children, variations in other genes, including those regulating major neurotransmitter systems, have been found to moderate relations between care experiences and reactivity of the HPA and sympathetic nervous system (Frigerio et al., 2009). Notably, although from a stress-diathesis perspective one might view genetic factors as increasing vulnerability to adverse early care, they may instead produce differential susceptibility to both the positive and negative qualities of early care (Belsky and Pluess, 2009).

25.4.6 Summary

Research on infants and children conducted over the last few decades has begun to illuminate the impact of postnatal experiences on the development of stress-mediating neurobiological systems. The human HPA axis continues to develop postnatally with significant changes in functioning over the first six postnatal months. Throughout infancy and early childhood the axis is under strong social regulation. Sensitive, responsive care maintains the axis in a relatively quiescent state and permits rapid returns to basal functioning following perturbations. There is increasing evidence that adverse care early in life impacts neurobehavioral development and impacts diurnal patterns of cortisol production assessed concurrently. There is emerging, but as yet sparse and sometimes conflicting, evidence that early neglect and abuse may be associated with long-term changes in the reactivity and regulation of the HPA axis and that effects on this neuroendocrine system may mediate some of the poor mental and physical outcomes of early maltreatment. In part, some of the conflicting findings appear related to the age at assessment as there may be changes in HPA functioning following early maltreatment or trauma that differ as a function of whether assessment is conducted before or after puberty. Some of the conflicting findings also appear to be related to whether or not the individual is suffering from an affective disorder or not, and if so, the nature of the disorder (i.e., depression, PTSD). Genetic variation likely contributes to the heterogeneity of outcomes noted both with regards to impacts on the HPA axis and on emotional functioning. Of particular note, however, are recent arguments that the same genes and/or emotional temperament that may result in heightened vulnerability to poor outcomes following early adverse care may also result in more optimal functioning, given positive early care experiences. Thus, while postnatal experiences appear to influence the developing neurobiology of stress reactivity and regulation, the role of individual differences and developmental timing are critical issues whose effects are still in need of a more complete explication.

25.5 FUTURE DIRECTIONS

The study of pre- and postnatal stress and its impact on neurodevelopment and health has thus far proceeded largely independently. It is time for this work to become integrated, both empirically and theoretically. While researchers studying prenatal stress have sometimes obtained measures of outcomes later in life, it is rare that postnatal experiences are examined as anything other than potential confounds to be controlled statistically. Yet, postnatal experiences have the potential to either ameliorate or exacerbate prenatal effects. In addition, alterations in infant functioning related to prenatal experiences may result in differential sensitivity to variations in early care experiences and/or behaviors that elicit different responses from caregivers. As noted, some researchers are beginning to address how the postnatal care interacts with prenatal stress exposure to influence cognitive, behavioral, and health outcomes. More of this work is needed.

From a fetal programming perspective, it is especially critical that conceptual models are examined via longitudinal studies that track postnatal development. Thus, if as some models posit, fetal programming via stress mediators prepares the fetus to survive in a harsh postnatal world (Gluckman and Hanson, 2004), then evidence is needed to support such a hypothesis. There is some evidence that this may be the case with regard to nutrition such that concordance in pre- and postnatal nutrition leads to more functional health outcomes than discordance (Armitage et al., 2005; Cleal et al., 2007). However, it is not known whether a similar adaptive advantage exists for other types of prenatal stressors and/or for other kinds of postnatal outcomes.

Consistent with early literature on outcomes for premature infants, it is also possible that a supportive postnatal environment may ameliorate and a harsh environment exacerbates the neurobehavioral sequelae of prenatal stress. In this case, discordance in the harshness of pre- and postnatal experience may predict better outcomes. Recent human studies have provided support for this possibility demonstrating that high-quality maternal care can compensate for the negative effects of prenatal stress exposures (Bergman et al., 2008, 2010). It remains likely that the effects of stress during the prenatal and postnatal periods will differ by developmental outcome and there is a clear need for prospective studies with multiple prenatal and postnatal assessments.

As noted earlier, there is an emerging literature that suggests that prenatal stress may operate on circuits that support enhanced behavioral inhibition or anxiety. If so, then an intriguing possibility is that prenatal stress may enhance the young child's sensitivity to its rearing context, resulting in more optimal outcomes under supportive conditions and poorer outcomes under harsh conditions than

may be noted for infants from nonstressed pregnancies. Whether this is the case has not been explored, but is an example of the need to integrate pre- and postnatal conceptual models.

Thus far, only these future direction comments on the value of incorporating research and theory on postnatal stress into models and research on prenatal stress have been focused upon. Perhaps a more critical need is for those studying postnatal stress to consider the role that prenatal stress may be playing in their findings. Certainly it seems likely that children who are abused, neglected, or abandoned to orphanage care may be the product of stressed pregnancies. It also is likely that they are the products of pregnancies complicated by poor nutrition and exposure to alcohol and drugs. Unfortunately, in many studies of postnatal stress there is meager information about prenatal conditions or even birth outcomes. Retrospective reports obtained from parents in studies, for example, of child maltreatment must be suspect. For children abandoned to orphanage care, often even the child's age at abandonment is unknown, let alone their gestational age and health at birth and any record of prenatal conditions. Nonetheless, despite the challenge of obtaining accurate information on prenatal conditions for children identified because of their poor postnatal care, studies are needed where such information can and has been obtained. This is particularly important in studies examining interventions to improve outcomes as prenatal conditions may moderate how the child responds.

Finally, one area that would seem ripe for integration into research on pre- and postnatal stress is the role that the dramatic hormonal changes that accompany pregnancy contribute to the quality of postnatal caregiving. Stress and reproductive hormones during pregnancy are associated with maternal cognitive functioning (Glynn, 2010), the development of postpartum depression (Yim et al., 2009), and the quality of maternal care (Feldman et al., 2007). The maternal hormonal milieu also impacts the developing fetus, as was discussed. Thus, to close the loop on the understanding of the ways in which stress impacts the developing fetus and young child, studies that incorporate the impacts of stress and maternal hormonal changes on the mother, her caregiving, and her response to her infant are needed.

SEE ALSO

Cognitive Development: The Neural Correlates of Cognitive Control and the Development of Social Behavior.

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