Steroid hormones, stress and the adolescent brain: a comparative perspective

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Abstract

Steroid hormones, including those produced by the gonads and the adrenal glands, are known to influence brain development during sensitive periods of life. Until recently, most brain organisation was assumed to take place during early stages of development, with relatively little neurogenesis or brain re-organisation during later stages. However, an increasing body of research has shown that the developing brain is also sensitive to steroid hormone exposure during adolescence (broadly defined as the period from nutritional independence to sexual maturity). In this review, we examine how steroid hormones that are produced by the gonads and adrenal glands vary across the lifespan in a range of mammalian and bird species, and we summarise the evidence that steroid hormone exposure influences behavioural and brain development during early stages of life and during adolescence in these two taxonomic groups. Taking a cross-species, comparative perspective reveals that the effects of early exposure to steroid hormones depend upon the stage of development at birth or hatching, as measured along the altricial-precocial dimension. We then review the evidence that exposure to stress during adolescence impacts upon the developing neuroendocrine systems, the brain and behaviour. Current research suggests that the effects of adolescent stress vary depending upon the sex of the individual and type of stressor, and the effects of stress could involve several neural systems, including the serotoninergic and dopaminergic systems. Experience of stressors during adolescence could also influence brain development via the close interactions between the stress hormone and gonadal hormone axes. While sensitivity of the brain to steroid hormones during early life and adolescence potentially leaves the developing organism vulnerable to external adversities, developmental plasticity also provides an opportunity for the developing organism to respond to current circumstances and for behavioural responses to influence the future life history of the individual.

Introduction

The role of steroid hormones in the development of the brain and behaviour has been a central topic within behavioural neuroendocrinology for over half a century (Wingfield, 2005; Wallen, 2009). In the 1950s, a ground-breaking study by Phoenix and colleagues showed that injecting pregnant female guinea pigs with testosterone resulted in female offspring that exhibited masculinised and defeminised behaviour in adulthood (Phoenix et al., 1959). Prenatal or perinatal treatment of female rats with testosterone was also shown to alter the development of sexually dimorphic nuclei within the brain (e.g., Gorski et al., 1978; Ito et al., 1986). A substantial body of literature has since confirmed that early exposure to gonadal steroid hormones exerts long-lasting, 'organisational' effects on the brain in a broad range of species (Cooke et al., 1998; Groothuis et al., 2005; Crews et al., 2009; Wright et al., 2010). Steroid hormones can exert such effects by crossing the blood-brain barrier and influencing processes such as neurogenesis, synapse formation, dendritic growth and cell death (Arnold, 2009; Charil et al., 2010).

Steroid hormones produced by the adrenal glands in response to stress are also known to influence neural development during early life (Weinstock, 2008; Lupien et al., 2009; Romeo et al., 2009; Charil et al., 2010; Henriksen et al., 2011). The term 'stress' is generally used to describe events that are threatening to an individual and that elicit stabilising behavioural and physiological responses (McEwen and Wingfield, 2003). Prenatal exposure to stress has been shown to influence the development of the brain and behaviour in mammals (e.g., Vallée et al., 1997), and injection of corticosterone into birds' eggs similarly impacts upon behavioural and neuroendocrine development (e.g. Love and Williams, 2008a; 2008b). In many instances, the effects of early exposure to stressors differ between the sexes (Weinstock, 2007; Charil et al., 2010), and such sex differences could partly result from the complex interactions between the developing gonadal and adrenal hormone systems (e.g., Ward et al., 2003; Bowman et al., 2004).

The effects of steroid hormone exposure on behavioural and brain development are particularly strong during delineated stages of development, known as 'sensitive periods'. While most research has focused on the effects of steroid hormone exposure during prenatal or early postnatal life, adolescence has been hypothesised to be another highly sensitive period of neural development (Spear, 2000; Romeo et al., 2002; Andersen, 2003; Sisk and Zehr, 2005; McCormick and Mathews, 2010). Adolescence is broadly defined as the period of life that includes attainment of sexual maturity (Spear, 2000), and, using this definition, adolescence can be considered to be a specific stage of life in a broad range of taxonomic groups. Research on human and non-human animals, such as primates, rodents and several songbird species, has confirmed that the brain undergoes significant re-organisation during adolescence in many taxa (Spear, 2000; McCormick and Mathews, 2010; Brenhouse and Andersen, 2011; Blakemore, 2012; Catchpole and Slater, 2008), and a growing number of studies have shown that the developing brain is sensitive to steroid hormone exposure during the adolescent period (Romeo, 2003; McCormick and Mathews, 2007; Schulz et al., 2009; McCormick and Mathews, 2010).

The aim of this review is to evaluate the current evidence that adolescent stress influences behavioural and brain development, focusing on two major taxonomic groups, namely mammals and birds. Taking a comparative perspective provides an opportunity to search for commonalities in the effects of steroid hormone exposure on brain development and to highlight the differences in hormone action across species with different life-histories. The effects of stress during adolescence are predicted to vary between species, depending upon the relative stage of neural development at the time of stress exposure and the relevance of the stressor to the particular species, and stress effects are also likely to vary within species, depending upon the sex of the individual and environmental factors, such as the presence of social partners (Kikusui et al., 2006; McCormick and Mathews, 2007; Oldehinkel and Bouma, 2011). Many studies on

mammals and birds provide relevant data with which to test these predictions, yet evidence from these two taxa are rarely evaluated together.

Development of the neuroendocrine systems in mammals and birds

The first section of the review provides a brief introduction to the neuroendocrine systems that are involved in steroid hormone production from the gonads and the adrenal glands. The ontogenetic development of these neuroendocrine axes is summarised from prenatal life to early adulthood.

i) Development of the hypothalamic-pituitary-gonadal axis

The hypothalamic-pituitary-gonadal (HPG) axis is highly conserved across mammals and birds (Lovejoy, 2005). In both taxonomic groups, gonadotrophin-releasing hormone (GnRH) is produced by the hypothalamus and travels through the hypophysial blood system to the pituitary gland. By binding to specific receptors in the pituitary, GnRH stimulates the release of gonadotrophins (luteinising hormone, LH, and follicle stimulating hormone, FSH). These hormones are then transported through the bloodstream to the gonads and stimulate production of the gonadal steroid hormones (e.g., testosterone, estradiol and progesterone). Hormone receptors are located in numerous tissues, including the brain (Pak and Handa, 2008), and negative feedback loops modulate the activity of the HPG axis via these conserved receptor systems (Meethal and Atwood, 2005). The HPG axis is intimately involved in sexual maturation and the onset of reproductive function in both mammals and birds (Johnson, 2007).

During early life, the HPG axis exhibits specific periods of activity and inactivity, depending upon the stage of development and sex of the animal. Many animal species (including Norway rats, *Rattus norvegicus*, house mice, *Mus musculus*, and most passerine birds) are altricial in nature; juveniles are born with their eyes closed and rely heavily on parental care and

feeding in order to survive the first few weeks of life. In altricial rodents, the fetal testes secrete testosterone during late gestation and during the first few hours after birth (e.g., Corbier et al., 1978; Weiss and Ward, 1980), while the fetal ovary is assumed to be inactive during comparable stages of life (Bakker and Baum, 2008). In rodents of both sexes, gonadal hormone and gonadotrophin levels are reported to be somewhat elevated again during the pre-weaning phase (prior to postnatal day, *pnd*, 21), remain low during early adolescence (pnd 21-33), then rise substantially during mid- (pnd 34-46) and late adolescence (pnd 47-59; age categories based on Tirelli et al., 2003) (e.g., Ojeda and Ramírez, 1972; Meijs-Roelofs et al., 1973; Paz et al., 1980; Zapatero-Cabellero et al., 2003; **Figure 1a**). In mammals, re-activated of the HPG axis during adolescence results from an elevation in GnRH pulsatility (Sisk and Foster, 2004). In some altricial bird species, the gonads are mostly inactive during prenatal and early postnatal life , while a diphasic post-natal response is observed: GnRH levels in both sexes surge in early post-natal life (e.g., day 4 in European starlings, *Sturnus vulgaris*; Williams et al., 1987), followed by a quiescent period regulated by several inhibitory factors, including Gonadotropin Inhibitory Hormone (GnIH), and then a second increase during puberty (Perfito and Bentley, 2009). However, in some species there is a lack of a quiescent period (e.g., zebra finch, *Taeniopygia guttata*), where testosterone levels are relatively high during both the post-natal and adolescent periods and then begin to increase further during puberty (around 75 days of age; Prove, 1983; but see Adkins-Regan et al. 1990; **Figure 1b**), while estradiol levels in females remain stable during the period of sexual maturation (Adkins-Regan et al., 1990).

In precocial and semi-precocial species, such as guinea pigs (*Cavia porcellus*), primates and birds such as the chicken (*Gallus gallus*) and Japanese quail (*Coturnix japonica*), juveniles are born in a more developed state than in altricial species, with eyes open and greater mobility. In precocial and semi-precocial mammals, the pattern of HPG axis activity is similar to that in altricial mammals; testosterone levels are higher in males than females *in utero*, immediately

after birth and during an early postnatal period (e.g., guinea pig; Rigaidière et al., 1976; rhesus macaques, *Macaca mulatta*: Resko, 1970; Brown et al., 1999; **Figure 1c**), and the hypothalamic-pituitary-ovarian axis is also transiently active during early postnatal life (e.g., human beings, *Homo sapiens*; Chellakooty et al., 2003). GnRH levels exhibit a peak during early postnatal life and another rise during adolescence (Plant, 2008). In precocial birds, there is often substantial pre-natal development of the HPG axis in comparison to altricial species. For example, in the precocial Japanese quail, sex-specific developmental patterns have been revealed *in ovo*: male embryos show a rapid peak in testosterone a few days before hatching (around day 14, where hatching is day 18), whilst females show a steady increase in estradiol throughout embryonic development (Ottinger et al., 2002). Gonadal hormone levels then gradually rise from low postnatal levels in both sexes to peak in adulthood (e.g, chickens: Heiblum et al., 2000; Japanese quail: Sedqyar et al. 2008; **Figure 1d**). In ducklings (*Anas platyrhynchos*: Ni et al., 2011), GnRH levels have been shown to be relatively low during early development (days 30-60) then rise steadily to sexual maturation (day 120), while inhibitory peptides show the opposite trend. Thus, the pattern of HPG axis maturation is partly dependent upon the developmental strategy of the species.

Studies of mammals have suggested that a substantially greater proportion of brain development occurs before birth in precocial species compared to altricial species (Matthews, 2002; Wallen and Baum, 2002) and that hormone manipulations during the early postnatal period have a much greater effect on behavioural development in altricial species (e.g., rats, Brand and Slob, 1988) than precocial species (e.g., rhesus macaques: Wallen et al., 1995; Brown and Dixson, 1999). The maturing brain has been shown to regain sensitivity to gonadal hormones during adolescence, as manipulating gonadal hormone levels during this period has significant effects on behavioural and brain development, affecting areas such as the hippocampus, medial amygdala, the pre-frontal cortex (e.g. anterior cingulate cortex) and the

hypothalamus (e.g., Hebbard et al., 2003; Ahmed et al., 2008; Sanz et al., 2008; Cooke and Woolley, 2009; Cyrenne and Brown, 2011). While developmental changes in the avian brain during the adolescence have been less well documented than in mammals, current evidence suggests that the early sensitive period for sexual differentiation ceases at a later stage in altricial compared to precocial birds (Balthazart et al., 2009). Whether the rate of HPG development prior to sexual maturity affects any long term responses to steroid hormone exposure during adolescence remains to be tested.

ii) Development of the hypothalamic-pituitary-adrenal axis

In all vertebrate animals, stress generally leads to the release of glucocorticoid hormones (Sapolsky et al., 2000). Stressful stimuli cause the hypothalamus to release corticotrophin releasing factor (CRF), which works in conjunction with arginine vasopressin (AVP: mammals) or vasotocin (AVT: birds) to promote the release of adrenocorticotrophin hormone (ACTH) from the pituitary gland (Lamberts et al., 1984; Romero & Sapolsky, 1996). ACTH then stimulates the synthesis and release of glucocorticoids (GC) from the adrenal cortex, which enter the blood stream to act on target tissues. The activity of the HPA axis is tightly regulated by classical negative feedback loops that utilise two receptor types; glucocorticoid receptors (GR), which are widespread in the brain and other organs and important in the regulation of acute stress responses, and mineralocorticoid receptors (MR), which are mainly found in the hippocampus, medial amygdala, lateral septum, brain stem nuclei and cerebellum and regulate basal hormone levels (Ahima and Harlan, 1990; De Kloet et al., 1998, McCormick and Mathews, 2007). Sex differences in adult functioning of the HPA axis have been reported in a range of mammalian species (Kudielka and Kirschbaum, 2005; Young et al., 2008; Walker and McCormick, 2009), with females generally having more pronounced stress-induced HPA activity than males (e.g., Pignatelli et al., 2006), although similar sex differences have only rarely been reported in birds.

In altricial rodents, the fetal adrenal glands begin to secrete glucocorticoids, mainly corticosterone (CORT), during gestation, and fetal surges of ACTH and CORT play a key role in initiating parturition (Johnson, 2007). Basal CORT levels remain high during the first post-natal day of life, and then drop to low levels over the following days (e.g., Laviola et al., 2002; Pignatelli et al., 2006; Womack and Delville, 2007; **Figure 2a**). Stressors generally fail to elicit a normal CORT response during this early postnatal period (e.g., Levine et al., 1991; Schmidt et al., 2003), partly due to reduced sensitivity of the adrenal glands to circulating ACTH, and this stage of development is commonly known as the Stress Hyporesponsive Period (SHRP; Levine, 1994; 2001). However, the SHRP does not represent a period of complete inactivity of the HPA axis, as exposure to substantial stressors, such as prolonged maternal separation, can trigger CORT release in altricial rodents (e.g., Levine et al., 1991; Rosenfeld et al., 1991). Similarly, while several altricial bird species show reduced adrenal responsiveness during early post-natal development (e.g., Northern mockingbirds, *Mimus polyglottos*: Sims and Holberton, 2000; white storks, *Ciconia* ciconia: Blas et al., 2006; white-crowned sparrows, *Zonotrichia leucophrys*: Wada et al., 2007; zebra finch: Wada et al., 2009), measurable increases in glucocorticoids can still occur following acute stress (Sims and Holberton, 2000; Blas et al., 2006; Wada et al., 2007: Spencer et al., 2009: **Figure 2b**).

The ‘developmental hypothesis’ (Schwabl, 1999; Sims and Holberton, 2000) predicts that adrenocortical capacity to respond to a stressor is likely to be correlated with developmental strategy and should develop in conjunction with the ability of the young animal to cope with and avoid stressors. In altricial species, as youngsters do not have some of the behavioural coping mechanisms that are available to more mobile precocial animals, the SHRP is likely to provide protection from detrimental stress effects (Wada, 2008). In contrast, in precocial and semi-precocial mammals, both infants and juveniles exhibit a strong corticosteroid response to stressors and apparently lack the SHRP (e.g., common marmosets, *Callithrix jacchus*: Pryce et

al., 2002; degu, *Octodon degus*: Gruss et al., 2006; rhesus macaques: Sanchez et al., 2010; **Figure 2c**). These observations fit with the developmental hypothesis, as precocial and semi-precocial species have behavioural mechanisms (e.g. moving away from stressors) to respond to the physiological changes in HPA activity. Thus, the timecourse of HPA reactivity differs markedly between altricial and precocial mammals (Matthews, 2002). In birds, the pattern is more mixed; some precocial species appear to lack an SHRP (e.g., wood ducks, *Aix sponsa*: DuRant et al., 2010; Japanese quail: Marasco, Robinson, Herzky and Spencer, unpublished data; **Figure 2d**), while others show evidence of blunted HPA axis activity post-hatching (e.g. chickens, Freeman, 1982); however, precocial species rarely have a total lack of response to stressful stimuli during this time. Recent work in the Japanese quail has shown that young chicks actually exhibit and exaggerated CORT response to an acute stressor than those in later developmental stages or adults, again in line with the developmental hypothesis as young chicks may have less experience of their environment (Marasco et al, unpublished data).

Following the SHRP, basal CORT levels rise gradually in altricial rodents and reach adult-like levels by mid-adolescence, with females having higher baseline levels than males from adolescence onwards (e.g., Pignatelli et al,. 2006; reviewed by McCormick and Mathews, 2007; Walker and McCormick, 2009). During early and mid-adolescence (around pnd 28-50), rodents exhibit a highly exaggerated CORT response to at least some stressors, with CORT levels taking longer to return to baseline in adolescents than in adults (e.g., Adriani and Laviola, 2000; Romeo et al., 2004; Hodes and Shors, 2005; Romeo et al., 2006; Goel and Bale, 2007; Foilb et al., 2011; reviewed by McCormick and Mathews, 2007; McCormick et al., 2010; Romeo, 2010a; 2010b). Stress-induced CORT responses then decrease again in adulthood in rodents (Romeo, 2010b), although not all results are consistent with this pattern across ages (e.g., Viau et al., 2005). In primates, basal CORT levels rise during adolescence (e.g., chimpanzees, *Pan troglodytes*: Seraphin et al., 2008; rhesus macaques, McCormack et al., 2009), and studies of human

adolescents have reported enhanced stress reactivity in adolescents compared to children (e.g., Gunnar et al., 2009; Stroud et al., 2009). Sex differences in HPA activity also emerge across the adolescent period (e.g., human beings: Yim et al., 2010). In many altricial bird species, basal and stress-induced CORT levels gradually increase during the period between hatching and fledging (Wada, 2008), with fairly stable levels after this; however, some studies showing an exaggerated HPA activity during this adolescent period compared to adulthood (e.g., American kestrels, *Falco sparverius*: Love et al., 2003), whilst others suggest no real variation in basal levels over time (e.g. zebra finch: Wada et al., 2009). Thus, several species (both altricial and precocial) exhibit pronounced stress-induced HPA activity during the adolescent period, although this effect is not consistently reported and could depend upon the type of stressor experienced.

Interactions between HPG and HPA axes

Both the HPG and HPA axes undergo considerable development during prenatal and postnatal life, and these systems appear to share similar developmental trajectories during some periods and to act antagonistically at other times. These correlations are perhaps unsurprising, as there is a large body of literature showing a significant number of complex interactions between these two neuroendocrine axes (Viau, 2002; Young et al., 2008; Walker and McCormick, 2009). For example, it is widely accepted that, in a range of taxa, CRH and glucocorticoids directly inhibit GnRH secretion in the hypothalamus, LH secretion in the pituitary and, to a lesser extent, steroid hormone synthesis in the gonads (Tilbrook et al., 2000), and this is thought to be the primary route for reproductive suppression during stressful events (Rivier and Rivest, 1991; Tilbrook et al., 2000). During adolescence, when HPG functioning is starting to reach a peak, it would therefore be advantageous to reduce stress-induced glucocorticoid release to facilitate normal reproductive development.

Several mammalian and avian studies have reported negative correlations between basal levels of glucocorticoids and gonadal hormones such as testosterone (Viau, 2002; Buchanan et al., 2004; Van Hout et al., 2010), and long-term chronic stress appears to have direct negative effect on both pituitary and gonadal secretion of LH and T (Deviche, 1983; Tilbrook et al., 2000; Chichinadze and Chichinadze, 2008). In contrast, acute stress can have both negative and positive effects on the functioning of the HPG axis (Tilbroook et al., 2000). For example, a recent study of adult male rufous-winged sparrows (*Aimophilia carpalis*) showed that, as corticosterone rises following handling stress, circulating testosterone levels are reduced by up to 50 percent via the direct action of corticosterone on testicular hormone production (Deviche et al., 2010). Similarly, stress resulted in a significant increase in GnIH-positive neurons in house sparrows (*Passer domesticus*) in breeding condition, leading to a reduction in pituitary gonadotropin release (Ubuka et al., 2006; Calisi et al., 2008). Conversely, a growing body of literature suggests that HPG activity is upregulated during acute stress in birds (e.g., Mays et al., 1991; Heiblum et al., 2000; Van Hout et al., 2010). In mammals, the relationship between HPA and HPG activity is also complicated and varies across age groups. For example, in adulthood, male rats show increases in testosterone levels following an acute stressor (Foilb et al., 2011), while juvenile rats show no change or inhibition of testosterone secretion (Gomez et al., 2002; Romeo et al., 2004; Foilb et al., 2011). These studies suggest that, while elevated stress in adolescence could have significant implications for HPG functioning in later life, the exact effects will depend upon factors such as the type and severity of the stressor.

In addition to glucocorticoids regulating HPG functioning, a reciprocal relationship between these two neuroendocrine axes exists: gonadal hormones have been shown to have direct effects on the HPA axis (McCormick and Mathews, 2007; Young et al., 2008; Solomon and Herman, 2009). For example, estrogen has been shown to have an excitatory effect on the HPA axis through numerous routes, including actions on corticosteroid binding globulin and GR

receptors (e.g., Burgess and Handa, 1992), while testosterone generally suppresses HPA activity (Viau, 2002). However, the nature of the relationship between the HPA and HPG axes can differ between age groups (e.g., Gomez et al., 2002; 2004; Romeo et al., 2004; Evuarherhe et al., 2009a); for example, in pre-adolescent rats, estrogens have been reported to suppress adrenal CORT production and neural GR activation (e.g., Evuarherhe et al., 2009a), while administration of testosterone fails to dampen the HPA activity in preadolescent male rats (Romeo et al., 2004), in contrast to the effects of these hormones on the adult HPA axis.

The interactions between the HPG and HPA axes are known to begin early in life, and exposure to gonadal hormones during the early postnatal period has long-term, organisational effects on the developing HPA axis (Walker and McCormick, 2009); for example, suppressing early postnatal testosterone activity in male rats increases stress-induced ACTH and CORT levels in adulthood, while treatment of female rats with T during this period reduces adult HPA activity (McCormick and Mahoney, 1999; Seale et al., 2005a; 2005b). In addition, current evidence from rodents suggests that developmental changes in HPA reactivity during adolescence are also dependent upon gonadal hormone exposure; for example, administration of testosterone to male rats that were castrated during preadolescence did not lead to the suppression of stress-induced corticosterone secretion, while testosterone treatment did suppress corticosteroid secretion in males that were castrated in adulthood (Evuarherhe et al., 2009b). These data suggest that exposure to gonadal hormones during adolescence has long-term effects on the developing HPA axis.

Given the cross-communication between the HPA and HPG axes, adolescent stress could have substantial consequences for a range of physiological systems and for brain development through interactions with the HPG axis, as well as via direct activation of the HPA axis (McCormick and Mathews, 2010). The effects of adolescent stress are likely to vary between male and female adolescents, as a result of sex differences in circulating gonadal hormone levels

and prior organisational effects of gonadal hormones on brain development (McComick and Mathews, 2007). Adolescent stress could to be particularly impactful in species in which the HPA is hyper-reactive during adolescence. However, species in which the HPA axis is dampened during adolescence are also likely to be susceptible to stress effects, particularly the regulatory feedback mechanisms, such as GR and MR; glucocorticoid levels can become elevated even during the well characterised post-natal SHRP in altricial rodents, and significant stress could thus potentially impact on brain development during later stages of dampened HPA activity. In the next section, we explore the evidence for the effects of adolescent stress on a range of behavioural and neural traits, and examine whether such effects differ between the sexes.

Effects of adolescence stress on behavioural and brain development

i) Mammals

Numerous studies of mammals have reported dramatic effects of prenatal and early postnatal stress exposure on the developing neuroendocrine systems (Weinstock, 2008; Lupien et al., 2009; Romeo et al., 2009; Charil et al., 2010). Early stressors are thought to 'programme' adult neuroendocrine responses through a range of mechanisms (Matthews, 2002), including epigenetic modification of steroid hormone receptors (McEwen et al., 2012). The adolescent period potentially provides another opportunity for neural and endocrine systems to respond to current environmental and social inputs, allowing for flexibility during development (Andersen, 2003). Given that some stress-induced changes in neuroendocrine functioning and hippocampal gene expression are potentially reversible (e.g., Morley-Fletcher et al., 2003; Weaver et al., 2006), adolescence has been described as a period of opportunity, when positive experiences could partial compensation for earlier adversity (Andersen, 2003). However, while positive

inputs can potentially mediate against earlier negative events, the sensitivity of the adolescent central nervous system can lead to enhanced vulnerability to further insults (Andersen and Teicher, 2008).

Over the past decade, a number of studies have investigated the effects of adolescent stress exposure on behaviour and brain function. Adolescent stress could directly impact behaviour by actions on the developing adolescent brain, leading to long-term changes in brain functioning, or indirectly by influencing the developing HPG and HPA axes. Current evidence suggests that adolescent stress has a negative impact on the adult HPG system (e.g., Laroche et al., 2009), which could have implications for sexual differentiation of the brain during adolescence and also for behavioural patterns that are sensitive to circulating levels of gonadal hormones in adulthood, such as sexual behaviour. In contrast, studies on HPA axis development are more inconsistent (McCormick et al., 2010). Adolescent stress exposure has been reported to either dampened (e.g., Toth et al., 2008), heighten (e.g., Isgor et al., 2004, Schmidt et al., 2007) or have no effect (e.g., McCormick et al., 2005) on HPA activity in adult rodents, and such effects are modest when compared to those of perinatal stress exposure (McCormick et al., 2010). Therefore, the effects of adolescent stress exposure on later stress-induced HPA responses appear variable, perhaps depending upon the type and extent of stress exposure and the method of assessing HPA activity in adulthood.

In contrast, recent studies of rodents have shown that exposure to stressors during adolescence has substantial, long-lasting effects on brain development, particularly those involved in learning and memory, such as the pre-frontal cortex and the hippocampus, those underlying the functioning and regulation of the HPA axis, such as the PVN (paraventricular nucleus of the hypothalamus) and the hippocampus (McCormick and Mathews, 2010; McCormick et al., 2010), and on behavioural profiles (Sachser et al., 2011). Given that brain regions involved in emotional regulation undergo considerable remodelling during adolescence

(e.g., amygdala, hippocampus, prefrontal cortex; McCormick and Mathews, 2010; Brenhouse and Andersen, 2011), these aspects of later life are predicted to be strongly affected by adolescent stressors. In line with this prediction, exposure to chronic social stress or deprivation during adolescence has been shown to alter emotional reactivity in adulthood, as measured by elevated-plus maze activity (e.g., McCormick et al., 2008; Doremus-Fitzwater et al., 2009; Wilkin et al., 2012), and exposure to adolescent stress reduces glucocorticoid receptor densities in the adult hippocampus (Schmidt et al., 2007) and elevates metabolic activation of hippocampus, basal amygdala and areas of the pre-frontal cortex (e.g. cingulate) during fear memory extinction tests (e.g., Toledo-Rodriguez et al., 2012). Adolescent stress has also been reported to have long-term, negative impacts on spatial cognition; for example, rats that were exposed to daily physical stressors during adolescence exhibited poorer performance on a water maze when tested in adulthood compared to controls, while performance on other memory tasks was unaffected, and stress-exposed males exhibit reduced hippocampal volume (Isgor et al., 2004; Sterlemann et al., 2009; McCormick et al., 2012).

Systems other than the HPA axis are likely to be involved in mediating the long-term effects of adolescent stress on later behaviour, including the serotonin and dopamine systems (Deville et al., 1998; Wommack and Deville, 2002). The serotonergic system is crucial in the response to stress, particularly social stress, and also modulates behaviours such as fear, aggression and memory (Dennis and Cheng, 2010; Kiser et al., 2012). There are significant interactions between the HPA axis and serotonin; for example when selective serotonin reuptake inhibitors (SSRIs) are used in fish to enhance synaptic serotonin levels, this potentiates behaviour driven by CRF, a fundamental component of the HPA cascade (Lowry and Moore, 2006). In addition, serotonin has an excitatory role in the regulation of CRF in the hypothalamus (Pomili et al., 2010). The mesocorticolimbic dopamine system also plays a key role in the stress response (Sullivan and Gratton, 2002) and undergoes significant modification during

adolescence (e.g., Andersen and Teicher, 2000; Andersen et al., 2000). The dopamine system has been found to be sensitive to stress during adolescence (Trainor, 2011); for example, exposure of adolescent rats to predator odour reduces levels of dopamine D2 receptor in the prefrontal cortex (infralimbic and dorsopeduncular regions) (Wright et al., 2008). Thus, the effects of adolescent stress on behaviour could be mediated by multiple routes, some of which may interact, in addition to the direct actions of CORT via GR and MR receptors.

In adult rodents, the effects of stress on neural functioning and behaviour often depend upon both the type of stressor and sex of the individual (e.g., Wood and Shors, 1998; Dalla et al., 2005). For example, while stress can sometimes enhance, rather than diminish, cognitive performance when individuals are learning about threatening stimuli (Shors, 2006), the direction of stress effects varies between the sexes (Luine et al., 2007). The effects of stress can also be moderated by social and environmental factors; studies have shown that social support and environmental enrichment can ameliorate some stress effects (Kikusui et al., 2006; Fox et al., 2006). Therefore, the effects of adolescent stress are likely to vary with the age and sex of the individual, the type of stressor, and social and environmental parameters (Romeo, 2010b). In line with this prediction, responses to adolescent stress have been reported to vary with these factors (e.g., Pohl et al., 2007; Toledo-Rodriguez et al., 2012; reviewed by McCormick et al., 2010; Sachser et al., 2011); for example, exposure of male and female adolescent rats to a chronic variable stress paradigm resulted in altered sucrose consumption and locomotor activity in adult females, with no effects in males (Bourke and Neigh, 2011).

ii) Birds

The majority of avian studies on early stress have focussed on pre- and post-natal manipulations, or observations, of stress and have tracked the short and long-term effects on behaviour, brain and physiology. One benefit of studying early development in birds, rather than mammals,

though, is that hormone levels in the egg can be manipulated independently of any influences on other maternal physiological systems (Henriksen et al., 2011). Some bird species also have the advantage of being easier to study in the wild than are small, nocturnal mammals, allowing for better integration of results from field and laboratory studies. Many studies of early stress have focused on relatively short periods within post-natal development, typically 1-3 weeks post-hatching, and the timing of these manipulations tends to finish prior to nutritional independence in altricial birds and pre-puberty in precocial ones (Spencer et al., 2003; Buchanan et al., 2004; Groothuis et al., 2005; Spencer and Verhulst, 2007; Wada, 2008). Whilst these studies are pre-adolescence, they provide a useful framework from which we can understand the potential long-term effects of stress during later development.

Studies of altricial species, such as the zebra finch and Western scrub jay (*Aphelocoma californica*), have shown that exposure to a short period of developmental stress can have several effects that manifest later in life, specifically during late adolescence and early adulthood, including elevated and prolonged CORT secretion in response to a standardised stressor, reduced competitive ability, reduced neophobia, and cognitive deficits (Pravosudov and Kitasysky, 2006; Spencer and Verhulst, 2007; 2008; Spencer et al., 2009). Further early stressed birds also exhibit increased mortality after breeding (Monaghan et al., 2012). Similar responses have also been seen in semi-precocial and precocial species, with early developmental stress causing reduced spatial and associative learning and increased fear responses (e.g., black-legged kittiwake, *Rissa tridactyla*: Kitaysky et al., 2003). Thus, exposure to stress prior to sexual maturation has been shown to have profound effects on development of the HPA axis, behaviour and life history in birds. However, if adolescence is defined as the period of life that includes attainment of sexual maturity, few bird studies have investigated the long-term effects of stress exposure during only this specific period of life; these studies are reviewed in the rest of this section.

Altered physiological responses to stress in later life could be due to a range of changes in the HPA axis; in mammals, prolonged responses have been linked to a reduction in the density of mineralocorticoid and glucocorticoid receptors, which reduces the negative feedback capability of the entire system. Indirect evidence in birds suggests that this may also be the case (Hodgson et al., 2007). Adult zebra finches from an F3 population selected for elevated CORT secretion in response to capture and restraint (Evans et al., 2006) exhibited reduced MR mRNA expression in the hippocampus, a brain area known to be actively involved in the negative feedback of the HPA axis in both birds and mammals (Hodgson et al., 2007). Interestingly, these birds were selected based on their CORT response during early adolescence (around 8 weeks of age, sexual maturity around 14 weeks). Whilst it is tempting to suggest that this study may provide a link between adolescent stress and later effects on the HPA axis, stress responses were not measured prior to adolescence and hence we can only speculate as to the relevance of this work. Other selection studies can also provide useful data on the long-term effects of elevated stress. A range of selection studies in the Japanese quail have shown that low CORT secretion following a standardised stressor during development correlates with accelerated puberty, enhanced T maze performance, increased sociality, damped CORT secretion in later life, reduced fearfulness and increased sexual behaviour (Satterlee et al., 2002; Marin et al., 2002; Martin and Satterlee, 2003; 2004). This work highlights the interaction between HPA activity and HPG functioning, as well as the potential programming of fear-related and social behaviour.

A few studies have experimentally manipulated stress during the adolescent period in birds, although to date there are no direct manipulations of CORT itself. It is well established that chronic stress can have deleterious effects on avian memory systems in the short term (Joels et al., 2006; Linqvist and Jensen, 2009). In a study using juvenile chickens exposed to 10 weeks of unpredictable light:dark cycles, Linqvist and colleagues (2007) showed that there can be long-term disruptions to spatial memory in later life. Housing conditions during adolescence can also

significantly alter later responses to stress: chickens individually housed in battery cages exhibit raised basal CORT levels and elevated adrenocortical activity in response to acute stress in later life, compared to animals housed in social groups (Heiblum et al., 2000). In addition, stress induced increases in testosterone concentrations were also higher in the battery housed group, suggesting not only altered HPA activity, but a change in the interaction between HPA and HPG responsiveness. These results could have implications for social behaviour, aggression and ultimately reproductive performance. A large literature on bird song has shown that the avian brain exhibits a sensitive period of development during adolescent life (Catchpole and Slater, 2008); for example, birds raised in social isolation between nutritional independence and sexual maturity display altered non-species specific song signals in later life coupled with changes in the volume of brain nuclei important in learning and producing song, such as the HVC and RA (robust nucleus of the arcopallium) (Spencer et al., 2007; Catchpole and Slater, 2008). Thus, adolescent stress exposure could impact upon courtship and mate selection.

Finally, another manipulation of housing conditions during adolescence in chickens has provided an insight into the importance of this life stage in mediating the serotonin system (Patzke et al., 2009). Birds were housed socially in either battery cages, litter pens or under a free range system from puberty to sexual maturity. In adulthood, free range hens developed larger cells in the dorsomedial hippocampus and exhibited greater asymmetry in dopaminerigic fibre density in the hippocampus; this is undoubtedly related to the differences in spatial complexity between the housing treatments, but could also impact on feedback mechanisms within the HPA (Hodgson et al., 2007). In addition, serotonergic innervation was altered in the Neostriatum caudolaterale (NCL) (mammalian homologue of the pre-frontal cortex and associated with behavioural flexibility; Kroner and Gunturkun, 1999), with free range hens exhibiting higher serotonin (5-HT) cell density (Patzke et al., 2009). Chickens given injections of a 5-HT agonist show immediate reductions in fear-related behaviour and neophobia (Dennis and Cheng, 2010),

and another study suggests that the ability to cope in unpredictable or stressful environments is linked to the density of 5-HT receptor 1A (Koolhaas et al., 2007). These combined results suggest that social experience during adolescence can alter stress responses in later life in birds, significantly reducing fear-related behaviour and potentially sociality. Unfortunately, Patzke and colleagues (2009) did not quantify the effects of their housing conditions on HPA activity during the manipulation and, therefore, we cannot relate CORT levels directly to the neural changes seen later.

Conclusions

The aim of this review was to bring together research on the effects of adolescent stress on behavioural and brain development in mammals and birds. Relevant data on these two taxonomic groups have tended to form distinct literatures, with mammalian studies being published in physiology and neuroendocrinology journals and bird studies being published in general endocrinology and behavioural ecology journals. By comparing the development of the HPG and HPA axis in these two groups, we have shown that the underlying neuroendocrine systems are strongly conserved and the developmental time courses are somewhat similar. A distinction between altricial and precocial species arises in both taxonomic groups, when comparing whether the prenatal sensitive period to steroid hormone exposure extends into the early postnatal period. We also presented evidence that the HPG and HPA axes are characterised by numerous interactions throughout the lifespan, suggesting that adolescent stress will impact upon the developing HPG axis and sexual differentiation of the brain and behaviour. Sex differences in the effects of adolescent stress could also involve interactions between the HPA and HPG axes.

Studies of adolescent stress have shown that the brain and neuroendocrine systems are sensitive to adrenal hormones during this stage of life in both mammals and birds, although the

literature on birds is more limited. Exposure to stress during adolescence appears to impact upon numerous brain areas and to influence several neurotransmitter systems, including the serotonergic and dopaminergic systems. By exhibiting sensitivity to steroid hormones during early periods of development, organisms can potentially gain information about the state of the environment, allowing the neural and endocrine systems to be 'programmed' to provide adaptive matches with the external environment. However, alternatives perspectives on development have been proposed (Sih, 2011), including the idea that organisms continually engage in complex interactions with the external environment (Laland et al., 2008). Such interactions provide the opportunity for an organism to influence later stages of its own development, for example by engaging in activities that lead to stress exposure, and steroid hormones are likely to play a key role in these interactions.

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Figure legends

Figure 1 Developmental timecourse (postnatal day, pnd; month, mth) of circulating testosterone (T) levels in males in: a) Norway rats (an altricial mammal) (based on Paz et al., 1980; Zapatero-Cabellero et al., 2003; the postnatal T surge immediately after birth is not depicted), b) zebra finches (an altricial bird) (based on Prove, 1983; Adkins-Regan et al., 1990), c) rhesus macaques (a semi-precocial mammal) (based on Mann et al., 1993; Brown et al., 1999; the postnatal T surge immediately after birth is not depicted), and d) quail (a precocial bird) (based on Sedqyar et al., 2008).

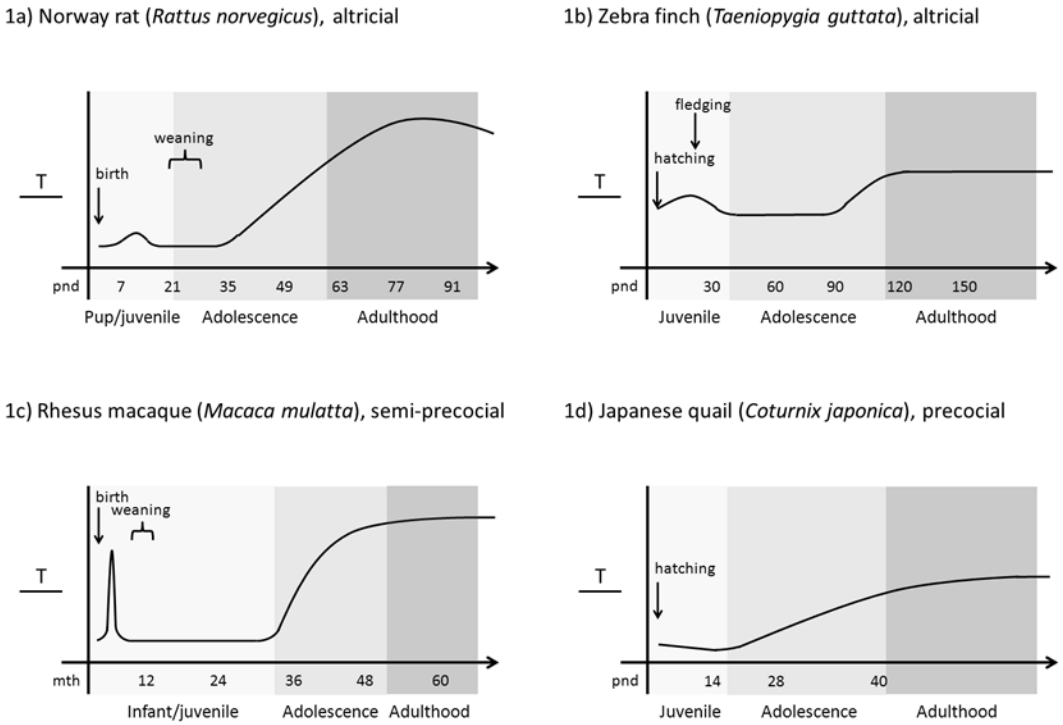

Figure 2 Developmental timecourse (postnatal day, pnd; month, mth) of circulating levels of CORT (corticosterone or cortisol) (solid lines) and stress-induced CORT responses (depicted in the small graphs as either exaggerated, average or low CORT responses; the shapes of the small graphs are not exact representations of CORT responses) in: a) Norway rats (an altricial mammal) (based on Romeo et al., 2004; Pignatelli et al., 2006; Foilb et al., 2011), b) zebra finches (an altricial bird) (based on Wada et al., 2008, 2009; Spencer et al., 2009), c) rhesus macaques (a semi-precocial mammal) (based on Bercovitch and Clarke, 1995; Sanchez et al., 2010), and d) quail (a precocial bird) (based on Marasco et al., unpublished data; Spencer, unpublished data).