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Review article

Cortisol and DHEA in development and psychopathology

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ABSTRACT

Dehydroepiandrosterone (DHEA) and cortisol are the most abundant hormones of the human fetal and adult adrenals released as end products of a tightly coordinated endocrine response to stress. Together, they mediate short- and long-term stress responses and enable physiological and behavioral adjustments necessary for maintaining homeostasis. Detrimental effects of chronic or repeated elevations in cortisol on behavioral and emotional health are well documented. Evidence for actions of DHEA that offset or oppose those of cortisol has stimulated interest in examining their levels as a ratio, as an alternate index of adrenocortical activity and the net effects of cortisol. Such research necessitates a thorough understanding of the co-actions of these hormones on physiological functioning and in association with developmental outcomes. This review addresses the state of the science in understanding the role of DHEA, cortisol, and their ratio in typical development and developmental psychopathology. A rationale for studying DHEA and cortisol in concert is supported by physiological data on the coordinated synthesis and release of these hormones in the adrenal and by their opposing physiological actions. We then present evidence that researching cortisol and DHEA necessitates a developmental perspective. Age-related changes in DHEA and cortisol are described from the perinatal period through adolescence, along with observed associations of these hormones with developmental psychopathology. Along the way, we identify several major knowledge gaps in the role of DHEA in modulating cortisol in typical development and developmental psychopathology with implications for future research.

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Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; 3βHSD, 3β-hydroxysteroid dehydrogenase; ACTH, Adrenocorticotropic hormone; ADHD, Attention deficit hyperactivity disorder; AVP, Arginine vasopressin; cAMP, Cyclic adenosine monophosphate; CBG, Corticosteroid binding globulin; CD, Conduct disorder; CRH, Corticotropin-releasing hormone; DBD, Disruptive behavior disorder; DHEA, Dehydroepiandosterone; DHEA-S, Dehydroepiandosterone sulfate; ED, Eating disorder; $GABA_A$, γ-Aminobutyric acid type A; GR, Glucocorticoid receptor; HPA, Hypothalamic-pituitary-adrenocortical; MR, Mineralocorticoid receptor; NMDA, *N*-methyl-D-aspartate; ODD, Oppositional defiant disorder; PFC, Prefrontal cortex.

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1. Introduction

The process of responding to stress involves direct and recursive actions of multiple stress-responsive systems interacting in a highly coordinated fashion. One system central to the biological response to stress is the hypothalamic-pituitary-adrenocortical (HPA) axis. The HPA axis is essential for maintaining an optimal homeostatic state for an individual by dynamically adapting to environmental demands (Juster et al., 2010). However, function of the HPA system can become rapidly dysregulated under conditions of prolonged stress, leading to alterations in levels and sensitivity of the hormones it produces (Egeland et al., 2015; McEwen, 2003). As these hormones exert broad and potent influences throughout the brain and body, changes in their function have widespread implications for physical health and psychological well-being. Moreover, adrenocortical hormones jointly impact a variety of processes related to immunologic, metabolic, and cognitive function. Thus, quantifying their relative abundance may provide different, but potentially important, information compared to levels of individual hormones.

The current review focuses on joint effects of two adrenal hormones central to the biological response to stress, cortisol and dehydroepiandosterone (DHEA). Both are secretory signaling molecules released by the HPA axis as outputs of a coordinated hormonal cascade. Both also exert pleiotropic actions in the brain and periphery (McEwen, 2003). DHEA can be further converted into a second hormone, dehydroepiandosterone sulphate (DHEA-S), which, due to a slow rate of clearance from circulation and long biological half-life, comprises the majority of DHEA in circulation. Along with being the most abundant hormones of the adrenocortical system, DHEA and DHEA-S are also highly developmentally sensitive and their levels change markedly with age (Kroboth et al., 1999; Orentreich et al., 1984). Because the two forms induce many of the same physiological effects in the brain and body (see Dong and Zheng, 2012; Stárka et al., 2015), unless specifically indicated otherwise, will hereafter be collectively referred to as DHEA(S).

As the endocrine arm of the biological stress response, the HPA axis innervates numerous regulatory systems with effects on stress responding, arousal, immunity, attention, and cognition. Accordingly, altered HPA axis activity is implicated in the etiology and severity of numerous physical and mental health outcomes. As cortisol and DHEA(S) serve interconnected but largely opposing functions as it pertains to these processes, there has been growing interest in the potential value of examining the two as a ratio reflecting their proportional levels (Chen et al., 2015; Sollberger and Ehlert, 2015). Such an approach supplants the traditional method of examining cortisol and DHEA(S) as separable markers of adrenocortical activity. Instead, it presumes that a more sensitive index of HPA axis function and associated risk for psychopathology is achieved by considering concentrations of the two hormones relative to one another.

Compared to a well-established literature on the physiology of cortisol in the brain and periphery (Joëls et al., 2012; Nicolaides et al., 2014) and cortisol's pre- and postnatal associations with stress system functioning and stress-related psychopathology (Hostinar et al., 2014; Zijlmans et al., 2015), a comparable understanding of DHEA(S) is still in the early stages. The extant literature on DHEA(S) is most extensive in aging and age-related alterations in physical health and cognitive function. However, little is known about the role of DHEA(S) early in development, particularly in mediating stress responses and risk for stress-related psychopathology. Despite this knowledge gap, evidence that DHEA(S) antagonizes effects of cortisol (Buoso et al., 2011; Karishma and Herbert, 2002; Pinto et al., 2015), thereby lessening its physiological potency, has called attention to the cortisol/DHEA(S) ratio and what it can tell us about neurobiological processes underlying the risk for disorder.

This review details contemporary knowledge regarding level and function of DHEA(S) and cortisol from the prenatal period through adolescence. Particular attention is paid to known and hypothesized effects of their interaction in typical development and developmental psychopathology. First, the HPA axis and the physiology and actions of DHEA(S) and cortisol in response to stress exposures are reviewed. Differing functions of the two hormones are highlighted, as are reasons why examining them as a ratio may enhance understanding of adrenocortical function. Next, age-related changes in levels of DHEA(S) and cortisol from the prenatal period through adolescence are detailed, along with the purported role played by the cortisol/DHEA(S) ratio in risk for psychopathology. Final sections discuss important considerations in the study of cortisol and DHEA(S) and areas of research that could advance understanding of the role of these hormones in development and psychopathology.

2. Synthesis and production of cortisol and DHEA(S)

Activation of the HPA axis sets in motion a complex signaling pathway tightly regulated by a series of feedback and feedforward mechanisms. Neurons in the medial parvocellular region of the hypothalamus release corticotropin-releasing hormone (CRH), as well as arginine vasopressin (AVP), into hypophyseal portal circulation via the median eminence (Cone et al., 2003; Herman et al., 2005). CRH binds to receptors on the anterior pituitary to stimulate the production of adrenocorticotropic hormone (ACTH). ACTH then travels through the bloodstream to the adrenals to initiate the synthesis and release of cortisol and DHEA(S) (Cone et al., 2003; Herman and Cullinan, 1997). Whereas the adrenals produce the totality of circulating cortisol in the body, they are responsible for approximately 80% of DHEA, with the remainder produced by the testes, ovaries, and brain (de Peretti and Forest, 1978; Labrie et al., 2011). Within the adrenals, production of cortisol and DHEA occurs in different layers, with cortisol produced in the zona fasiculata and DHEA in the zona reticularis.

ACTH binding to receptors in the plasma membrane of adrenal cells activates adenylyl cyclase, which in turn elevates intracellular levels of cyclic adenosine monophosphate (cAMP). This leads to activation of cAMP-dependent protein kinase and, ultimately, to the enzymatic steps necessary for the biosynthesis of cortisol and DHEA (Tsai and Beavo, 2011). Steroidogenesis begins with transport of cholesterol from intracellular stores to the inner mitochondrial membrane, facilitated by translocator protein-18 kDa and steroidogenic acute regulatory protein. Next, cleavage of the cholesterol side chain by the cholesterol side chain cleavage enzyme (encoded by cytochrome P450scc/CYP11A1) generates pregnenolone, the rate-limiting step of adrenal steroidogenesis (Han et al., 2014; Hu et al., 2010). The P450c17/CYP17 enzyme then catalyzes the 17α-hydroxylase reaction that converts

pregnenolone into 17α-hydroxypregnenolone. P450c17/CYP17 is found in both the fasciculata and reticularis zones of the adrenals, consistent with its role in both cortisol and DHEA synthesis (Auchus and Rainey, 2004).

Biosynthesis of DHEA ends with its hydroxylation at the C-17 position and side-chain cleavage by P450c17, in conjunction with P450 oxidoreductase (an electron donor for P450c17) and cytochrome *b*5 (an allosteric factor promoting 17,20-lyase reaction; Webb et al., 2006). Contributing to its pleiotropic actions, DHEA can be further converted into other biologically active metabolites (Lu et al., 2008; Rainey and Nakamura, 2008). DHEA is readily interconverted between its sulfated and non-sulfated forms by the actions of the cystolic sulfotransferase, SULT2A1, and the microsomal enzyme, steroid sulfatase, respectively (Lu et al., 2008). It is also converted into androstenedione via the actions of 3β-hydroxysteroid dehydrogenase (3βHSD) and, subsequently, into the sex hormones, estradiol or testosterone, by 17β-hydroxysteroid dehydrogenase.

Whereas 3βHSD is inversely associated with biosynthesis of DHEA(S), its expression is essential for that of cortisol by converting pregnenolone into progesterone and 17α-hydroxyprogesterone (Rainey and Nakamura, 2008). Final steps involve the conversion of progesterone into 11-deoxycortisol by 21-hydroxylase and into cortisol by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). Notably, the 11β-HSD enzymes are essential to maintaining appropriate concentrations of active glucocorticoids in cells and tissues; 11β-HSD1 promotes reduction of 11-keto-derivatives into active cortisol while 11β-HSD type 2 (11β-HSD2) catalyzes cortisol's conversion to inactive cortisone (Webb et al., 2006).

Not only does the release of distinct steroid-metabolizing enzymes by the various zones of the adrenals lead to their steroid-specific production, but this pattern of enzyme release is age-dependent. This results in a ratio of cortisol to DHEA(S) that varies across the life course. Consistent with this, the fetal adrenals, which produce vast amounts of DHEA(S), contain little 3βHSD (Narasaka et al., 2001; Rainey and Nakamura, 2008). Similarly, during adrenarche, the zona reticularis experiences a significant decline in its production of 3βHSD, precipitating the spike in DHEA(S) seen at this time (Endoh et al., 1996; Rainey and Nakamura, 2008). These developmental changes in enzymatic action are thought to underlie the production of high levels of DHEA(S) during pregnancy and again at the initiation of puberty without change in level of cortisol (Goto et al., 2006).

3. Mechanisms of action of cortisol and DHEA(S)

Once synthesized, cortisol and DHEA(S) are able to exert widespread effects throughout the body via genomic and non-genomic mechanisms. For cortisol, genomic effects in target tissues are a product of its binding to two specific receptors as a ligand-dependent transcription factor (Duma et al., 2006). This dual receptor system is comprised of high affinity mineralocorticoid receptors (MR) and low affinity glucocorticoid receptors (GR; Groeneweg et al., 2012; Joels and de Kloet, 1994). Owing to a 10× stronger affinity for cortisol, MR are bound during basal cortisol secretion and at the onset of stress, whereas GR are increasingly bound when cortisol levels rise during the response to stress and at the peak of its daily rhythm. In the absence of ligand, MR and GR reside in the cytoplasm of cells as part of a multimeric complex containing chaperone heat-shock proteins (HSP90, HSP70, HSP56; Juruena et al., 2004; Pratt, 1993). Upon binding by cortisol, the receptor undergoes a conformational change whereby it hyper-phosphorylates and dissociates from the multiprotein complex. At this point, MR or GR translocate to the nucleus to bind to DNA recognition sites termed glucocorticoid response elements (GREs) in the promoter region of target genes. Cortisol then affects gene expression directly by activating or repressing transcription, depending on GRE sequence and promoter context, or indirectly by interacting with other transcription factors (Carlberg and Seuter, 2010; Chrousos and Kino, 2005; Lu et al., 2006). Cortisol exerts additional genomic actions indirectly by affecting membrane receptors and second messengers (Jiang et al., 2015). It thereby influences the release of excitatory amino acids and induction of endocannabinoid synthesis (see for review McEwen et al., 2015).

In contrast to the nuclear receptors that bind cortisol, no specific receptor for DHEA(S) has been identified thus far (Traish et al., 2011; Widstrom and Dillon, 2004). Nonetheless, DHEA(S) has been shown to activate specific transcriptional pathways to directly alter cellular function (Mannic et al., 2013; Simoncini et al., 2003; Traish et al., 2011). For instance, DHEA has direct, genomic actions in stimulating nitric oxide synthesis that occurs independently of estrogen, progesterone, glucocorticoid, or androgen receptors (Simoncini et al., 2003).

Slower genomic effects of cortisol and DHEA(S) are complemented by more rapid non-genomic actions. These fast-acting mechanisms enable the rapid behavioral responses needed to contend with a stressor (Dallman et al., 2005; Strelzyk et al., 2012). Non-genomic actions of cortisol are mediated by membrane receptors and G-protein-coupled receptor signaling (Borski et al., 2002; Evanson et al., 2010; Groeneweg et al., 2012). Similar non-genomic actions of DHEA(S) through its binding to membrane receptors in various tissues have been reported (Liu and Dillon, 2004; Nakashima et al., 1995; Tsuji et al., 1999). Additional non-genomic actions of DHEA(S) include altering plasma membrane biophysical properties (Morissette et al., 1999), modifying the release and metabolism of monoamines (Charalampopoulos et al., 2005), and modulating effects on voltage-gated ion channels (Hill et al., 2015).

It is also via non-genomic mechanisms that cortisol and DHEA(S) affect activity of several neurotransmitter systems with effects on circuits related to reward processing, attention regulation, executive function, mood, and emotion. For cortisol, these include serotonin, γ-aminobutyric acid type A ($GABA_a$), glutamate, dopamine, and acetylcholine (Joca et al., 2009; Karst and Joëls, 2005). For instance, stress-induced cortisol release in the prefrontal cortex (PFC) leading to overstimulation of dopamine D1 and α1 noradrenergic receptors has been linked to impaired PFC function and deficits in working memory (Shansky and Lipps, 2013). On the other hand, by diminishing the availability of the serotonin precursor, tryptophan, cortisol has been linked to reductions in the synthesis, release, and metabolism of serotonin and, in turn, to increased risk for depression (Cowen, 2002; Lanfumey et al., 2008).

In the same manner, DHEA(S) affects a variety of processes relevant to psychopathology by modulating pre- and postsynaptic neurotransmitter receptors (see for reviews Pérez-Neri et al., 2008; Pluchino et al., 2015). DHEA(S) acts as an excitatory neurosteroid that antagonizes $GABA_A$ and glycine receptors (Demirgören et al., 1991; Majewska et al., 1990), and stimulates *N*-methyl-D-aspartate (NMDA), glutamate, and σ1 receptors (Dong et al., 2007; Miller, 2009). Stronger and longer lasting effects on GABA and dopamine release have been reported for DHEA-S compared to DHEA (Charalampopoulos et al., 2005; Imamura and Prasad, 1998). DHEA has been further linked to changes in acetylcholine and dopamine release via σ1 receptor-dependent mechanisms (Dong et al., 2007; Zheng, 2009). In addition, direct agonist actions on ERβ and weak antagonist actions on the androgen receptor have been reported (Chen et al., 2005). Broad impacts of cortisol and DHEA(S) on activity of neurotransmitter systems subserving motivation, emotion, sensory processing, and behavior is consistent with roles for these hormones in the etiology of numerous behavioral and emotional health problems.

Through these varied mechanisms of action, the HPA axis innervates nearly every organ and neurotransmitter system in the body and communicates extensively with higher-order brain regions. It is cortisol's widespread actions across the brain and body that enable it to coordinate physiological and psychological responses to stress and concomitant behavioral displays (Herman et al., 2005; Papadimitriou and Priftis, 2009). As a result, acute mobilization of the HPA axis and its release of stress hormones are critical for contending both with challenges

that threaten survival on a physiological level and with psychosocial stressors ubiquitous in contemporary society.

Primary actions of stress-induced increases in cortisol are to release glucose necessary for supplying energy to organs and mediating changes in arousal and immunity important for restoring bodily homeostasis (Lee et al., 2012). At the same time, heightened release of cortisol temporarily inhibits non-essential functions such as growth and reproduction. In order to avoid extended disruption of these processes, a well-functioning HPA axis is regulated by multi-level feedback loops that terminate the release of cortisol once a stressor has passed.

Negative feedback loops initiated when cortisol levels rise act on GR in the hypothalamus and pituitary to inhibit the further release of CRH and ACTH. This helps bring the system back to baseline and limit total tissue exposure to cortisol (de Kloet et al., 1998). Because they express high densities of GR receptors, certain brain regions also show a high sensitivity to cortisol. GR-mediated effects in the hippocampus and prelimbic/anterior cingulate PFC contribute to negative feedback via inhibitory GABAergic inputs to the paraventricular nucleus (McEwan et al., 1997; Mora et al., 2012). On the other hand, excitatory inputs to the amygdala initiate a feedforward mechanism that has a long-term enhancing effect on HPA axis reactivity (Ulrich-Lai and Herman, 2009). Another process limiting cortisol's bioavailability is its binding to corticosteroid binding globulin (CBG). By forming an inactive complex with cortisol in plasma, CBG prevents all but the free percentage (~10%) from reaching its receptors (Lewis et al., 2005). However, this glycoprotein possesses a low binding capacity that is readily exceeded when cortisol levels rise due to stress (Perogamvros et al., 2012; Rosner, 1990).

Extensive processes for inhibiting cortisol release contrast an absence of feedback mechanisms identified for DHEA(S) (Labrie, 2010; Wolf et al., 1998). Although ACTH stimulates both cortisol and DHEA(S) from the adrenals, DHEA(S) does not directly contribute to the negative feedback loop influencing ACTH secretion (Arafah, 2006). Despite lack of a specific binding protein identified for DHEA(S), both variants do bind to albumin, and a smaller proportion to sex hormone binding globulin. This leaves only about 5% of DHEA(S) unbound (Cekan et al., 1984; Rutkowski et al., 2014). Stronger binding of DHEA-S to albumin in blood contributes to its slow clearance from circulation.

Along with mediating the response to stress, the HPA axis is essential to maintenance of basal homeostasis. Even during non-stressful situations, CRH and AVP continue to be secreted in a pulsatile fashion. This has the effect of stimulating cortisol release in accordance with a well-defined circadian rhythm (Chrousos et al., 2009). Cortisol levels generally peak within 30–40 min after waking and subsequently decline across the rest of the day. This decline is rapid in the morning and becomes more gradual in the afternoon and evening, until reaching its lowest concentration around sleep onset (Smyth et al., 1997; Weitzman et al., 1971). The intrinsic rhythmicity of cortisol release is observed in infants as young as two months of age (de Weerth et al., 2003; Price et al., 1983); although, adult-like patterns of circadian regulation are not stably achieved until about the third year of life (Watamura et al., 2004).

DHEA follows a similar diurnal rhythm marked by high levels in the morning and a decline across the rest of the day (Ghiciuc et al., 2011; Hucklebridge et al., 2005; Wilcox et al., 2014). Unlike cortisol, DHEA's diurnal rhythm is less marked by about two-fold and lacks the significant spike after awakening (Hucklebridge et al., 2005). Circulating DHEA-S differs from both cortisol and DHEA by exhibiting neither strong diurnal rhythm nor day-to-day variation owing its low rate of metabolic clearance and longer half-life (Longcope, 1996). DHEA-S may, therefore, represent a more stable index of adrenocortical activity and stress accumulated over time. In comparison, DHEA may better reflect the response to stress acutely experienced (Leowattana, 2004; van Niekerk et al., 2001). In support of this assertion, studies by Lennartsson et al. (2012) measuring both variants simultaneously have shown a significantly greater response of DHEA to an acute social stressor, but associations of only DHEA-S with long-term perceived stress (Lennartsson et al., 2013).

In this review we try to limit our focus to biological actions mediated directly by cortisol and DHEA(S). It is important to note that DHEA also exerts many of its physiological effects by acting as a metabolic intermediate in the production of sex hormones (Labrie, 2010; Labrie et al., 1998). Metabolism of DHEA into estrogens or androgens in peripheral tissues, depending upon the local expression of steroid-forming enzymes (Labrie, 2015), enables an even broader range of effects during development (see Labrie, 2010; Tchernof and Labrie, 2004). Indeed, there is increasing attention being paid to the joint effects of stress-sensitive hormones such as cortisol alongside estrogens/androgens; although, estrogen and testosterone in that literature are typically discussed as gonadal hormones due to a surge during adolescence that coincides with rising rates of psychopathology (Han et al., 2015; Johnson et al., 2014; Ruttle et al., 2013). Nonetheless, as concluded in a review by Traish et al. (2011), DHEA and DHEA-S are active hormones in their own right – independent of their conversion to sex hormones – with active roles in modulating neurotransmitter synthesis and release, immunity and inflammation, endothelial and cognitive function, and neurogenesis and neuronal survival.

4. Opposing regulatory functions of cortisol and DHEA(S)

Despite a corresponding site of origin and conversion by a similar set of prohormones, cortisol and DHEA(S) mediate largely opposing biologic, neurologic, and immunologic functions. This antagonistic dynamic between the two suggests that measuring their levels simultaneously may be an important indicator of net glucocorticoid activity (Chen et al., 2015; Goodyer et al., 2001; Mocking et al., 2015). Quantifying the ratio of circulating cortisol to DHEA(S) focuses on the relative, rather than the absolute, abundance of the two analytes. Such an approach has been recommended when the analytes are expected to have opposing biological effects, as in the case of cortisol and DHEA(S) (Chen et al., 2015; Sollberger and Ehlert, 2015).

A potential benefit of assessing cortisol and DHEA(S) as a ratio is that it captures the preferential production of one hormone over the other. In the case of cortisol and DHEA(S), the traditional assumption is that the *unopposed* effect of cortisol (i.e., a higher cortisol/DHEA(S) ratio) results in greater stress-related mental or physical health risk. However, this conclusion has been based largely on studies linking the ratio to physical or cognitive deterioration in older adults (Buford and Willoughby, 2008; Phillips et al., 2010), serious disease states such as tuberculosis (Bozza et al., 2007) or human immunodeficiency virus (Christeff et al., 2002), and specific mental disorders in adulthood such as treatment-resistant depression and schizophrenia (Markopoulou et al., 2009; Ritsner et al., 2004). Whether this is the case for more normative processes or for psychopathology occurring earlier in life remains to be determined.

Cortisol is well shown to have neurotoxic effects under conditions of repeated or prolonged stress exposure. For instance, in rodents, elevated levels of corticosterone resulting from experimentally-induced chronic stress led to dendritic atrophy in the CA3 region of the hippocampus and reduced hippocampal function, alongside impairments in hippocampal-dependent learning and memory tasks (e.g. Diamond et al., 2006; Sebastian et al., 2013). Similarly, stress-induced retraction of apical dendritic branches in the prelimbic and infralimbic medial PFC, a brain region critical for executive function, working memory, and emotion regulation (Holmes and Wellman, 2009), was reported in numerous studies of long-term stress (e.g., Dias-Ferreira et al., 2009; Leuner et al., 2014). In humans, similar impairments in memory and cognitive performance have been shown as a result of prolonged cortisol exposure (see for reviews de Quervain, 2006; Sapolsky, 2003). Others studies reported negative associations of endogenous morning cortisol with cognitive measures of processing speed (Reynolds et al., 2010) and executive function (Venero et al., 2013).

In contrast, when administered exogenously to laboratory animals, DHEA(S) has been shown to offset neurotoxic effects of corticosterone in the hippocampus (Kimonides et al., 1999) and prevent corticosterone-induced suppression of neurogenesis in the dentate gyrus (Karishma and Herbert, 2002). In rodent models, DHEA(S) counteracted impairing effects of corticosterone on memory and primed-burst potentiation (Fleshner et al., 1997), reduced intracellular glucocorticoid availability (Balazs et al., 2008), and reversed weight gain induced by elevated glucocorticoids (Browne et al., 1993). Similar neuroprotective effects in humans were seen in the stimulatory effect of DHEA on neural stem cells (Suzuki et al., 2004) and its attenuation of the impairing effect of high cortisol on episodic memory in older and young adult males (Alhaj et al., 2006; van Niekerk et al., 2001). While it cannot be presumed that a higher level of DHEA(S) is in all cases beneficial as it pertains to health, these findings do support the assumption that neural tissues are more vulnerable to neurotoxic effects of cortisol in the context of a low DHEA(S) environment.

A similar pattern emerges when considering effects of cortisol and DHEA on the immune system. DHEA(S) and cortisol have immunomodulating actions that are often in opposition (Bauer, 2005; Buford and Willoughby, 2008). As an anti-inflammatory, cortisol acts via GR-mediated pathways to help contain inflammatory responses and enhance production of type 2 cytokines that induce humoral immunity (Elenkov, 2004). Although highly adaptive under acute stress conditions, excess release of cortisol can have a weakening effect on the immune system by inhibiting the synthesis, release, and/or efficacy of cytokines and other compounds that promote immune and inflammatory reactions. At high levels, cortisol also blocks T-cell proliferation (an essential component of cell-mediated immunity) and reduces lymphocyte and antibody production, making it harder to recover from illness (Boldizsar et al., 2010; Pitzalis et al., 2002; Raison and Miller, 2003).

In light of immunosuppressive effects of prolonged cortisol exposure on cytokine, lymphocyte, and antibody production, DHEA(S) emerges as an important regulator of immune function. This is achieved by augmenting production of immunity-enhancing IL-2, increasing T-cell number and cytotoxicity critical to innate immunity, inhibiting the release of inflammatory cytokines, and enhancing host resistance to viral and bacterial pathogens (Hazeldine et al., 2010). For instance, Arlt et al. (2006) found that during septic shock, serum DHEA levels increased significantly compared to healthy controls and were associated with better prognosis. In other studies of acute physical illness or injury, DHEA antagonized suppressive effects of cortisol on neutrophil and lymphocyte production (Blauer et al., 1991; Butcher et al., 2005). On the other hand, a higher ratio of cortisol/DHEA-S following injury or illness predicted a higher mortality rate or risk of infection (Beishuizen et al., 2002; Butcher et al., 2005; Phillips et al., 2010). Taken together, research suggests that maintaining appropriate levels of both hormones may be important for preserving the sensitive balance of cortisol- and DHEA(S)-mediated effects on the immune system.

The distinct secretory pathways and functional actions of cortisol and DHEA(S) illustrate the complexity of responding to stress: the HPA axis needs to be able to shut itself down quickly in order to avoid damage caused by prolonged cortisol exposure. Yet, in the presence of chronic stress, the HPA system is taxed to maintain a high level of cortisol release in order to cope effectively. In the long-term, this can result in down-regulation of cortisol receptors in brain regions that mediate HPA axis negative feedback and perpetuate ongoing release of cortisol, potentially at the expense of other adrenocortical hormones. As a consequence, long-term stress exposure may initiate a shift in pregnenolone metabolism away from androgens and towards corticosteroid pathways (Beishuizen et al., 2002; Parker et al., 1985; Strelzyk et al., 2012). Similar to that seen in aging or clinical burnout, this shift likely involves a decrease in the number of cells in the zona reticularis and/or enzymatic activity within it aimed at DHEA(S) production (Jeckel et al., 2010; Lennartsson et al., 2015; Parker et al., 1997). Alteration of the cortisol/DHEA(S) ratio by long-term physical or psychological stress may have meaningful impacts on health by disrupting the dynamic balance of these two hormones acting together on immune, metabolic, cognitive, and psychological function, culminating in vulnerability to disease and increased risk for mental disorder (Elenkov, 2004; Gill et al., 2008; Graves and Kayal, 2008).

5. Responses of cortisol and DHEA(S) to stress

Levels of both cortisol and DHEA(S) rise in response to physically and psychologically stressful events. Decades of research corroborate the high sensitivity of cortisol to psychosocial stress. Varied laboratory-based social stress paradigms, including public speaking and conflict resolution, reliably evoke a cortisol response among adolescents and adults (Denson et al., 2009; Dickerson and Kemeny, 2004; Kudielka et al., 2009). DHEA concentrations also increase temporarily among adults following acute psychosocial stress (e.g. Fang et al., 2014; Izawa et al., 2008; Lennartsson et al., 2012, 2015). In studies of adolescents, elevations in DHEA have been reported following a public speaking task (Shirtcliff et al., 2007), venipuncture (Marceau et al., 2012), and MRI scan (Eatough et al., 2009).

A cortisol response can be elicited during infancy and early childhood using developmentally appropriate social stressors such as maternal separation and stranger approach (Gunnar et al., 1992; Kertes et al., 2009; Yim et al., 2015). An important determinant of the impact of early life stress on cortisol production is the presence of a responsive and supportive caregiver, which acts as a buffer against overexposure to cortisol during a sensitive life stage (Ahnert et al., 2004; Gunnar and Cheatham, 2003). Whether the same is true for DHEA(S) is currently unknown as there are no studies examining the DHEA(S) response to acute stress in infancy and early childhood. Responsiveness of DHEA to acute stress during middle childhood is suggested by studies documenting a significant rise following mildly stressful events such as sports competition (McHale et al., 2016).

On a functional level, upregulation of DHEA(S) concomitant with that of cortisol may be important in responding adaptively to stress (Charney, 2004; Maninger et al., 2010). For instance, adolescents with successful MRI scans showed greater DHEA reactivity compared to those with unsuccessful scans (Eatough et al., 2009). This is consistent with studies in adults that found the cortisol/DHEA(S) ratio to correlate negatively with performance during military stress (Morgan et al., 2004) and positively with symptoms of dissociation and negative affect (Izawa et al., 2008; Morgan et al., 2009; Rasmusson et al., 2004; van Niekerk et al., 2001).

In comparison to moderate acute stress, chronic or severe early life stress is associated with both enhanced and reduced stress system activity, depending on the type and duration of the stressor (Lupien et al., 2009). Low maternal sensitivity during infancy and childhood has been linked to elevated cortisol reactivity to stress (Brennan et al., 2008; Murray et al., 2010; Pendry and Adam, 2007). On the other hand, reduced basal and diurnal cortisol have been observed among children exposed to trauma or abuse (Trickett et al., 2010) and long-term foster or institutionalized care (Fisher et al., 2011; Kertes et al., 2008). This body of work suggests that in order to cope with chronically sustained HPA axis activity, the stress system launches an initial pattern of hypercortisolism that, over time and repeated increases, transitions to down-regulation (Miller et al., 2007a). In other words, during conditions of long-term stress, upstream changes in CRH and ACTH acting on the adrenals may result in reduced production of cortisol. Such a model would account for findings of hypercortisolism in children exposed to short-term stress versus hypocortisolism in long-term or severely exposed children (Gustafsson et al., 2010).

This model also accounts for reduced basal levels of DHEA(S) found in studies of chronic stress (e.g. Bellingrath et al., 2009; Izawa et al., 2012; Lennartsson et al., 2013; do Vale et al., 2011; but see Lac et al., 2012; Mommersteeg et al., 2006). In two recent reports, adults who experienced long-term stress or clinical burnout exhibited significantly

attenuated serum DHEA-S levels and a higher cortisol/DHEA-S ratio in response to an acute laboratory stressor compared to those reporting low stress levels (Lennartsson et al., 2013, 2015). In other studies of healthy adults, an elevated ratio was associated with workdays compared to weekends (Kim et al., 2010), a greater number of stressful life events over the past year (Heaney et al., 2014), training stress among female cyclists (Bouget et al., 2006), and psychological strain among caregivers of Alzheimer's patients (Vedhara et al., 2002).

In the only study to date examining levels of cortisol and DHEA among children experiencing long-term stress, Cicchetti and Rogosch (2007) measured daytime basal concentrations of both hormones in a sample of maltreated and non-maltreated children. Controlling for maltreatment status, lower DHEA and a higher cortisol/DHEA ratio were observed in both the morning and afternoon for children who exhibited better socio-emotional functioning (higher social competence and lower internalizing and externalizing problems). However, among maltreated children only, rising DHEA from morning to afternoon was observed for those with higher socio-emotional functioning. For the maltreated children, maintaining the capacity to elevate DHEA may have enabled them to better meet the demands of chronic stress and adapt competently (Cicchetti and Rogosch, 2007).

These findings might be interpreted as evidence of a shift in adrenal steroidogenesis to cortisol at the expense of DHEA(S) during chronic stress. Adrenal fatigue as a result of frequent HPA axis activation would manifest first as down-regulation of DHEA(S), followed later by that of cortisol. Thus, the ability to elevate DHEA(S) in the context of long-term or severe early life stress may be an adaptive neurobiological mechanism representing a greater ability to regulate adrenocortical function and mitigate some of the negative effects of chronic stress (Cicchetti and Rogosch, 2007; Petros et al., 2013; Russo et al., 2012). Longitudinal follow-up with youth samples is necessary to illuminate the trajectory of cortisol and DHEA(S) production over time and in response to prolonged stress.

6. Developmental change

Hormone-behavior associations are affected both by changes in enzymatic activity that lead to different concentrations across the lifespan, as well as changes in brain maturation and hormone sensitivity that make certain life stages more susceptible to neurotoxic and neuroprotective effects of stress. Thus, the functional actions of HPA axis hormones can only be fully understood by taking developmental context into consideration (Lupien et al., 2009; Rogosch et al., 2011). A growing body of research in animal models and human studies suggest that exposure to stress-sensitive hormones during the pre- and perinatal periods has organizational effects impacting long-term vulnerability for a host of stress-related disorders. In contrast, exposure to those same hormones following the transition to adolescence is likely to have activational effects, prompting expression of latent vulnerability (Lupien et al., 2009). Evidence that HPA axis hormones, especially cortisol, have differing effects on health depending on the developmental timing of exposure necessitates a basic understanding of developmental changes in production of these hormones.

6.1. Perinatal period

Activity of adrenal hormones in the perinatal period is dependent on a developmentally unique structure. The fetal adrenals consist of a distinct morphology composed of three zones: the fetal zone, transitional zone, and definitive zone (Ishimoto and Jaffe, 2011). The fetal zone is the site of most prenatal steroidogenic activity, but is specialized to pregnancy and disappears rapidly after birth through apoptosis (Spencer et al., 1999).

Activation of the adrenal glands by ACTH spikes prenatally, resulting in elevated release of both cortisol and DHEA(S), albeit at different phases of pregnancy (Keelan et al., 2012; Oh et al., 2006). Starting at 8–10 weeks gestation and throughout most of pregnancy, fetal steroid production is directed towards the abundant release of DHEA(S) (Goto et al., 2006; Mesiano et al., 1993). Production of cortisol is suppressed because expression of HSD3β2, the enzymatic substrate necessary for conversion from its 17α-hydroxyl intermediates, is reduced until approximately 23 weeks gestation (Ishimoto and Jaffe, 2011; Narasaka et al., 2001). As the fetal adrenals are also low in steroid sulfatase activity, prenatal steroidogenesis favors conversion of DHEA to DHEA-S, which is then converted into estrogens required for the maintenance of pregnancy (Ishimoto and Jaffe, 2011; Quinn et al., 2015). An abundance of placental estrogens further perpetuates low levels of cortisol throughout most of pregnancy by facilitating conversion of active cortisol into inactive cortisone (Ng, 2000). Cortisol release by the transitional zone spikes in late gestation (32–36 weeks) and remains high through parturition (Lindsay and Nieman, 2005; Obel et al., 2005). High levels of cortisol in late gestation and the perinatal period promote fetal growth and physiological processes necessary for normal labor progression including enhanced glucose availability and organ maturation, while also preparing the fetus for the stress of delivery and postnatal adaptation (Benfield et al., 2014; Dahlen et al., 2013; Dipietro, 2012). By inducing calcium influx into embryonic neocortical neurons, a key function of DHEA(S) prenatally is to promote neuronal growth and brain maturation (Azizi et al., 2009; Compagnone and Mellon, 1998; Quinn et al., 2015). Moreover, through its conversion to estrogen, high concentrations of maternal and fetal DHEA(S) facilitate parturition by contributing to cervix maturation and myometrium activation that precedes uterine contractions (Iliodromiti et al., 2012; Seadawy et al., 2013).

Following birth, levels of cortisol continue to increase linearly through the first six months of life (Garagorri et al., 2008). Similarly, the disappearance of placentally-mediated conversion of DHEA-S to estrogen results in a rapid increase in DHEA-S immediately after birth. This is followed by a precipitous drop in its levels between 6 and 12 months of age (Guran et al., 2014). At this time, the fetal zone regresses and is replaced by the definitive adrenal cortex which initially synthesizes little DHEA(S) (Nykänen et al., 2007; Rainey and Nakamura, 2008).

Not only is the fetus exposed to hormones of its own production, but also those of maternal origin. Prior to birth, maternal hormones reach the fetus via the placenta. Following birth, both cortisol and DHEA(S) can be transmitted via breastmilk (Cao et al., 2009; Neelon et al., 2015; Sahlberg and Axelson, 1986).

Maternal cortisol levels increase two- to four-fold over the course of pregnancy (Sandman et al., 2006). Although fetal exposure is limited by the actions of 11β-HSD2 (Murphy and Clifton, 2003), this placental enzyme provides only a partial barrier. As a result, some degree of biologically active cortisol continues to pass through the placenta to the fetus (Gitau et al., 2001), consistent with evidence that levels of prenatal maternal cortisol correlate strongly with those in the fetus (Field et al., 2004). Thus, for mothers experiencing frequent or prolonged stress during pregnancy, the resulting overproduction of cortisol may expose her fetus to excess levels.

In humans, exposure to high levels of cortisol during pregnancy has been linked to birth outcomes that include lower gestational age, smaller head circumference, and reduced birth weight (e.g. Baibazarova et al., 2013; Bolten et al., 2011). During infancy, prenatal maternal cortisol has been linked to a larger biological stress response, more negative reactivity, and impaired mental and psychomotor development (e.g., Buitelaar et al., 2003; Davis and Sandman, 2010; O'Connor et al., 2013; Werner et al., 2013). Effects have been shown to persist into childhood and adolescence in the form of greater physical and psychological health problems, lower IQ, and higher basal and stress responsive cortisol levels (see for review Zijlmans et al., 2015). Additional studies reported links between prenatal stress and impairments in attention, effortful control, and emotion regulation (Clavarino et al., 2010; Gutteling et al., 2006; Mennes et al., 2009), as well as clinical rates of attention deficit hyperactivity

disorder (ADHD), affective disorder, and conduct disorder (Barker and Maughan, 2009; O'Connor et al., 2003; Rice et al., 2010; Ronald et al., 2010).

In contrast to an extensive literature on programming effects of prenatal cortisol, there is limited research on impacts of prenatal exposure to DHEA(S) on developmental outcomes either peri- or postnatally. There is also a dearth of studies examining effects of prenatal maternal stress on DHEA(S) levels among offspring. The one exception is a study by Tegethoff et al. (2011) that demonstrated higher DHEA concentrations in the fingernails of three-week-old infants whose mothers experienced at least one life event involving high subjective strain during pregnancy. Despite this lack of basic science research, impacts of prenatal stress on DHEA(S) are indirectly implicated by clinical studies examining neonatal health. Low birth weight has been associated with lower DHEA-S levels in blood and urine among newborns (Ong et al., 2002). However, during childhood and adolescence, being born low birth weight or small for gestational age predicted higher serum DHEA-S levels (Ibáñez et al., 1999; Tenhola et al., 2002). Although the reason for this reversal in DHEA-S from the neonatal period to later life is unclear, one possibility is the rapid 'catch-up' in weight gain often experienced by low birth weight children (Ong et al., 2002). Additional prenatal stress effects on DHEA(S) are implicated by some studies reporting elevated levels in cord blood following pregnancy complications including fetal inflammation, preeclampsia, and gestational hypertension (Carlsen et al., 2005; Kacerovsky et al., 2012). Moreover, Oh et al. (2006) demonstrated a significantly higher median cortisol/DHEA-S ratio in the cord blood of newborns born via active labor compared to elective C-section. The exact role played by DHEA-S in high-risk pregnancies is not yet known. It is possible that, similar to the response mounted when faced with acute stress, enhanced production of DHEA-S is a protective mechanism employed by the maternal or fetal HPA axis to increase the fetus' chances of survival.

These findings highlight the role of DHEA(S) as a mechanism of prenatal stress effects on offspring outcomes. Given known programming effects of prenatal cortisol exposure on HPA axis function postnatally and that prenatal concentrations of DHEA-S are high (Keller-Wood and Wood, 2001; Schulte et al., 1990), future research is warranted to determine the role of the prenatal cortisol/DHEA(S) ratio on postnatal development. Exploration of potential effects of prenatal DHEA(S) exposure on long-term developmental outcomes is also needed.

6.2. Childhood

Following the drop in DHEA(S) during the second half of the first year of life, basal levels remain low until adrenarche commences at approximately 6–8 years of age. During early childhood, basal cortisol concentrations remain constant or increase only gradually (Bailey et al., 2013), resulting in a ratio skewed in favor of cortisol. At the same time, the cortisol response to psychological stress is attenuated starting at about two years of age and throughout early childhood (Jansen et al., 2010). Considered together, low levels of DHEA(S) combined with reduced sensitivity of cortisol to stress suggest a period of relative quiescence for the HPA axis during childhood.

Explanations for the reduced cortisol stress responsivity observed in early childhood include the relatively mild nature of stressors used with this age group, a still-maturing sense of social threat and evaluation, and the buffering role played by parents and other important social partners (Gunnar and Donzella, 2002). Considering the joint effects of cortisol and DHEA(S), an alternate explanation is that reduced stress reactivity of the HPA axis in early life is adaptive to limit the brain's exposure to cortisol at a time when basal DHEA(S) levels are low. Notably, although young children on average are less stress responsive compared to young infants and older children starting at about age seven, some children do display a measurable cortisol response to stress. These tend to be children with temperamental vulnerability, poor attachment quality, or less sensitive caregiving (Ahnert et al., 2004; Badanes et al., 2012; Kertes et al., 2009).

A notable lack of studies employing DHEA(S) in young children leaves several basic questions regarding activity of the HPA axis in childhood unanswered. These include whether psychosocial stress prompts elevations in DHEA(S) at this age and, if so, how such elevations relate to behavioral outcomes. Thus, more research is needed on the causes and consequences of stress-induced rises in DHEA(S) at a time when basal levels are typically low. It is also unclear whether the synchronous release of cortisol and DHEA(S) is as important to functioning of the HPA axis during childhood as it appears to be during adolescence and adulthood when there are higher basal concentrations of DHEA(S). Lastly, knowing that a greater cortisol response to stress is expected for children with temperamental vulnerability or a history of insecure attachment, understanding DHEA(S) activity among this subgroup of children may be particularly informative. Unanswered questions such as these represent significant gaps in understanding the potential functional anti-glucocorticoid effects of DHEA(S) in humans suggested by neurobiological studies using animal models.

6.3. Adolescence

Whereas early childhood is marked by low levels of DHEA(S), late childhood and adolescence are defined by an increase in adrenal hormones. Specifically, at adrenarche (6–7 years in girls and 8–9 years in boys) expansion of the androgen-producing zona reticularis is followed biochemically by a rise in production of DHEA(S) (Auchus and Rainey, 2004; Miller, 2009; Nguyen and Conley, 2008). The source of this increase is maturational changes in enzymatic activity within the zona reticularis favoring enhanced DHEA(S) production. These include increased expression of 17,20-lyase and cytochrome *b*5, coupled with decreased expression of HSD3β2 (Gell et al., 1998; Rainey and Nakamura, 2008). This surge in DHEA(S) prompts the first signs of puberty and stimulation of other systems that become active at adolescence.

DHEA(S) levels continue to increase substantially through adolescence and early adulthood until reaching a peak at 25–30 years of age (Labrie et al., 1998; Young et al., 1999). In contrast to the marked surge in DHEA(S) occurring at adrenarche, basal concentrations of cortisol remain largely stable throughout the transition from childhood to adolescence (Kenny et al., 1966; Saczawa et al., 2013). Variation in stress responsivity by pubertal stage has, however, been observed in several studies (e.g. Gunnar et al., 2009; Shirtcliff et al., 2012; Stroud et al., 2009).

A greater cortisol response to stress during adolescence compared to earlier ages fits with a broad set of behavioral and biological changes described as representing heightened reactivity to stress (Foilb et al., 2011; Spear, 2000). A hallmark of the adolescent transition is entrance into an array of new interpersonal and social situations that test adolescents' emerging psychosocial capacities (Collins and Steinberg, 2006; Smetana et al., 2006). At the same time, there are dramatic shifts in various neurobiological and anatomical systems (Foilb et al., 2011). Among these are the cortex and limbic systems, which continue to develop well into young adulthood (Blakemore, 2012; Gogtay et al., 2004). Higher basal levels and stress-induced elevations of hormones modulating neural circuits involved in reward processing, emotionality, and arousal during adolescence may, in turn, influence risk for psychopathology (Arain et al., 2013). Administration of DHEA in young adult males has been linked to reduced activation of the amygdala and hippocampus and enhanced connectivity between them, with these changes associated with reduced self-report of negative affect (Sripada et al., 2013). Given DHEA's antiglucocorticoid properties, higher levels may help protect the adolescent brain from cortisol neurotoxicity resulting from increased exposure to socially and biologically stressful events (Campbell, 2006; Flinn et al., 2011). Further research is needed to elucidate the expected trajectory of cortisol and DHEA(S) production during

this time and what altered ratios mean for health and well-being throughout the adolescent transition.

7. Role of the cortisol/DHEA ratio in developmental psychopathology

The widespread actions of cortisol and DHEA(S) in the brain and body and their interaction with various neurotransmitter systems suggest a central role for both hormones in the cognitive, attentional, emotional, and behavioral processes underlying psychological disorder. However, there currently exists little empirical evidence to support this assertion, particularly among children and adolescents. This is problematic in light of research showing that half of all lifetime cases of mental disorder begin by age 14 (Kessler et al., 2005). The sections below summarize what little is currently known about DHEA(S), both singularly and in interaction with cortisol, in affecting the risk for emotional and behavioral problems in youth. This review focuses on the most common internalizing and externalizing disorders in children and adolescents: depressive and affective disorders, ADHD, and conduct problems (Centers for Disease Control and Prevention (CDC), 2013). Eating disorders are also included, both because symptoms escalate starting in early adolescence (Jacobi et al., 2004) and because they represent one of the few areas where the cortisol/DHEA(S) ratio has been studied in adolescents. As research on the joint effects of cortisol and DHEA(S) is still in the early stages, limitations and unanswered questions are highlighted to fruitfully inform future research.

7.1. Internalizing disorders

Research on internalizing disorders offers some of the strongest evidence for a pattern of adrenocortical activity favoring production of cortisol over DHEA(S). In fact, a higher level of cortisol is one of the most well-replicated findings in studies examining biological correlates of depression (see for review Stetler and Miller, 2011). Patients with treatment-resistant depression have both higher cortisol and a higher cortisol/DHEA ratio compared to healthy controls, even during remission (Juruena et al., 2004; Markopoulou et al., 2009; Mocking et al., 2015). Recent studies with children and adolescents reported a similar positive association between the cortisol/DHEA-S ratio and internalizing problems (Chen et al., 2015; Cicchetti et al., 2015). It is not yet clear, however, whether an altered ratio of cortisol to DHEA(S) is a cause or consequence of internalizing problems.

On the one hand, adrenal production favoring cortisol over DHEA may potentially deprive the brain of the purported antidepressant and anxiolytic actions of DHEA(S). Support for this hypothesis would require evidence that an altered cortisol/DHEA(S) ratio predates symptoms of depression or anxiety (Angold, 2003; Majewska, 1992). Several prospective studies have identified a higher cortisol/DHEA ratio as a risk factor prior to the onset of major depressive disorder among children and adolescents (Angold et al., 1999; Goodyer et al., 1996; Goodyer et al., 2000a, 2000b; Goodyer et al., 2001). Notably, the association of hormone levels and depressive/anxiety symptoms in these studies was independent of the effects of recent and long-term psychosocial adversities and concurrent depressive symptoms, implicating an altered ratio as a precursor to depressive onset.

Alternatively, because depression and anxiety are persistent and distressing conditions, they may induce neurobiological alterations similar to those seen during chronic stress. As in long-term stress, these include impaired negative feedback of the HPA axis and increased production of cortisol. Consistent with this, a higher basal cortisol/DHEA ratio has been linked to the persistence of major depression, as well as more protracted illness length and an increased occurrence of disappointing life events among depressed youth (Goodyer et al., 1998, 2003). Studies examining stress responsivity, however, suggest increased DHEA in response to stress. Children with higher internalizing problems during middle childhood showed greater DHEA reactivity to an anxiety task during adolescence (Han et al., 2015). Among boys aged 10–14 years, higher DHEA reactivity predicted more negative emotionality one year later (Marceau et al., 2012). Similarly, adolescent girls with higher internalizing problems showed an atypical pattern of rising DHEA levels following a public-speaking task compared to girls with low internalizing problems (Shirtcliff et al., 2007). Thus, compared to basal levels of DHEA that tend to be reduced among depressed children and adolescents, higher stress responsive levels are observed among youth with depressive or internalizing symptoms.

One challenge to understanding the role of adrenally-produced DHEA(S) in internalizing disorders is whether potentially ameliorative effects are direct or mediated by DHEA's conversion into sex hormones. The latter was shown in a study by Angold et al. (1999) in which previously significant associations of DHEA-S and depression among 9–15 year old girls became nonsignificant when controlling for testosterone and estrogen levels. As sex hormone levels are associated both with risk for internalizing disorders and change in response to stress, disentangling direct actions of adrenal DHEA from those occurring after its conversion requires simultaneously assessing estrogen and testosterone levels and controlling for them in statistical models. Moreover, conversion from DHEA contributes to only a percentage of circulating estrogens and androgens in the body. Human studies are limited in that sex hormones are sampled from general circulation, which cannot distinguish between those produced by conversion from DHEA in the adrenals vs. those produced in the gonads. This current limitation is an important caveat to interpreting associations of DHEA(S) and internalizing problems that frequently emerge during adolescence.

Another challenge is reconciling anxiolytic and antidepressant actions of DHEA(S) with their inhibitory effects on the $GABA_A$ receptor (e.g. Eser et al., 2006; Maninger et al., 2009). As GABA is the most prevalent inhibitory neurotransmitter (Brambilla et al., 2003; Möhler, 2006), DHEA(S) would be expected to result in an increase in depressive or anxiety symptoms by reducing GABA's restraining influence. At least two models have been proposed to account for this paradox. One is that DHEA(S) decrease levels of molecules like pregnenolone sulfate that negatively modulate the $GABA_A$ receptor or influence the release of other molecules that positively modulate it (Crowley and Girdler, 2014; Young et al., 1996). Another model supported by neurobiological evidence is that DHEA stimulates GABAergic neurotransmission under certain conditions while inhibiting it under others (Xilouri and Papazafiri, 2006). Further research on the functional mechanisms by which DHEA(S) contribute to depression and anxiety would expand knowledge of how and under which conditions DHEA(S) affect the risk for psychopathology.

7.2. Externalizing disorders

Externalizing disorders are among the most common behavioral problems in youth (Centers for Disease Control and Prevention (CDC), 2013). This broad diagnostic category encompasses a range of conditions that include ADHD, disruptive behavior disorder (DBD), oppositional defiant disorder (ODD), and conduct disorder (CD). Common among them is the widely accepted notion of a neurobiological substrate involving stress-regulating systems at their origin (see for reviews Golubchik et al., 2007; Moffitt and Scott, 2009). However, studies of the cortisol/DHEA(S) ratio in externalizing disorder have yielded mixed results, in part because of the broadness of this diagnostic category.

In general, a pattern of lower cortisol compared to DHEA(S) is reported among children with conduct-related externalizing problems. Research examining cortisol shows lower basal levels in boys with CD, ODD, or those at risk for antisocial behavior (e.g. Brotman et al., 2007; Dorn et al., 2009; Oosterlaan et al., 2005; Shirtcliff et al., 2005; but see McBurnett et al., 2005). In other reports, children with ODD showed a lower cortisol response compared to controls following a frustration-provoking task, despite no difference between the groups at baseline (Fairchild et al., 2008; Snoek et al., 2004; van Goozen et al., 2000).

Research on DHEA demonstrates higher basal levels among boys with CD or those with a greater intensity of aggressive, delinquent, and disruptive behavior (Dmitrieva et al., 2001; Golubchik et al., 2009; Miczek et al., 2003). While children diagnosed with DBD showed lower DHEA levels compared to healthy controls, children with DBD and whose parents were rated higher in parenting quality had DHEA levels that approached those of non-DBD children (Dorn et al., 2009).

Lower basal levels of cortisol and higher levels of DHEA found among conduct disordered children are complemented by studies showing a lower ratio of the two. In a community sample of 15–17 year old girls, those with CD showed a lower cortisol/DHEA ratio compared to controls without psychiatric disorder (Pajer et al., 2006). Girls scoring highest in aggressive and antisocial behavior had the lowest cortisol/DHEA ratio. A lower cortisol/DHEA-S ratio was similarly reported in a retrospective study with adult male cocaine addicts with a history of CD (Buydens-Branchey and Branchey, 2004). In this case, a lower ratio was associated with poorer prognosis. However, two other studies reported no significant differences in the cortisol/DHEA ratio for 14–19 year old delinquent adolescents (Golubchik et al., 2009) or 6–11 year old children with CD and ODD (Dorn et al., 2009) compared to healthy, matched controls.

Acute elevations in cortisol in response to stress that are appropriate in magnitude and duration relative to the stressor are considered important for a well-functioning stress response system and for maintaining appropriate levels of arousal (Avanzino et al., 1983). Among conduct-disordered children, reduced ability to both mount a cortisol response and experience a state of arousal may be an underlying cause of their disorder. Because a low level of cortisol is an aversive physiological state, it may prompt some children to engage in externalizing behaviors as a way to increase their physiological arousal (Zuckerman and Neeb, 1979). This "hypoarousal" model is supported by studies showing lower levels of cortisol both at waking and in response to psychosocial stress among conduct disordered children compared to healthy, matched controls (Fairchild et al., 2008; Popma et al., 2007). It is also in line with evidence that antisocial children who retained the ability to initiate a cortisol stress response benefited more from therapeutic intervention than those who did not (van de Wiel et al., 2004). As cortisol is linked to greater levels of arousal, and DHEA to subjective reports of higher positive mood and lesser anxiety (Alhaj et al., 2006; Grillon et al., 2006), it may be that a ratio shifted too far in the direction of DHEA contributes to the under-aroused state that leads some children to engage in risky or disruptive behaviors.

These findings add to the complexity of drawing conclusions about hormone-behavior associations. Rather than assuming that a low level of cortisol and a high level DHEA(S) are optimal, it is likely that both hormones need to be maintained at certain levels depending on biological and psychological states. Unlike the pattern of adrenocortical activity seen in internalizing disorders, for conduct disordered children, an overabundance of DHEA(S) may be a contributor to their behavior problems. The role of DHEA(S) as a negative modulator of the $GABA_A$ receptor is one way in which it may act indirectly to increase aggression, in line with evidence that GABA is related to largely inhibitory effects on aggressive behavior (see for review Narvaes and de Almeida, 2014). Moreover, as a primary precursor to testosterone, a second indirect route by which DHEA may contribute to aggression is observed. Although these propositions require further investigation, evidence of a role for both cortisol and DHEA(S) in the symptoms of conduct disorder emphasize the need to further explore what varying levels of both hormones and their interaction mean in the risk for externalizing disorder.

The literature on externalizing disorders starts to diverge when considering adrenocortical activity among children with ADHD compared to those with more conduct-related problems. The two types of externalizing conditions share an association with significantly reduced cortisol levels (see for review Scassellati et al., 2012). In studies with children, greater symptoms of inattention/hyperactivity were associated with a lower diurnal decline in cortisol from morning to evening (Susman et al., 2007) and lesser reactivity to a laboratory stressor (Randazzo et al., 2008). Associations of ADHD diagnosis with cortisol may, however, be dependent upon comorbidities. Reduced basal and stress responsive cortisol levels have been reported among children diagnosed with ADHD with comorbid ODD, but not among children with non-comorbid ADHD or ADHD comorbid with CD or anxiety (Freitag et al., 2009; Kariyawasam et al., 2002; Snoek et al., 2004).

Contrasting the research on conduct disorders, in the few studies quantifying DHEA(S) levels among ADHD children, a significantly lower level of DHEA and higher cortisol/DHEA ratio compared to controls were reported (Strous et al., 2001; Wang et al., 2011b). Among the children with ADHD, higher DHEA levels and a lower cortisol/DHEA ratio were also associated with lower scores of distractibility and impulsivity (Wang et al., 2011b). A low level of DHEA(S) associated with inattention or distractibility is consistent with research using adults in which administration of DHEA led to improvements in attention (Ritsner et al., 2006; Wolf et al., 1998). Among children, pharmacological treatment for ADHD similarly resulted in a significant increase in DHEA(S) levels (Lee et al., 2008; Maayan et al., 2003; Wang et al., 2011a, 2014).

7.3. Eating disorders

Eating disorders (ED) are chronic conditions with serious implications for health and well-being (Vitousek et al., 1998). Similar to disorders falling on the internalizing spectrum, symptoms of eating-related pathology emerging during adolescence pose long-term risk for adult disorder (Hoek and van Hoeken, 2003; Sonneville et al., 2012). Developmental studies consistently show dysregulation of the HPA axis involving the elevated production of cortisol in adolescents with ED (see for reviews Campbell and Peebles, 2014; Spruijt-Metz, 2011). As it pertains to this review, ED is one of the few areas of developmental psychopathology in which DHEA(S) has been examined, although studies including both DHEA and cortisol, especially among youth, are scant.

As a result, little is known about the ways in which DHEA(S) might contribute to eating-related pathology early in life. At present, there are only two studies that have examined cortisol and DHEA(S) concurrently among adolescents with ED. One inpatient treatment study reported no difference between 15 and 19 year old female AN patients and controls in basal levels of plasma cortisol, DHEA, and DHEA-S at pre-treatment; however, AN patients showed a significant decrease in cortisol levels and a trend towards decreased cortisol/DHEA and cortisol/DHEA-S ratios at four months post-treatment (Stein et al., 2005). In another study examining cortisol and DHEA across the diurnal cycle among female adolescents aged 10–18 years, those with early-onset AN showed higher concentrations of both hormones throughout the day compared to controls (Oskis et al., 2012).

These findings are consistent with a larger body of research with adult women diagnosed with AN or BN, who showed elevated levels of cortisol and DHEA(S) at waking and throughout the day (e.g. Galderisi et al., 2003; Lawson et al., 2013; Miller et al., 2007b; Monteleone et al., 2014). In a prospective study of adult women with AN, a higher level of cortisol predicted the development of severe medical events (e.g., heart failure, severe arrhythmia, gastric rupture, and severe infection) three months later (Estour et al., 2010). A decrease in cortisol levels has been reported among women with BN following successful response to treatment and an increase in body fat and menstrual recovery (Shibuya et al., 2011).

The apparent hyperproduction of DHEA(S) in adolescents and adults with ED is difficult to explain. In animal models, DHEA administration led to a decrease in food intake and body weight (Abadie et al., 1993; Porter and Svec, 1995). However, in humans, DHEA administration to women diagnosed with AN was associated with a significant increase in body mass index (Bloch et al., 2012). It was also linked with increased bone formation and density and lower ED and anxiety symptoms among adolescent girls (Gordon et al., 1999, 2002). These findings

suggest a role, at least in humans, for DHEA in improving some of the biological and psychological symptoms associated with ED.

Thus, studies examining cortisol and DHEA in youth are few in number but relatively consistent with the adult literature in documenting altered production of adrenocortical hormones as it relates to disordered eating behaviors and cognitions. Whereas high cortisol on its own appears to contribute to the onset or persistence of ED symptoms, a concomitant increase in DHEA(S) may help offset this risk. While an intriguing notion, the scarcity of studies employing both cortisol and DHEA(S) makes it difficult to draw conclusions about the directionality of the cortisol/DHEA(S) ratio in adolescent ED and implications for prognosis.

8. Limitations of research on cortisol and DHEA(S) in developmental psychopathology

A limitation of previous studies on the role of cortisol and DHEA(S) in psychopathology has been the lack of systematic consideration of pubertal stage. Pubertal maturation is associated both with changes in hormone release and psychological adjustment (Marceau et al., 2012). The importance of including pubertal stage as a covariate in statistical models is highlighted by a 2010 report by Hankin et al. In that study, postpubertal depressed adolescents showed an increased cortisol response similar to that of depressed adults following psychosocial challenge; in contrast, children who had not yet entered puberty showed hyporesponsive cortisol release. The matter is complicated further by the psychosocial effect of pubertal timing relative to one's peers on associations of cortisol and DHEA(S) with symptoms of disorder. One study of early adolescent girls found that those who entered menarche earlier than their peers and had a high level of DHEA-S showed greater emotional arousal and depressive symptoms (Graber, 2008). It may be that the social and emotional implications of being off-time with one's peers results in an increased risk for depression and other emotional problems (Graber et al., 2004), distinct from the biological effect exerted by cortisol or DHEA(S).

A related problem is the inclusion of samples that are heterogeneous both in age and diagnostic status. The latter is especially problematic in the literature on externalizing disorders. Particular constellations of symptoms (i.e. attentional difficulties vs. disruptive behavior) are likely to be associated with particular patterns of adrenocortical activity. This may be a reason why research on externalizing disorders includes findings that are often divergent, if not contradictory. Another consequence is that the ability to isolate effects of cortisol and DHEA(S) specific to youth compared to adults is limited. This precludes knowledge of whether patterns of adrenocortical activation and associations with psychopathology are the same across development or vary based on life stage and the developmental processes occurring at that time. Due to developmental shifts in hormone production and brain maturation, age and developmental phase are necessary considerations to further understanding of the role of cortisol and DHEA(S) in these disorders.

A second issue that remains to be adequately addressed is comorbidity. Comorbidity is common in childhood psychopathology, with clinical samples often composed of youth with multiple and overlapping diagnoses. Small sample sizes and an associated lack of power often limit the ability to look at specific disorders individually. However, treating subcategories of disorder as unitary (e.g., AN and BN grouped as eating disorders) or failing to account for comorbidities across a broader range of psychopathology (e.g., anxiety and conduct problems) may obscure distinct patterns of hormonal activity at their origin, thereby hindering the ability to replicate findings across studies with different rates or types of comorbidities. In a prime example of this, comorbid internalizing disorders have been shown to significantly mitigate the hypocortosolism associated with CD and ODD (McBurnett et al., 1991; van Goozen et al., 1998). With evidence that environmental risk factors differentially impact risk for comorbid vs. non-comorbid disorders (e.g., Liu et al., 2015), it is plausible that hormonal profiles of individuals with and without comorbid conditions may differ.

A final concern is the potential effects of medication use. In the study by Snoek et al. (2004), nearly all of the ADHD children and half of the ODD children were being treated with the stimulant methylphenidate at the time of assessment. This is meaningful because pharmacological treatment can exogenously alter hormone levels, consistent with studies showing stimulant medications to cause a significant increase in salivary and serum levels of DHEA(S) and a decrease in the cortisol/DHEA ratio (Kariyawasam et al., 2002; Maayan et al., 2003; Wang et al., 2011a, 2014). There are also developmental differences in how children metabolize medications. Only by clarifying the complex relationships between biological factors acting during development can individual differences in the risk for psychopathology be fully understood.

9. Conclusions and future directions

Considerable progress has been made in understanding how circulating levels of cortisol a) contribute to regulatory processes within the brain and body, b) change in response to acute and chronic stress, c) are impacted by stressors across the life course, and d) are associated with risk for psychopathology. Although research on DHEA(S) and their role in these processes continues to progress at a much slower pace, several findings are noteworthy. At the biological level, there is evidence that DHEA(S) change in response to acute and chronic stress and impact synaptic plasticity and neurogenesis. There is also evidence that DHEA(S) have agonist and antagonistic actions on several neurotransmitter systems and initiate biological changes at the transition to puberty. Moreover, DHEA(S) show predictable, age-related shifts in circulating concentrations, peaking in the perinatal period and rising again at adrenarche. With respect to developmental psychopathology, there is preliminary evidence that administration of DHEA has antidepressant effects in adolescents and alleviates symptoms of eating disorders. These findings highlight the broad and physiologically meaningful role played by DHEA(S) in health and development.

There remain, however, several major knowledge gaps in our understanding of the role of DHEA(S) in development, in particular, the impact of altered ratios with cortisol. At present, little is known about how DHEA(S) shape or are shaped by experiences in early life, or whether large shifts in their circulating concentrations have developmentally-specific impacts on brain and behavioral responses to stress. Since long-term, programming effects of early life stress on cortisol are well documented, clarifying the role of high DHEA(S) in the perinatal period and adolescence, as well as their quiescence during infancy and early childhood, may prove especially informative.

Given the lack of studies examining cortisol and DHEA(S) simultaneously in early life, it is premature to speculate on whether examining the cortisol/DHEA(S) ratio has more predictive power for developmental outcomes, including developmental psychopathology, compared to quantifying absolute concentrations of either or both hormones. Complicating this pursuit is the lack of clarity on whether a high or low cortisol/DHEA(S) ratio is expected for different psychopathological outcomes. In addition, it is not known what the functional implications of developmental changes in absolute DHEA levels are for associations of the cortisol/DHEA(S) ratio with psychopathology at different ages.

Central to understanding the role of DHEA(S) and the cortisol/DHEA(S) ratio in typically-developing and clinical populations of youth will be identifying mechanisms influencing the preferential production of one hormone over the other. Genetic and epigenetic mechanisms are likely to have an impact but are at present unknown. Gender, along with biological sex differences in gonadal hormone production, are also likely to prove central given differences in the incidence of various disorders for males and females (Šulcová et al., 1997). Lastly, aspects of the social environment already known to predict cortisol response to stress, including early life care, parental stress, race/ethnicity, and socioeconomic status (Taylor, 2012; Turecki and Meaney,

2016), require equal attention as predictors of DHEA(S) and the cortisol/DHEA(S) ratio.

A primary aim of this review was to call attention to the parallel and oftentimes opposing activity of two hormones released in tandem from the adrenals. Evidence is emerging that cortisol and DHEA(S) play important roles in development, both in absolute concentrations and relative abundance. This speaks to the need more for more studies incorporating the two biomarkers. Including DHEA(S) in developmental studies will augment current understanding of how early experiences shape reactivity and regulation of the HPA axis throughout life. Particularly intriguing is the potential differential impact on health and behavioral outcomes of stress-induced elevations in cortisol that occur synchronously with versus unopposed to DHEA(S). Determining the causes and consequences of co- or preferential production of cortisol and DHEA(S) will advance our understanding of the role of these adrenal hormones in typical development and developmental psychopathology.

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