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Review

HPA function in adolescence: Role of sex hormones in its regulation and the enduring consequences of exposure to stressors

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Abstract

The hypothalamic–pituitary–adrenal (HPA) axis is one of the physiological systems involved in coping with stressors. There are functional shifts in the HPA axis and its regulation by sex hormones over the lifespan that allow the animal to meet the challenges of the internal and external environment that are specific to each stage of development. Sex differences in HPA function emerge over adolescence, a phenomenon reflecting the concomitant initiation of regulatory effects of sex hormones. The focus of this review is recent research on differences between adolescents and adults in HPA function and the enduring effects of exposure to stressors in adolescence. During adolescence, HPA function is characterized by a prolonged activation in response to stressors compared to adulthood, which may render ongoing development of the brain vulnerable. Although research has been scarce, there is a growing evidence that exposure to stressors in adolescence may alter behavioural responses to drugs and cognitive performance in adulthood. However, the effects reported appear to be stressor-specific and sex-specific. Such research may contribute toward understanding the increased risk for drug abuse and psychopathology that occurs over adolescence in people.
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Contents

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1. Introduction

The means by which an animal negotiates the demands of the environment shift over the lifespan. This shift occurs primarily as a function of developmental changes in anatomy and physiology and of changes in the behavioural repertoire. Each stage of development is associated with unique environmental demands. For example, the primary challenge for the neonatal rodent is physical growth and maturation and its negotiation of the environment is highly regulated by, and mostly limited to, interactions with mother and littermates (Levine, 2005). Adolescence is a time of transition that prepares the animal for adulthood, the time during which the animal negotiates the challenges of reproduction and survival and a larger, more varied environment. The challenges of adulthood differ for males and females (related directly or indirectly to reproductive behaviour), and adolescence is when many sex differences in behaviour emerge coincident with increased pituitary–adrenal function and further sexual differentiation of physiology (see review by Sisk and Foster, 2004).

The hypothalamic–pituitary–adrenal (HPA) axis is one of the physiological systems involved in coping with environmental challenges. Through the actions of glucocorticoid hormones in the brain, the HPA axis is involved in programming responses to future challenges, thereby potentially rendering the animal more vulnerable or more successful at coping. Much research attention has focused on the programming effects of the HPA axis in early life and on understanding HPA function in response to stressors in adulthood. In comparison, there has been relatively little research on adolescence, a time of significant brain development particularly in the frontal lobe (e.g., O'Donnell et al., 2005; Sowell et al., 2001) and a time which is of great importance for mental and physical health. For example, the risk in people for various psychopathologies such as schizophrenia, depression, and drug abuse increases in adolescence (see reviews by Hayward and Sanborn, 2002; Masten, 2004; McGue and Iacono, 2005), and stressors have been implicated as predisposing factors in these disorders (see reviews by Goodyer, 2002; Grant et al., 2003).

Only recently has there been increased research using animal models that investigates HPA function in adolescence and that addresses how adolescence, like perinatal life, may be a sensitive period for the programming of the brain (reviewed in later sections). How an animal negotiates the challenges and stressors of adolescence may determine its future risk and resilience. One limitation in the available literature is that much of the research at all stages of development has used males only, and yet the demands of development and of the environment differ for males and females. It thus may not be surprising that the HPA axis is highly regulated by sex hormones or that the consequences of exposure to stressors may be very different for females than for males. The following provides a brief review of the HPA axis and its regulation by sex hormones. We then focus on reviewing the available research on HPA function over adolescence in response to acute and chronic stressors. The last sections address the extent to which adolescence is a unique period of vulnerability for stressors and describes recent research investigating whether stressful experiences in adolescence have enduring effects on the brain and behaviour.

2. Overview of the HPA axis

2.1. HPA function in adulthood

Glucocorticoid hormones are produced in the cells of the adrenal cortex and have actions on almost all cell types of the body (Dallman et al., 1987). In the central nervous system, glucocorticoids influence protein synthesis, neuronal excitability, and neurotransmitter metabolism (Keller-Wood and Dallman, 1984; McEwen, 1980). In addition, glucocorticoids are important regulators of brain development and neuronal plasticity: They can influence virtually all aspects of neural development, including neurogenesis, synaptogenesis and dendritic morphology, and cell death (McEwen, 2000a). The secretion of glucocorticoids is under the control of the HPA axis: Adrenocorticotropin (ACTH) from the anterior pituitary acts on the adrenal cortex to initiate the release of glucocorticoids. The release of ACTH, in turn, is under the control of hypothalamic secretagogues, notably corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) from the parvocellular paraventricular nucleus (PVN) (Whitnall, 1993). There are diurnal rhythms in HPA function: For example, ACTH and glucocorticoid levels are highest in the rat (a nocturnal species) in the evening and lowest in the morning (Dallman et al., 1987). These rhythms are generated and controlled by inputs from the suprachiasmatic nucleus to the CRH systems (Abe et al., 1979; Cascio et al., 1987; Watts and Swanson, 1987, 1989) and feedback effects of glucocorticoids on the HPA axis (Akana and Dallman, 1992; Akana et al., 1992).

The HPA axis is involved in allostasis; that is, the regulation of threats to homeostasis (McEwen, 2000a; Munck et al., 1984). The HPA axis can be activated by a wide variety of stressors. Some of the most potent stressors are psychological or processive stressors (i.e., stressors that involve higher order sensory-cognitive processing, as opposed to physiological or systemic stressors) (Anisman and Matheson, 2005; McEwen, 2000b). Many psychological stressors are anticipatory in nature based on expectations as the result of learning and memory (e.g., conditioned stimuli) or species-specific predispositions (e.g., avoidance of light in rodents) (reviewed in Herman et al., 2003). An important role of the HPA response to stressors is to restore physiological balance to prevent overreaction of defense mechanisms to stress (Munck et al., 1984). For example, glucocorticoids increase the availability of energy substrates which enables the organism to cope more effectively with stress. Glucocorticoids not only mobilize energy stores, they improve cardiovascular tone and alter immune function. Through actions in the brain, glucocorticoids promote goal-directed behaviour and facilitate the formation of memories and thus shape behavioural and physiological reactions to a new stressor. However, prolonged exposure to high levels of glucocorticoids has damaging effects on many systems of the body, including the central nervous system (McEwen, 2000a). A rapid halt of the HPA response following the end of the stress experience limits

the potentially damaging effects of excessive exposure to glucocorticoids.

Glucocorticoids are involved in the suppression of their own release through fast (seconds to minutes), delayed (minutes to hours), and slow (hours to days) negative feedback systems that inhibit the release of ACTH (Dallman et al., 1987; Keller-Wood and Dallman, 1984). These feedback systems operate primarily at the level of the hypothalamus and pituitary, although other brain sites such as the hippocampus and medial prefrontal cortex also are involved in the regulation of HPA activity (e.g., Diorio et al., 1993; Jacobson and Sapolsky, 1991). The actions of corticosterone, the main glucocorticoid in rats, are mediated by two types of intracellular receptors (Beaumont and Fanestil, 1983; Krozowski and Funder, 1983) that regulate gene transcription when bound to DNA response elements or by interactions with other transcription factors (Joëls et al., 2004). These receptors have been cloned and appear identical to the mineralocorticoid receptors of the kidney and the glucocorticoid receptors of the liver (Arriza et al., 1988; Fuxe et al., 1985). There is a differential distribution of corticosteroid receptors in the brain, with mineralocorticoid receptors located primarily in lateral septum, hippocampus, medial amygdala and brain stem nuclei, and with glucocorticoid receptors more widespread and with higher concentrations in the hippocampus, PVN, and frontal cortex (Agnati et al., 1985; Reul and de Kloet, 1985, 1986; van Eekelen et al., 1987). Both receptor types are involved in the regulation of the HPA axis under circadian basal and stress conditions. Mineralocorticoid receptors have a higher affinity for corticosterone than do glucocorticoid receptors, which is a basis for the differential actions of corticosteroids in the brain (de Kloet and Reul, 1987). For example, at low basal levels of corticosterone (A.M. in the rat), at least 80% of hippocampal mineralocorticoid receptors are occupied, whereas only 10–15% of hippocampal glucocorticoid receptors are occupied (Reul and de Kloet, 1985; Reul et al., 1988). When levels of corticosterone are high, as under stress conditions, there is an increase in the occupation of hippocampal glucocorticoid receptors (Dallman et al., 1987). However, percent occupancy of corticosteroid receptors under basal and stress conditions varies among brain areas and among locations in the periphery (Miller et al., 1990; Spencer and McEwen, 1990). The selectivity of glucocorticoid receptors and mineralocorticoid receptors actions is mediated by several factors beyond receptor concentrations such as, for example in the hippocampus, association with accessory proteins (reviewed in Rashid and Lewis, 2005).

2.2. Sex differences in the adult HPA axis

Adult females have higher basal and stress levels of ACTH and corticosterone than do males (e.g., Allen-Rowlands et al., 1980; Critchlow et al., 1963; Kant et al., 1983; Kitay, 1961; Lesniewska et al., 1990a). The higher basal levels of corticosterone in females are partly buffered by their higher levels of corticosteroid binding globulin (CBG) (Gala and Westphal, 1965; McCormick et al., 2002a) as only unbound corticosterone is generally considered to be biologically active (Mendel, 1989; Rosner, 1990). However, females have higher levels of free corticosterone in response to stressors, as CBG levels take several hours to change after exposure to a stressor (e.g., Tannenbaum et al., 1997). Females also have higher levels of CRH (Hiroshige et al., 1973) and increased levels of CRH messenger RNA (mRNA) in the PVN (Patchev and Almeida, 1995; Watts and Swanson, 1989). In addition, there are sex differences in the neural circuitry involved in the control of ACTH: For example, AVP innervation of neural areas (de Vries et al., 1984; Wang et al., 1993) and the responses of AVP and oxytocin to stress (Williams et al., 1985) are sexually dimorphic.

Sex differences in HPA function are largely due to sex hormonal regulation of the HPA axis. Females have higher CRH, ACTH and corticosterone levels during proestrus, the phase of the cycle in which estradiol levels are high, than during other phases of the estrous cycle (Atkinson and Waddell, 1997; Bohler et al., 1990; Buckingham et al., 1978; Critchlow et al., 1963; Hiroshige et al., 1973; Raps et al., 1970; Walker et al., 2001). Further, plasma ACTH and corticosterone levels in response to stress are higher during proestrus than during other phases of the cycle (Carey et al., 1995; Pollard et al., 1975; Viau and Meaney, 1991). There is estrous cycle variation in oxytocin and AVP gene expression and content in the supraoptic and paraventricular nuclei (Greer et al., 1986; Van Tol et al., 1988). Neurotransmitter systems implicated in the control of HPA function (Kaneko and Hiroshige, 1978; Plotsky et al., 1989) show variations related to the estrous cycle and are sensitive to gonadal steroid levels (Bigeon and McEwen, 1982; Rance et al., 1981a,b; Rozsahegyi et al., 1973). Ovariectomy of adult rats reduces plasma ACTH and corticosterone levels, and replacement of estradiol returns ACTH and corticosterone levels to control values (Burgess and Handa, 1992; McCormick et al., 2002a; Seale et al., 2004a; Viau and Meaney, 1991). In sum, the preponderance of evidence suggests that estradiol has excitatory effects on the HPA axis in adulthood. However, there has been some evidence that estradiol may increase glucocorticoid negative feedback (Redei et al., 1994; Young et al., 2001). Studies of animals orchiectomized as adults and given androgen replacement indicate that androgens typically inhibit the HPA response to stress (Bingaman et al., 1994a; Handa et al., 1994; McCormick et al., 1998a; McCormick and Mahoney, 1999; Seale et al., 2004a; Viau and Meaney, 1996), although there are some reports of no effect of adult orchiectomy on corticosterone levels (Chen and Herbert, 1995; Lesniewska et al., 1990a,b).

Some of the control of HPA function by sex hormones may involve actions in the periphery. Sex hormones influence adrenal steroidogenesis (Colby and Kitay, 1972; Nowak et al., 1995), with testosterone decreasing and estradiol increasing corticosterone levels in the adrenal gland (Malendowicz and Mlynarczyk, 1982). Androgens decrease plasma CBG levels in both sexes whereas estradiol increases CBG levels in males only (Feldman et al., 1979; McCormick et al., 2002a; Nock et al., 2000; Paulmyer-Lacroix et al., 1996; Viau and Meaney, 2004). However, there is evidence of regulation of HPA function by sex hormones at central levels. For example, androgen inhibits hypothalamic CRH (Almeida et al., 1992; Bingaman et al., 1994b); CRH mRNA levels are higher during proestrus, when

estradiol levels are highest (Bohler et al., 1990), and are reduced in ovariectomized rats (Seale et al., 2004a) [but levels may be inhibited by prolonged high levels of estradiol treatment (Paulmyer-Lacroix et al., 1996)]; estrogen decreases glucocorticoid receptor (GR) binding and mRNA levels in various brain areas (e.g., Burgess and Handa, 1992; Carey et al., 1995; Peiffer and Barden, 1987); replacement of androgens or estradiol limited to the medial preoptic area decreased and increased, respectively, corticosterone release in response to stress in gonadectomized rats (McCormick et al., 2002a; Viau and Meaney, 1996) and testosterone in the medial preoptic area increased GR levels in the medial preoptic area (Viau and Meaney, 1996). In addition, androgens regulate CRH and AVP levels in the PVN (Bingaman et al., 1994b; Bohler et al., 1990; Viau et al., 1999; Watts and Swanson, 1989) and in brain areas upstream from the PVN (Viau et al., 2001).

2.3. Organizing effects of sex hormones on the adult HPA axis

The above illustrates activational effects of sex hormones in adulthood on the HPA axis. There are also organizational effects. Indirect evidence for the latter is that sex differences in HPA function often persist in animals when gonadectomized as adults (Nock et al., 1998; Sibilia et al., 2000; Wilson and Biscardi, 1994) and are only partially attenuated by equivalent sex hormone replacement regimens (McCormick et al., 2002a; Sillence and Rodway, 1990). More direct evidence of a role for sex hormones in early development on later HPA function comes from experiments in which gonadal steroid levels were manipulated in neonates. Libertun and Lau (1972) reported no effect of neonatal castration on basal corticosterone levels, whereas testosterone administration to females on the first day of life decreased basal corticosterone levels compared to controls. However, these rats were tested prepubertally before the sex difference in HPA function typically emerges and before the increase in testosterone levels that occurs over adolescence (discussed in greater detail later). Neonatally-castrated males given testosterone replacement as adults had higher corticosterone release in response to a stressor compared to adult-castrated rats given the same testosterone replacement (McCormick et al., 1998a) which suggests that neonatal testosterone influences the ability of sex hormones to regulate HPA function in adulthood. Consistent with this suggestion, male rats treated with the androgen receptor blocker flutamide during the perinatal period had higher ACTH and corticosterone levels in response to stressors in adulthood than controls despite having higher testosterone levels (McCormick and Mahoney, 1999; Seale et al., 2004b). Flutamide-treated neonatal rats also had higher levels of CRH mRNA and AVP mRNA in the PVN and lower levels of GR as adults (Seale et al., 2004b).

Androgen's effects in early development on later HPA function may involve direct actions of testosterone at androgen receptors and/or may involve aromatization of testosterone to estradiol. Blockade of aromatization in neonatal males also leads to increased corticosterone release in adulthood and higher glucocorticoid receptors levels (Seale et al., 2004b) and either injection of estradiol or testosterone in castrated neonates attenuated the increased corticosterone release in response to stress in adulthood found in vehicle-treated castrated neonates (all were given testosterone replacement in adulthood) (McCormick et al., 1998a).

Organizational effects of sex hormones on HPA function have been investigated in females as well. Females treated neonatally with estradiol were compared to diestrus females and to males as adults (Patchev and Almeida, 1995). The pattern of differences in PVN levels of CRH mRNA, AVP mRNA and GR found in these neonatally-treated females differed from both groups, but tended to be in the direction of that of males. When the three groups were subsequently gonadectomized as adults and treated with estradiol, neonatally-treated females and males did not show the increased CRH mRNA and AVP mRNA levels in the PVN evident in control females. In contrast, in a different study, females treated with testosterone on the first day of life showed decreased HPA function in response to stressors in adulthood compared to controls, but the decrease in HPA function was found to be secondary to reduced circulating estradiol levels at the time of testing since the groups did not differ when ovariectomized and given comparable estradiol replacement (Seale et al., 2005). Thus, the extent to which the HPA axis can be organized by exposure to sex hormones in neonatal life is more evident for males than for females.

2.4. HPA function and role of sex hormones over early development

From about postnatal day 3 to 14, rats are hyporesponsive in terms of corticosterone release in response to stressors which is thought to protect the developing nervous system from deleterious effects of high levels of glucocorticoids. Small changes in corticosterone release may have greater functional effects at this stage of development in that plasma CBG levels are very low and thus there is a higher proportion of biologically-active corticosterone in the neonate than in the adult (Henning, 1978; Viau et al., 1996). Although the HPA axis can still be activated by stressors during this period (e.g., Walker and Dallman, 1993; Walker et al., 1991), the HPA axis is immature and is regulated primarily by maternal behaviour (Levine, 2001). Sex differences in HPA function are typically not observed during the stress hyporesponsive period (e.g., McCormick et al., 1998b; Schoenfeld et al., 1980; van Oers et al., 1998). However, there have been a few reports of sex differences that have been linked to activational effects of sex hormones in neonates. Hary and colleagues (Hary et al., 1986; Hary et al., 1981) reported higher ACTH levels in 8-day-old females than males in response to ether inhalation, and reported that the higher ACTH levels of the females could be attenuated by injection of testosterone on the first day of life. Castration, however, did not increase ACTH release to ether on day 8 in males. Shanks and Meaney (1994) reported greater ACTH and corticosterone levels after injection of an endotoxin in 3-day-old females than in males, and in a subsequent study, the sex difference was reversed when pups were gonadectomized (Shanks et al., 1994). A recent study reported increased adrenal sensitivity to ACTH in 14-day-old females than in males, and that neonatal castration increased

adrenal responses in 14-day-old males whereas treatment with testosterone for 7 days after birth decreased adrenal responses of females and castrated males when tested at 14 days of age (Yoshimura et al., 2003). Nevertheless, the possibility of activational effects of sex hormones on HPA function in the neonate is a matter of debate, because other evidence suggests that the regulation of HPA function by sex hormones commences in late adolescence. The emergence of regulation of HPA function by sex hormones and other transitions in HPA function that occur over adolescence is discussed next.

3. Adolescence

3.1. Defining adolescence and puberty

Adolescence is a transitional time from childhood to adulthood that involves the maturation of social and cognitive behaviour (Sisk and Foster, 2004). For example, adolescence is the time in which adult-typical social behaviour of males (Primus and Kellogg, 1990) and risk-taking behaviours (Spear, 2000a) emerge. There are marked differences in the behaviour of adolescents compared to adults. For example, adolescents have greater levels of novelty-seeking and impulsivity and reduced stress and anxiety in response to novelty than adults (reviewed in Adriani et al., 2003). Adolescence lacks clear markers of onset and offset. Puberty, or attainment of sexual/reproductive maturity, is attained during adolescence and involves augmented pulsatile gonadotropin-releasing hormone secretion and activation of the hypothalamic–pituitary–gonadal axis (e.g., Payne et al., 1977; Wiemann et al., 1989).

Physical markers have been used as estimates of pubertal onset. In males, a marker is balanopreputial separation (separation of the prepuce from the glans penis) which occurs at approximately 40 days of age and precedes motile sperm production and the rise in testosterone levels which peaks at approximately 65 days (Korenbrot et al., 1977). In females, a marker is vaginal opening which occurs at approximately 35 days of age and precedes vaginal estrus and ovulation (Evans, 1986). However, there is a significant variation in the literature for days of balanopreputial separation (32 to 46 days) and day of vaginal opening (32 to 38 days), even when only one strain of rat is considered, in part due to variation in assessment practices (reviewed in Lewis et al., 2002). Additionally, age at which preputial separation and vaginal opening occurs can be influenced by developmental and environmental factors [e.g., diet, daily handling, exposure to glucocorticoids, maternal age (Korenbrot et al., 1977; Lewis et al., 2002; Pereira and Piffer, 2005; Rivest, 1991; Smith and Waddell, 2000; van Weissenbruch et al., 2005)]. Although these markers are linked to rises in gonadal hormone levels, puberty is best characterized in terms of changes in the brain as opposed to the gonads, because many pubertal changes are independent of gonadal hormones (reviewed in Sisk and Zehr, 2005).

In addition to the variability in the timing of such markers of puberty, there are no clear markers for onset and offset of adolescence. Thus, there is variability from lab to lab in terms of the ages used to define adolescence. One general system of classification of adolescence for the rodent has three stages, a prepubescence/early adolescence period from days 21 to 34 of age (rats are weaned typically at 21 days of age), a mid-adolescence period from days 34 to 46 of age, and a late adolescence period from days 46 to 59 of age (Tirelli et al., 2003). Another commonly used system is to consider 28 through 46 days-of-age as adolescence, which still leaves a period of days until what has typically been considered as adulthood (Spear, 2000a). Day 60 onward is commonly agreed upon as adulthood in that the animal has achieved physical and sexual maturity. The same age spans have been used for both males and females when designating an animal as “adolescent”.

3.2. HPA function in adolescence: acute stress

Adult levels of corticosterone are observed by approximately the fourth week of life (prepubertally; approximately 21–28 days) (e.g., Sapolsky and Meaney, 1986; Schoenfeld et al., 1980; Schroeder and Henning, 1989), although other aspects of the HPA axis reach adult levels at different points in time [e.g., GR levels within the first 2 weeks of life, (Meaney et al., 1985a,b); pituitary content of ACTH by 2 mos of age, (Walker et al., 1986a,b); adult levels of CRH-responsive cells in the anterior pituitary by 2 mos of age (Senovilla et al., 2005)]. Rats in early adolescence (prepubertal) have a delayed rise and a more prolonged corticosterone release to several types of stressors than do adult rats (e.g., Goldman et al., 1973; Vazquez and Akil, 1993). The prolonged release of corticosterone is due to incomplete maturation of negative feedback systems and not the result of different clearance rates of corticosterone in adolescence or reduced adrenal sensitivity to ACTH (e.g., Goldman et al., 1973; Gomez et al., 2002; Vazquez and Akil, 1993). However, the affinity and levels of MR and GR in the brain do not differ between adolescents and adults (Vazquez, 1998). Whereas adult males showed Fos-immunoreactivity (a widely used marker of neuronal activation) in a variety of brain regions after restraint stress, Fos responses in adolescent males were restricted primarily to the parvocellular PVN (Kellogg et al., 1998). It is unknown whether the restricted neuronal activation is related to the delayed glucocorticoid negative feedback of adolescents.

Research by Viau et al. (2005) also points to differences in the parvocellular PVN that may be related to the prolonged release of glucocorticoids in response to a stressor in adolescence. Despite similar levels of basal CRH mRNA in the parvocellular PVN, 60-day-old males, and not 30-day-old males, showed increased CRH mRNA levels in response to restraint. In contrast, 30-day-old males had increased Fos protein expression and AVP heteronuclear (hn) mRNA expression in the parvocellular PVN in response to 30 min of restraint compared to 60-day-old males (Viau et al., 2005). Further, both Fos protein and AVP hn mRNA expression were negatively correlated with plasma testosterone levels in 60-day-old males but not 30-day-old males, which may reflect a floor effect in the young males. However, changes in the brain over adolescence may be required for the regulation of HPA function by sex hormones, as other research indicates that the prolonged corticosterone release in response to stressors in prepubertal

males is not the result of reduced levels of testosterone. When adult (77 days) and prepubertal (28 days) males were castrated and given one week of testosterone replacement, prepubertal males continued to show prolonged elevation of corticosterone levels after 30 min of restraint despite somewhat higher levels of plasma testosterone compared to the adult males (Romeo et al., 2004a).

Pubertal increases in testosterone levels have been suggested to alter central regulation of HPA responses when rats of 40 days of age are compared to rats of 60 days of age (Gomez et al., 2004). Thus, regulation of HPA function by sex hormones may begin in mid-adolescence. Romeo et al. (2004a) suggested that ongoing development of the MPOA, a site of sex hormonal regulation of HPA function (McCormick et al., 2002a; Viau and Meaney, 1996), may be responsible for the reduced effectiveness of testosterone to inhibit stress-induced corticosterone release in prepubertal/early adolescent males. In addition, reduced levels of androgen receptors have been found in adolescent compared to adult males (e.g., Romeo et al., 2000). Certainly, many of the neural regions implicated in the control of the HPA axis such as the medial prefrontal cortex, bed nucleus of the stria terminalis, hippocampus, and amygdala (reviewed in Herman et al., 2003) are undergoing developmental changes over adolescence (reviewed in Spear, 2000a,b), and are potentially involved in the increase in sensitivity of the HPA axis to sex hormones.

There have been fewer studies of adolescent females. However, the available research indicates that sex differences in HPA activity emerge during adolescence. For example, the higher adrenal weight and adrenal content of corticosterone of females than males were reported to emerge only by about day 50 days of age, although higher stress-induced levels of plasma corticosterone may be found earlier (Sencar-Cupovic and Milkovic, 1976). A sharp rise in afternoon levels of CRH were found at the time of vaginal opening in females (Honma and Hiroshige, 1977). The differences in HPA function evident in young adolescent compared to adult females do not appear to be completely explained by differences in gonadal hormone levels. Prepubertal females had prolonged corticosterone release in response to 30 min of restraint compared to adult females, and this difference was also evident when ovariectomized prepubertal and adult females were compared (Romeo et al., 2004b). However, no difference was found in basal or in peak corticosterone levels after restraint between prepubertal and adult females. In contrast, Viau et al. (2005) found that adult females had significantly higher basal and stress-induced corticosterone levels in response to 30 min of restraint than prepubertal females. Neither study found age-related differences in basal or stress-induced ACTH levels. Romeo et al. (2004b) suggested the age difference in corticosterone levels in the absence of an age difference in ACTH levels may reflect a differential sensitivity of the adrenal to ACTH in adolescence. However, differences were found in central levels of the HPA axis by Viau et al. (2005), with adult females having higher basal levels of CRH mRNA in the parvocellular PVN than prepubertal females. There were no differences between prepubertal and adult females in CRH mRNA, Fos and AVP hn mRNA expression in response to restraint. Thus, females show a different pattern of maturation of HPA regulation over adolescence than do males, but in neither sex can the differences be explained by circulating sex hormone levels. The available evidence suggests that HPA regulation by sex hormones for both sexes likely requires changes in the maturation of the brain.

3.3. HPA function in adolescence: repeated stress

In adulthood, the neuroendocrine response to many stressors such as restraint is reduced after repeated or chronic exposure (reviewed in Girotti et al., 2006). The reduced response to repeated stressors serves to protect the animal from high levels of glucocorticoids and yet does not diminish the capacity of the HPA axis to respond to a new type of stressor (reviewed in Armario et al., 2004). The reduced HPA response to repeated stressors in adults contrasts to what is found in neonatal animals, in which repeated exposure to the same stressor (i.e., 1 h of isolation) leads to a potentiated release of ACTH and corticosterone (Kehoe et al., 2001; Knuth and Etgen, 2005; McCormick et al., 1998b). Thus adolescence may be a time of transition in HPA responses to repeated stressors as it is for acute stressors. Romeo et al. (2006) found that 28-day-old male rats had as high levels of plasma ACTH and corticosterone after the 7th episode of 30 min of restraint as rats of the same age undergoing a first restraint. In contrast, adult rats secreted far less ACTH and corticosterone to a 7th episode of restraint than to a first episode. However, the adult rats had not diminished their ACTH and corticosterone release 45 min after the 7th episode of restraint, and thus had higher levels than the prepubertal animals at this time point. These results contrast with their findings (and are consistent with the findings described above) with acute restraint whereby prepubertal rats had prolonged ACTH and corticosterone release compared to adults. No differences were found in CBG levels of the prepubertal and adult male rats in either the acute-stressed or repeated-stressed rats. In sum, these results indicate that the HPA axis responds differently to acute and to chronic stress depending on the developmental stage of the animal. Table 1 summarizes the experiments that involved direct comparisons of HPA function in adolescents and adults.

We have found that in mid-adolescence the extent to which habituation is evident in corticosterone release is sex-specific and depends on the type of stressor (McCormick et al. in preparation and Merrick et al., 2006). Male and female rats underwent daily 1 h isolation in small containers from day 30 to day 44 of age. After each isolation, rats were returned to their original cage partner (ISO; isolation only) or to a new cage partner (SOC; isolation + social stress). The response of these groups to isolation on day 45 (16th episode) was compared to control groups of males and females undergoing a first isolation on day 45 of age. The three groups did not differ in pre-stress levels of corticosterone on day 45. Corticosterone levels were higher in females than in males in pre-stress and post-stress samples. ISO males and females had lower levels of corticosterone after isolation than did rats undergoing their first isolation. Corticosterone levels of SOC females were as high after 16 episodes of isolation as control females undergoing a first isolation. In contrast, SOC males, like ISO males, had lower levels of corticosterone to the 16th episode. However, because SOC rats

Table 1
Studies directly comparing adolescent and adult HPA responses to stressors

Strain and sex	Ages (in days)	Stressor	Measure	Result	Reference
Acute stress					
Long Evans (males)	25 and 65	1.5 min exposure to ether	Corticosterone	Ado>Adult	Goldman et al. (1973)
	25, 45 and 65	60 s of foot shock over 1.5 min	Corticosterone	25>65 and 45; 45=65	
	27–28 and 81–86	Dexamethasone (100 μg/100 g) i.p.; ether exposure 4 h later	Corticosterone	Ado>Adult	
	25 and 65	Hydrocortisone or dexamethasone pellet in median eminence; ether stress 48 h later	Corticosterone	Ado=Adult	
Sprague Dawley (males)	25 and adult	3 min exposure to ether	Corticosterone and ACTH	Ado>Adult	Vazquez and Akil (1993)
Long Evans (males)	28 and 60	15 min or 2 h of restraint	Fos-immunoreactivity	Ado<Adult	Kellogg et al. (1998)
Sprague Dawley (males)	28 and 77	30 min restraint	Corticosterone and ACTH	Ado>Adult	Romeo et al. (2004a)
			Corticosterone and ACTH after castration+testosterone	Ado>Adult	
Sprague Dawley (males)	28 and 77	30 min restraint	Corticosterone and ACTH	Ado>Adult	Romeo et al. (2006)
Sprague Dawley (females)	28 and 77	30 min restraint	Corticosterone (intact and ovariectomized)	Ado>Adult	Romeo et al. (2004b)
			ACTH (intact and ovariectomized)	Ado=Adult	
Sprague Dawley (males)	28–32 and 58–62	30 min restraint	CRH mRNA in PVN	Ado<Adult	Viau et al. (2005)
			Fos and AVP hn mRNA in PVN	Ado>Adult	
Sprague Dawley (females)	28–32 and 58–62	30 min restraint	Corticosterone	Ado<Adult	Viau et al. (2005)
			CRH mRNA, Fos, and AVP hn mRNA in the PVN	Ado=Adult	
Repeated stress					
Sprague Dawley (males)	40–41 and 60–61	3 h of restraint for 3 days	ACTH (day 1; n.s. other days)	Ado>Adult	Gomez et al. (2002)
			Corticosterone (day 2; n.s. other days)	Ado>Adult	
Sprague Dawley (males)	40–41 and 60–61	3 h of restraint for 3 days	AVP-immunoreactivity in the PVN	Ado=Adult	Gomez et al. (2004)
		3 h of restraint for 3 days+flutamide	AVP-immunoreactivity in the PVN	Ado>Adult	
Sprague Dawley (males)	22 and 70	30 min of restraint for 7 days	Corticosterone and ACTH (after first stress exposure)	Ado>Adult	Romeo et al. (2006)
			Corticosterone and ACTH (after last stress exposure)	Ado>Adult	
			Corticosterone and ACTH (45 min after last stress exposure)	Ado<Adult	
			CRH and Fos double-labeled cells in the PVN (all time points)	Ado>Adult	

had lower levels of CBG than ISO and controls at day 45, both SOC males and females had higher levels of free corticosterone than ISO rats. We are currently investigating CRH mRNA levels in these animals to investigate whether differences in response to repeated stressors in mid-adolescence are evident in the brain.

Although investigation of HPA function in response to chronic stressors in adolescence is only beginning to be investigated, the results described suggest that repeated stress in adolescence may lead to greater exposure to glucocorticoids than similar experiences in adulthood (although see Restrepo and Armario, 1987). Thus, adolescents may be at greater risk for the deleterious effects of chronic stress than adults.

4. Enduring effects of stressors in adolescence

That the brain is undergoing vigorous maturation over adolescence suggests that it may be more susceptible to stressors and the concomitant exposure to high levels of glucocorticoids in adolescence than in adulthood. Consistent with the latter possibility that adolescents are more susceptible to the effects of stressors than are adults, increased levels of corticosterone before puberty, but not after puberty, altered the gene expression of NMDA receptor subunits in the hippocampal formation (Lee et al., 2003). Adolescence is a time of extensive pruning of synapses and of reorganization of many neurotransmitter systems (reviewed in Spear, 2000b). There are significant changes in neurotransmitter levels, activity, and receptors in the brain over adolescence (e.g., Andersen et al., 2000; Lee et al., 2003; Teicher et al., 1995). There is increased development of synapses and extensive myelination in the cerebral cortex over adolescence (Cunningham et al., 2002; Juraska and Markham, 2004). The effects of stressors on behaviour are different in adolescence than in adulthood (e.g., Douglas et al., 2003, 2004; Stone and Quartermain, 1997).

There is a vast literature indicating that stressors in prenatal or neonatal life alter ongoing brain development and thereby produce relatively permanent changes in behaviour and physiology in adulthood (e.g., Meaney, 2001; Weinstock, 2001). The same may be true for adolescence, and more research in recent years has investigated the possibility of long-lasting effects of

stressors in adolescence. The research on the long-lasting effects of stressors in adolescence is reviewed in the next sections (see Table 2). However, as with studies at other ages of development, there has been a greater investigation of males than of females.

4.1. Effects on HPA responses

Although neither handling nor unpredictable-varied stressors between the ages of 21 and 32 days affected corticosterone release in male rats as adults (Maslova et al., 2002a), the variable stress exposure did increase acoustic startle reflexes in adulthood (Maslova et al., 2002b). No difference was found in the effects of footshock to juvenile rats (shock given between the ages of 28 and 36 days) compared to footshock to adult rats on later gastric ulceration or corticosterone levels in response to stressors in adulthood (Overmier and Murison, 1991). In contrast, exposure to variable stressors for six weeks beginning at 31 days of age blunted HPA responses to a new stress experience five days after the chronic stress exposure in both males and females (Goliszek et al., 1996). Variable physical stressors (forced swim, restraint, loud noise, cold exposure, ether exposure) or variable social stressors (isolation, novel environment, crowding, litter-shifting, subordination) daily between the ages of 28 to 56 days prolonged corticosterone release in males to a new stressor when tested 24 h after the last stressor (Isgor et al., 2004). However, when tested three weeks after the adolescent-stress exposure in adulthood, only those exposed to physical stressors showed prolonged corticosterone release to a new stressor (Isgor et al., 2004). Consistent with the results of Isgor et al. (2004), no differences in corticosterone responses to restraint in adulthood were found in either males or females exposed to a different social stress procedure (repeated daily one hour isolation followed by pairing with a new cage mate, as described above) compared to controls (McCormick et al., 2005).

In sum, the effects of repeated stress exposures in adolescence on adult HPA responses to stressors are modest at best, despite the findings that the responses of adolescents to acute and repeated stressors differ significantly from those of adults. These results contrast with the significant changes in adult HPA function following stress exposure prenatally and neonatally that

Table 2
Experiments investigating effects of stressors in adolescence on adult function

Strain and Sex	Age at stress	Age at testing	Chronic stressor in adolescence	Experiment in adulthood	Measure	Result compared to controls	Reference
Effects on HPA axis							
S.D. (males)	28–36	96	3 footshock sessions 2 days apart (predictable OR non)	Footshock stress	Corticosterone	No effect	Overmier and Murison, 1991
WKY (males and females)	28–70	74–75	5 days/wk, varying immobilization, white noise, and heat for 30 min daily	CRH injection and 3 min ether	ACTH	Blunted	Goliszek et al. (1996)
Wistar (males)	21–32	33–36 and 120	Repeated handling OR unpredictable stress	1 h restraint stress	Corticosterone	No effect	Maslova et al. (2002a)
S.D. (males)	28–56	57 or 77	Variable physical stress Variable social stress	15 min on open arm of elevated plus maze	Corticosterone	Enhanced No effect	Isgor et al. (2004)
L.E. (males and females)	33–48	69	Daily 1 h isolation, novel cage and mate	30 min restraint	Corticosterone	No effect	McCormick et al. (2005)
Effects on drug responses							
S.D. (males)	28–56	57	Variable physical stress Variable social stress Variable physical stress Variable social stress	Repeated amphetamine (1 mg/kg) Dose of amphetamine 1 wk later (0.5 mg/kg)	Locomotor activity Locomotor sensitization	No effect No effect No effect Blunted	Kabbaj et al. (2002)
L.E. (males and females)	33–48	72	Daily 1 h isolation, novel cage and mate	Repeated nicotine (0.5 mg/kg)	Locomotor sensitization	Males: no effect; Females: enhanced	McCormick et al. (2004)
L.E. (males and females)	33–48	77	Daily 1 h isolation, novel cage and mate	Amphetamine (0.5 mg/kg)	Locomotor activity	Males: no effect; Females: enhanced	McCormick et al. (2005)
Effects on cognitive behaviour							
Wistar (males)	21–32	33–38 and 120	Chronic variable stress	Acoustic startle reflex	Startle amplitude	Enhanced	Maslova et al. (2002b)
S.D. (males)	28–56	77	Variable physical stress Variable social stress	Water maze	Spatial learning and hippocampal volume	Impaired No effect	Isgor et al. (2004)
Wistar (males)	26–28	90	Repeated exposures to a black elevated platform	Water maze	Spatial learning Spatial learning after adult stress	Impaired Enhanced	Avital and Richter-Levin (2005)
S.D. (males)	27–29 or 33–35	≈60	Forced swim, elevated platform, and footshock administered over 3 days	Shuttlebox, open field and avoidance learning	Learning	Impaired	Tsoory and Richter-Levin (2005)

S.D. = Sprague Dawley; L.E. = Long Evans; WKY = Wistar Kyoto.

have been reported (e.g., Maccari et al., 1995; McCormick et al., 1995; Plotsky and Meaney, 1993).

4.2. Effects on drug responses

It is well-established that the behavioural and neurochemical responses to various drugs of abuse of adolescents differ from those of adults (e.g., Adriani and Laviola, 2000; Collins and Izenwasser, 2004; Crews et al., 2000; Faraday et al., 2001; Faraday et al., 2003; Klein, 2001; Spear et al., 1982; Trauth and Slotkin, 2000). Based on evidence from behavioural models of drug abuse and addiction such as locomotor sensitization, conditioned place preference, and self-administration, adolescents appear to be more vulnerable to the rewarding properties and detrimental effects on the nervous system of various drugs than are adults (see reviews by Barron et al., 2005; Leslie et al., 2004; Spear, 2000a; Tirelli et al., 2003). Exposure to stressors in the prenatal or neonatal periods has been found to increase susceptibility to the effects of many drugs in adulthood, which suggests that later drug responses may be programmed by early life events (Koehl et al., 2000; Kosten et al., 2000; Li et al., 2003; McCormick et al., 2002b; Meaney et al., 2002). However, there have been few studies examining the effects of stressors in adolescence on later behavioural responses to drugs.

Kabbaj et al. (2002) found that social stress, but not physical stress, from age 28 to 56 decreased locomotor sensitization to amphetamine in male rats when the exposure to amphetamine began immediately after the last day of stress. Whether these effects would remain in adulthood was not tested. Consistent with the latter results using a different social stress procedure in adolescence (isolation and new cage mate daily for 16 days, as described above), we found decreased locomotor activating effects to repeated doses of nicotine in both males and females compared to controls when testing began the day following the last stress exposure (McCormick et al., in preparation; McCormick, 2006). Adolescent rats that underwent daily isolation only did not differ from controls in locomotor activity to repeated doses of nicotine.

We also found that the effects of the adolescent social stress persisted into adulthood in females. When tested several weeks after the adolescent social stress, females now showed increased locomotor sensitization to nicotine and increased locomotor-activating effects of amphetamine compared to control females (McCormick et al., 2004, 2005). Adolescent-stressed males and control males did not differ in their behavioural responses to these psychostimulants as adults (McCormick et al., 2004, 2005). Thus, females may be more vulnerable than males to the enduring effects of certain stressors in adolescence. As noted earlier, females showed much greater and persistent elevations of corticosterone in response to the repeated social stress procedure in adolescence than did males. This greater exposure to glucocorticoids in adolescent females may be why lasting effects on the locomotor-activating effects of drugs were found in females only. Another possibility is that sex differences in brain development, and notably of the mesolimbic dopamine system (e.g., Andersen et al., 1997) may be involved in the differential enduring effects of the social stressors in males and females.

4.3. Effects on cognitive behaviour

As noted earlier, there are differences in the behavioural repertoire of adolescents and adults, and such differences extend to performance on cognitive tasks. For example, adolescents differ from adults on attentional set-shifting tasks that are thought to reflect maturational changes in the prefrontal cortex (Leslie et al., 2004). Thus, exposure to stressors in adolescence may alter ongoing brain development leading to altered cognitive performance in adulthood. These effects may be sex-specific, given that there are sex differences on certain cognitive tasks. For example, sex differences in spatial performance were found to emerge after puberty (e.g., Kanit et al., 2000; Krasnoff and Weston, 1976), as did sex differences in the effects of an acute stressor on an associative task (trace eyeblink conditioning) (Hodes and Shors, 2005). However, to date the effects of stressors in adolescence on cognitive performance in adulthood have been investigated in males only.

Variable physical stress, but not social stress, from age 28 to 56 decreased performance in a water maze when tested three weeks later in adulthood (Isgor et al., 2004). These animals also had marked reductions in volume of several layers of the hippocampal formation. Of interest, these differences in hippocampal morphology were not evident immediately after the stressor exposure but were evident in adulthood. In contrast, when chronic stress is administered in adults, the effects on hippocampal morphology are evident immediately after chronic stress and tend to dissipate with time (e.g., McEwen, 2000b; Sousa et al., 2000).

Another study also found that adult male rats stressed in adolescence (forced swim, elevated platform days 26–28) had reduced performance in a water maze task compared to controls (Avital and Richter-Levin, 2005). However, when these rats were stressed in adulthood just before testing, they had better performance in the water maze task and increased startle responses compared to rats that were only stressed as adults before testing. In a separate study, rats were exposed to different stressors (forced swim, elevated platform, footshock) over days 27–29 or over days 33–35 and then tested as adults (Tsoory and Richter-Levin, 2005). Both groups showed reduced exploratory behaviour in a shuttlebox and in an open field compared to controls. They also showed reduced avoidance learning, and the poorer performance was greater in those stressed at the earlier age than at the later age of adolescence. Thus, stress in adolescence leads to both impaired performance on cognitive tests in adulthood and altered effects of new stressors on cognitive performance.

5. Summary and concluding remarks

In summary, HPA function differs in adolescence than in adulthood in responses to both acute and chronic stressors and in its regulation by gonadal hormones. As indicated above, one consequence of exposure to stressors in adolescence appears to be more prolonged exposure to glucocorticoids, hormones that influence ongoing brain development and program future behavioural and physiological responses. Because the brain is continuing to mature and develop over adolescence, the

consequences of exposure to stressors may be different from or greater than in adulthood. The literature reviewed above suggests that exposure to stressors in adolescence leads to relatively permanent changes in cognitive behaviour and in behavioural responses to drugs and, perhaps, in differences in neuroendocrine responses to stressors. In addition, because the HPA axis is a sexually differentiated system acting on a sexually differentiated substrate undergoing further sexual differentiation in adolescence, the consequences of exposure to stressors likely differ for males and females. Research from our lab suggests that females may be more vulnerable than males in adolescence to stressors that involve social instability. This review has focused on the research on drug-related behaviour, cognitive function, and neuroendocrine function in adulthood because most of the available – and nevertheless limited – research on enduring effects of stressors in adolescence has investigated these. This focus is in part due to a desire to develop animal models for the increased risk in adolescence for the development of drug abuse and psychopathologies, which also involve altered neuroendocrine function and cognitive performance (Hayward and Sanborn, 2002; Masten, 2004; McGue and Iacono, 2005).

Thus, there is an increasing evidence that adolescence is a time of heightened plasticity, and may indeed be a sensitive period of development similar to the perinatal period for the effects of stressors (Grant et al., 2003; Spear, 2000a,b). However, much more research is required on the effects of stressors in adolescence to uncover at which ages/stages of maturation in adolescence are females and males most vulnerable to stressors and to which type of stressors. This review has focused on the role of sex hormones in regulating HPA function over development, however it is important to note that HPA activation in turn influences gonadal systems (Chrousos et al., 1998; Wingfield and Sapolsky, 2003), and stress-induced alteration of gonadal systems may also be involved in some of the enduring effects of stressors on a wide range of behaviours [e.g., sexual behaviour (Almeida et al., 2000) and aggression (Ferris, 2000)]. Understanding how stress systems and gonadal systems interact over all stages of development is necessary for understanding physical and mental health over the lifespan. Recent initiatives by funding agencies such as the National Institutes of Health in the US and Canadian Institutes of Health Research to promote research in adolescence should serve to correct the relative neglect of this period of development.

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