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Minireview

Glucocorticoids: Mediators of vertebrate ontogenetic transitions

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Abstract

In adult vertebrates, glucocorticoids are thought to trigger transitions between life history stages within breeding cycles. This review explores possible roles of glucocorticoids as mediators for vertebrate ontogenetic transitions. Overall, glucocorticoids prepare organisms and trigger transitions into the subsequent life history stage. Across taxa, ability to secrete glucocorticoids appears to depend on functional maturity at birth. Slow strategist or precocial species tend to have larger, fewer, and more mature young that can secrete glucocorticoids earlier than fast strategist or altricial species. Across life history transitions, glucocorticoids have direct and permissive effects on various ontogenetic transitions in vertebrates. Glucocorticoids directly (1) promote maturation of critical organs before birth/hatch in mammals and birds, (2) initiate parturition events in mammals and possibly controls hatching in birds and reptiles (but not in "small"-egg fish), (3) facilitate acquisition of osmoregulatory ability in fish during smoltification, and (4) affect dispersal behavior in mammals, birds, and reptiles and are potential candidates for the timing of fledging in birds, although further studies are needed to determine the causal relationship. Glucocorticoids also have a permissive action on thyroid hormones in amphibian and fish metamorphosis.

Keywords: Glucocorticoids; Life history; Vertebrates; Ontogeny; Birth; Hatch; Fledging; Dispersal; Metamorphosis; Smoltification

1. Introduction

Numerous physical and physiological mechanisms are critical in life history transitions such as birth, puberty, senescence, as well as seasonal breeding cycles. In adult vertebrates, glucocorticoids (GCs: corticosterone (CORT) and cortisol) are implicated as one of the hormones to trigger transitions within breeding cycles. For instance in birds, CORT triggers transitions from regular to emergency life history stages, such as breeding to irruptive migration (Wingfield and Kitaysky, 2002). Similarly, CORT facilitates finer transitions between behavioral stages across taxa, such as from courtship to flight (Orchinik, 1998). However, the effects of GCs on life history or behavioral stages are not universal: they are context-dependent due to receptor characteristics and interactions with other neuropeptides (Orchinik, 1998).

Elevations of GCs also coincide with ontogenetic life history transitions. It is well established that fetal cortisol triggers parturition in certain mammals (see below). But GCs may trigger or modify other physiological changes necessary for ontogenetic processes as well. This review will (1) discuss the ontogeny of the hypothalamic-pituitary-adrenal/interrenal (HPA/HPI) axes in relation to ontogenetic events, (2) explore the direct or permissive actions of GCs in diverse ontogenetic transitions across vertebrate taxa including hatching/birth, fledging/dispersal, metamorphosis, and smoltification, and (3) bring to light common elements of GCs during such transitions.

Some aspects of this review are extensively studied and well reviewed elsewhere. The aim of this review is not to provide details on each of the subjects, rather to bring a comparative view on the role of GCs in different ontogenetic transitions. This review focuses mainly on the role of GCs but it is important to keep in mind that GCs inter-

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act with other hormones during ontogeny, e.g. thyroid hormones, prolactin, and growth hormone. Thus, one should not overlook the importance of those hormones as well as their interactions.

In order to determine the roles of GCs in various ontogenetic events, this paper will first review the age-specific changes in baseline and stress-induced levels of GCs across vertebrate taxa. How do they compare and what are the conserved trends? Then, it will explore the observational and experimental studies on GCs actions during each ontogenetic event (e.g. birth/hatch, metamorphosis, etc). Do GCs trigger transitions or maturation during such events?

2. Costs and benefits of GC secretion during development

Young may face a trade-off between the benefits and costs of GCs' action (Kitaysky et al., 2003). GCs stimulate begging behavior in birds (Kitaysky et al., 2001; but also see Rubolini et al., 2005), food intake (Kitaysky et al., 2003), and locomotor activity in young (Crespi and Denver, 2004; Freire et al., 2006), processes necessary to escape from and cope with various challenges. GCs also play an important role in metabolism, mobilizing glucose when needed (Sapolsky et al., 2000). At the same time, excess GCs impair growth (Glennemeier and Denver, 2002c; Hayward and Wingfield, 2004; Janczak et al., 2006; Mashaly, 1991; Meylan and Clobert, 2005; Morici et al., 1997; Saino et al., 2005; Spencer et al., 2003; Wan et al., 2005), cognition (Kitaysky et al., 2003; but also see Catalani et al., 2000), and immune function (Morici et al., 1997; Rubolini et al., 2005) and can cause neuronal death (Howard and Benjamins, 1975) and high mortality (Mashaly, 1991; Saino et al., 2005; Janczak et al., 2006; Eriksen et al., 2006; but also see Meylan and Clobert, 2005). GCs may also alter sensitivity to stress later in life (Catalani et al., 2000; Hayward and Wingfield, 2004;Meaney, 2001). Thus the timing of HPA/HPI axes regulation is critical; it would appear important to strictly regulate the exposure to GCs during certain period of development, so as to avoid the costs associated with elevated levels.

3. Ontogeny of the HPA/HPI axis and endocrine responses to challenges

3.1. Mammals

Ontogeny of the HPA axis is well documented in mammals, particularly in rodents. Total (bound and unbound to binding proteins) baseline CORT of the rat fetus increases just prior to birth, reaching adult-like levels (Henning, 1978; Hiroshige and Sato, 1971; Martin et al., 1977; Meaney et al., 1985; Tinnikov, 1993; van Baelen et al., 1977) (Fig. 1a). This increase in CORT secretion is independent of maternal CORT secretion and is accompanied by decrease in fetal corticosteroid binding globulin (CBG), allowing free (unbound) CORT to elevate even further. Total CORT then declines sharply to very low levels in the first couple of days after birth and stays low until the 2nd week of life. The levels then increase gradually to adult levels by ~15 days.

The development of the HPA axis appears to depend on the developmental maturity at birth. Altricial mammals show a brief period of HPA axis quiescence, called the stress hyporesponsive period (SHRP) during the first days of life (first described as non-responsive period by Schapiro 1962, reviewed in Sapolsky and Meaney, 1986; Walker et al., 2001; Vazquez, 1998). The SHRP is thought to be beneficial, especially for altricial species, considering the negative effect of CORT on growth. Rat fetuses and neonates can respond to various challenges (e.g. leg fracture, maternal ether inhalation, and histamine injection) by secreting CORT and adrenocorticotropic hormone (ACTH) in late gestation and soon after birth (Cohen et al., 1983; Cote and Yasumura, 1975; Milkovic and Milkovic, 1963; Milkovic et al., 1973). However, the responsiveness declines shortly after birth and various challenges (e.g. ether, shock, heat, histamine injection) elicit no or blunted adrenocortical response until the 2nd week of life (Butte et al., 1973; Cote and Yasumura, 1975; Guillet and Michaelson, 1978; Haltmeyer et al., 1966; Tang and Phillips, 1977). It was later discovered that certain stressors and corticotropin releasing factor (CRF) can elicit age-dependent but significant ACTH and/or CORT responses during the SHRP, and neonates have a functional negative feedback by CORT (Guillet and Michaelson, 1978; Schoenfeld et al., 1980; Walker et al., 1986, 1991). Furthermore, maternal separation longer than 24 h can enhance the sensitivity to ACTH during this period (Levine et al., 1991). Therefore, the SHRP in rats is context-dependent and the blunted CORT response may be due to an age-dependent suppression of response at the adrenal level.

Ontogeny of the stress response in non-human primates (non-altricial, intermediate; Starck and Ricklefs, 1998) differs from that of rodents. In rhesus macaques (*Macaca mulatta*), 2-day-old neonates can mount an adult-like stress response to a brief maternal separation and rotation (Bowman and Wolf, 1965). In common marmosets (*Callithrix jacchus*), baseline cortisol and ACTH of 1-week-old neonates are significantly higher than adults (Pryce et al., 2002). In fact, baseline cortisol is approximately 10 times higher in neonates. This remarkably high level of cortisol is partly due to relatively large adrenals compared to adults. Furthermore, cortisol and ACTH responses to isolation stress are higher in 2-month-old compared to 12-month sub-adults. Extremely high levels of cortisol in addition to delayed shutdown of stress responses in young suggest a dampened cortisol negative feedback in this species.

3.2. Birds

The precocial–altricial spectrum mentioned above refers to a broad array of functional maturity at birth seen in birds and mammals (Starck and Ricklefs, 1998). Newly hatched nestlings and neonates differ in their mobility, sen-

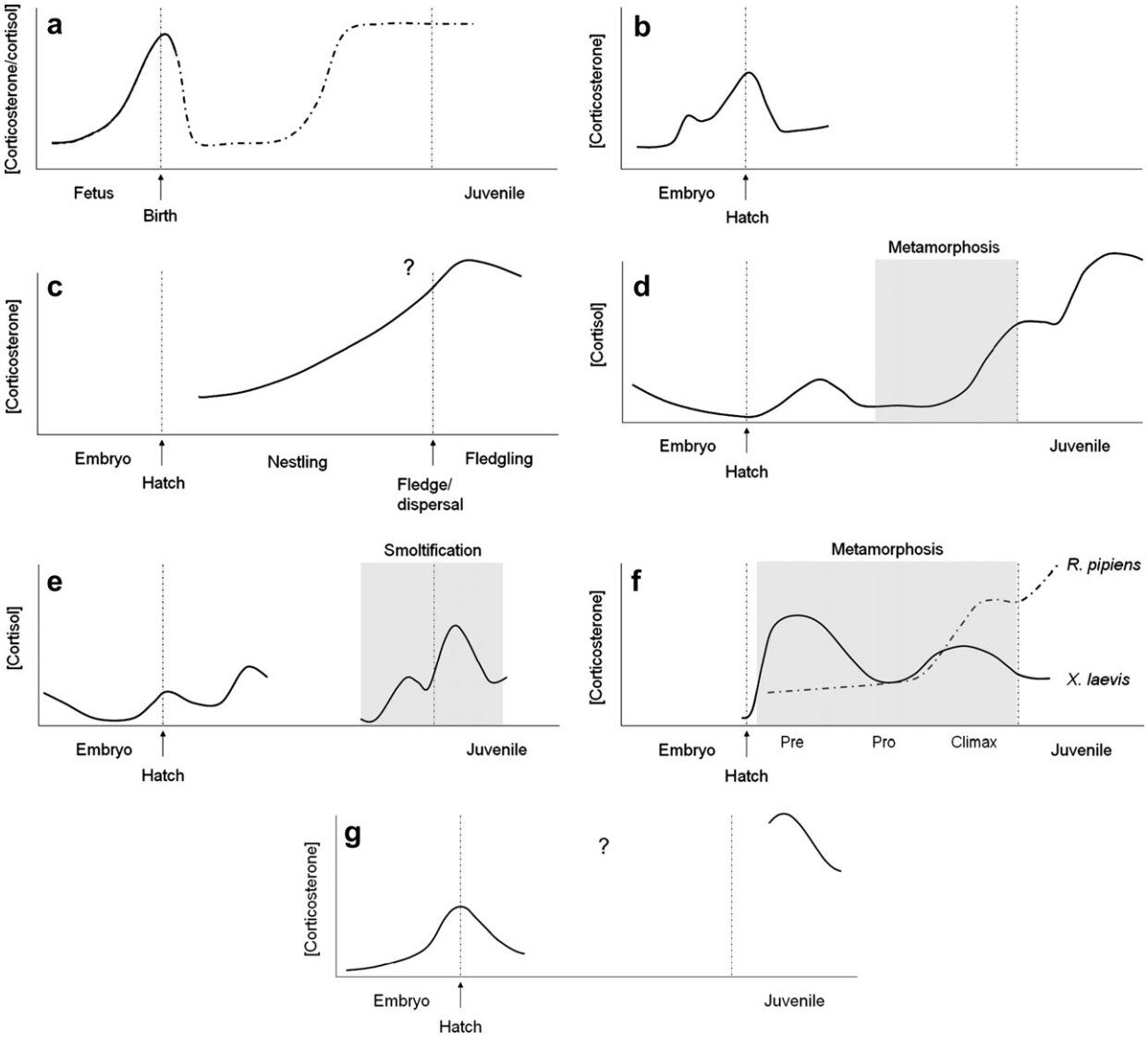

Fig. 1. Schematic representations of changes in baseline GCs concentrations from embryonic to juvenile stage in (a) mammals (dotted lines are for rodents), (b) precocial birds, (c) non-precocial birds, (d) non-salmonids fish (“small”-egg species, such as tilapia, flounder, sea bass, sea bream, and yellowtail), (e) salmonids (“large”-egg species), (f) amphibians, and (g) reptiles.

sory organ development, and feather development or thermoregulatory ability, leading to variation in extent of dependency to parents for feeding and thermoregulation. Precocial young, for example, are born with down/hair and with their eyes open, mobile, and some are capable of feeding on their own (Starck and Ricklefs, 1998). On the other hand, altricial young are born with their eyes closed, without any down/hair, relatively immobile, and are dependent on parents for feeding and thermoregulation. Thus, the balance between costs (delayed development) and benefits (increased locomotor activities and glucose mobilization) of GCs secretion depends on the state of maturation at hatching/birth and when they begin to leave the nest, forage, and become independent (developmental hypothesis) (Blas et al., 2006; Kitaysky et al., 2003; Schwabl, 1999; Sims and Holberton, 2000; Wada et al., 2007). The development of the HPA axis could reflect this spectrum. In birds, it is hypothesized that precocial species with capacity to escape challenges may develop the HPA axis earlier than altricial species (nest-bound, parent-dependent), which would suffer more from detrimental effects of GCs. The altricial species should develop a functional HPA axis by the time it is beneficial to respond to a challenge, e.g. fledging.

Baseline CORT secretion before hatching is observed at least in domesticated and wild precocial species, e.g. chickens (*Gallus domesticus*), turkeys (*Meleagris gallopavo*), and mallard ducks (*Anas platyrhynchos*) (Davis and Siopes, 1985; Holmes et al., 1990; Jacobs, 1996; Jenkins and Porter, 2004; Scott et al., 1981; Wise and Frye, 1973). Chicken embryos start to secrete CORT around 14 days of the 21-day incubation (Scott et al., 1981; Wise and Frye, 1973) and the sensitivity to ACTH peaks around hatching (Carsia et al., 1987). Similarly, mallard duck embryos start to

secrete CORT by the 15th day of their 27-day incubation period and both baseline and ACTH-induced CORT levels increase gradually until hatching (Holmes et al., 1990) (Fig. 1b).

Some evidence suggests that chickens undergo a transient SHRP similar to mammals. Chicken embryos can elevate CORT significantly in response to 43 °C heat stress for 2 h in the last few days of incubation (Jacobs, 1996). After hatching, cold and/or handling stress can elicit stress response in 2- and 21-day post-hatch (dph) chicks but both stressors fail to stimulate a stress response in 1 dph chicks (Freeman, 1982; Freeman and Flack, 1980; Freeman and Manning, 1984). This suggests that chicken hatchlings undergo a stress hyporesponsive period lasting ~48 h.

In non-precocious species, fewer data are available. There are no data on embryonic CORT secretion, thus the existence of a true stress hyporesponsive period remains unclear. However, non-precocious species appear to develop the HPA axis later than precocial species (Fig. 1c). In semi-altricial (hatched with down, some with eyes open, depended on parents, and stay in the nest; Starck and Ricklefs, 1998) and semi-precocial species (same as semi-altricial but all have their eyes open and stay only around nest area), baseline CORT (Heath, 1997; Belthoff and Dufty, 1998; Love et al., 2003; Quillfeldt et al., 2007; but also see Romero et al., 2006; Walker et al., 2005) and adrenocortical response to handling (Love et al., 2003; Walker et al., 2005) increase with age during nestling and fledgling period, reaching an adult-like level or higher. In altricial species, nestlings of some species can respond to handling stress (white stork, *Ciconia ciconia*, Blas et al., 2005, 2006; white-crowned sparrow, *Zonotrichia leucophrys*, Wada et al., 2007) while nestlings and fledglings of other species cannot (Northern mockingbirds, *Mimus polyglottos*, Sims and Holberton, 2000; redpolls, *Carduelis flammea*, Romero et al., 1998). Interestingly, younger altricial nestlings which failed to elicit a stress response to handling are sensitive to ACTH challenges (Sims and Holberton, 2000; Wada et al., 2007), indicating a dampened sensitivity at the level of pituitary or higher. There is variation in ontogeny of the stress response within altricial species; however, the HPA axis becomes functional later in life compared to precocial species.

Considering the functional maturity and dependency to parents, hatching in precocial species may be equivalent to fledging in altricial species. In another word, developmental and baseline CORT profiles may be similar between two ends of the precocial–altricial spectrum, except for the timing of hatch (Fig. 2). Thus, it is possible that the peak of CORT seen in precocial birds near hatching corresponds to the rise in CORT near fledging in non-precocial species.

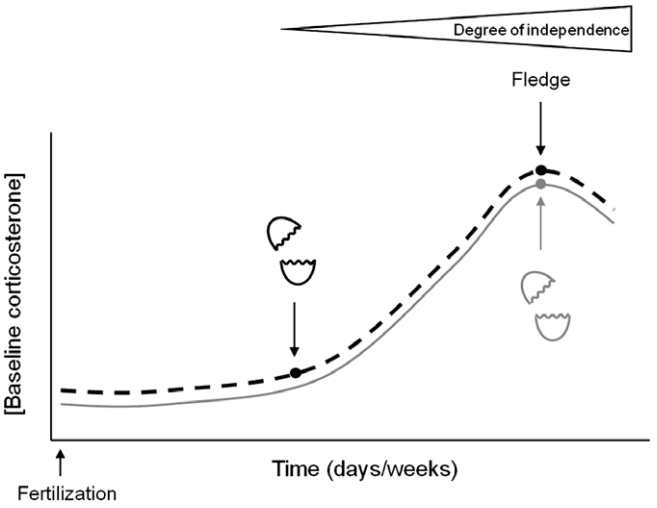

Fig. 2. Plausible changes in baseline CORT in respect to hatching and fledging in altricial and precocial species. Dotted and solid lines represent changes in baseline CORT in altricial and precocial birds, respectively.

3.3. Fish

In fish, more specifically in teleosts, there is a wide range of egg size, egg number, incubation period, developmental maturity, and body size at hatch (Falk-Petersen, 2005). For instance, marine pelagic fish like Gadidae (e.g. cods and haddocks), Pleuronectidae (e.g. halibuts and flounders), and Sparidae (e.g. porgies) lay relatively small eggs (0.8–3.0 mm, Falk-Petersen, 2005), hatch with immature organs, and have long larval period. On the other hand, Salmonidae (e.g. salmon and trout) lay large eggs (~6–7 mm, Moffett et al., 2006), hatch at more developed state and larger size. The ontogeny of the HPI axis reflects such variation. Interrenals of fish from "small" eggs do not appear until several days after hatching (Tanaka et al., 1995). Thus, baseline cortisol concentrations are very low at hatching (Japanese sea bass *Lateolabrax japonicus*, Perez et al., 1999) and baseline and magnitude of stress response increase gradually during larval stage until metamorphosis or later (yellowtail *Seriola quinqueradiata*, Sakakura et al., 1998; tilapia *Oreochromis mossambicus*, Pepels and Balm, 2004; but also see common carp *Cyprinus carpio*, Stouthart et al., 1998) (Fig. 1d).

On the other hand, evidence shows that some fish from "large" eggs can mount a stress response before hatching. Rainbow trout embryos (*Oncorhynchus mykiss*) secrete cortisol in response to ACTH *in vitro* (Barry et al., 1995b). However, the same species cannot mount a stress response to handling *in vivo* until 2 weeks post-hatching (Barry et al., 1995a,b) suggesting a possible stress hyporesponsive period at the level of the pituitary or higher in this "large"-egg species. Patterns in baseline cortisol at hatch may also be categorized according to egg size. "Large"-egg salmonids increase cortisol levels around hatching while "small"-egg non-salmonids often decrease cortisol until hatching (Ayson et al., 1995; de Jesus et al., 1991; de Jesus and Hirano, 1992; Feist and Schreck, 2001; Hwang and Wu, 1993; Hwang et al., 1992; Sampath-Kumar et al., 1995) (Fig. 1d and e). Similarly, "large"-egg rainbow trout hatchlings have 3–6 times higher cortisol than tilapia and more than

60 times higher than those of yellowfin bream hatchlings (*Acanthropagrus latus*) (Hwang et al., 1992). The difference between "small" and "large"-egg species appears similar to precocial–altricial spectrum, and "small"-egg species are hatched earlier on the similar developmental profile (Fig. 2; Falk-Petersen, 2005). More studies are needed to determine the ontogeny of endocrine systems in marine and freshwater fish to confirm this pattern.

3.4. Reptiles and amphibians

Far less is known about the ontogeny of the stress response in reptiles and amphibians. In amphibians, the CORT level remains low all though pre- and pro-metamorphosis but increases during metamorphosis climax and post-metamorphosis, paralleling the rise in thyroid hormones (Denver et al., 2002; Glennemeier and Denver, 2002a; Krug et al., 1983) (Fig. 1f, dotted line). In contrast to most amphibians studied, CORT is undetectable before hatching in African clawed-frogs (*Xenopus laevis*) (Kloas et al., 1997). Whole-body CORT of *X. laevis* begins to increase from Nieuwkoop–Faber (NF) stage 36 (Nieuwkoop and Faber, 1956; soon after hatching) and peaks at NF stage 46 (pre-metamorphosis) (Glennemeier and Denver, 2002a; Kloas et al., 1997) (Fig. 1f, solid line).

Pre- and pro-metamorphic amphibian tadpoles can mount a CORT response to confinement/shaking, intraspecific competition, and food deprivation, however, the CORT profiles depend on the type of challenges and age of tadpoles (Belden et al., 2003; Crespi and Denver, 2005; Glennemeier and Denver, 2002a,b). Furthermore, premetamorphic *X. laevis* and *Rana pipiens* tadpoles are sensitive to ACTH challenges (Glennemeier and Denver, 2002a). Although doses used in the study are different, sensitivity to ACTH is established later in pro-metamorphosis in Bullfrogs (*Rana catesbeiana*) (Krug et al., 1983).

In reptiles, CORT increases from embryonic stage to hatching (Jennings et al., 2000; Medler and Lance, 1998) (Fig. 1g). There is an evidence that embryonic snake can respond to ACTH *in vitro* (Girling and Jones, 2006). By the time young reach juvenile stage, turtles secrete significantly higher baseline and stress-induced CORT in response to capture and restraint stress than non-breeding adults (Jessop and Hamann, 2005; Jessop et al., 2004).

3.5. Summary

Overall, there are variations in the timing of HPA/HPI axes development within taxa, especially in mammals, birds, and fish. However, shared characteristics are seen *across* taxa. These variations in the timing of HPA/HPI axes development are largely attributed to different life history strategies (slow vs. fast or precocial vs. altricial) (Table 1). Slow strategist and precocial species are born or hatched at more mature state and are more independent from their parents than fast strategist and altricial species. Thus, they can benefit from mounting a stress response earlier and have an earlier development of the HPA/HPI axes than fast strategist and altricial species.

Table 1
Comparisons of offspring characteristics between two extremes of life history strategies, precocial species or slow strategist and altricial species or fast strategist

Life history strategies	Slow/precocial ⟷	Fast/altricial
Clutch size	Small	Large
Size of eggs/young	Large	Small
Incubation/gestation length	Long	Short
Maturity at birth	Mature	Immature
Dependency to parents (mammals, birds)	Short	Long
Ability to secrete GCs	Early	Late

4. Across ontogenetic transitions

4.1. Birth/hatching

Whether GCs are involved in birth/hatching appear to be determined by the developmental mode of each taxon. Many fish and amphibians are non-amniotes and go through indirect development where larvae undergo metamorphosis into an adult form. On the other hand, mammals, birds, and reptiles are amniotes which allow embryos to develop further before hatch/birth, and go through direct development. Consequently, fish and amphibians are hatched at more immature stages and many do not develop their adrenals/interrenals until after hatching. Thus GC levels are low at hatching in most fish and amphibians.

4.1.1. Preparation for the world outside

In mammals, fetal GCs rise rapidly in the last days of gestation (see below). This elevation of GCs is critical for maturation of many organs, namely lung, small intestine, liver, adrenals, and kidney (Liggins, 1994). Proper functions of these organs are vital for neonates' survival but were not necessary *in utero*. GCs stimulate development of these organs in anticipation of birth, a switch from continuous supply of oxygen and nutrition from placenta to breathing through lungs and intermittent feeding.

For example, it is well established that GCs promote lung maturation at multiple levels. It enhances surfactant protein and phospholipids synthesis leading to secretion of surfactant (Ballard, 1989; Liggins, 1994; Mendelson and Boggaram, 1991; Pepe and Albrecht, 1995). Surfactant is essential in extra-*utero* life, because it reduces surface tension within the alveoli preventing them from collapsing. GCs also facilitate structural development such as increasing compliance as well as glycogenolysis.

In birds, CORT has a similar effect on embryonic lung development. The embryonic lung of chickens shows a rapid and immense growth between 14 and 18 days of the 21-day incubation (Hylka and Doneen, 1983). This

coincides with the commencement of endogenous CORT secretion (Scott et al., 1981; Wise and Frye, 1973). *In vitro*, CORT, dexamethasone (Dex, synthetic GC), or epinephrine treatment all stimulate surfactant phospholipids synthesis in lung tissue (Hylka and Doneen, 1983; Sullivan and Orgeig, 2001). *In vivo*, hypophysectomy in the first days of incubation prevents a normal lung growth and decreases pulmonary surfactant phospholipids, which is partially rescued by CORT treatment or pituitary cell transplant later in development (Hylka and Doneen, 1983).

In respect to other critical organs, GCs stimulate Na^+–K^+ ATPase activities in the kidney tubules and in small intestine, synthesis of sucrase and alkaline phosphate in small intestine, and various enzyme activities necessary for glycogen synthesis and possibly gluconeogenesis in the liver (Liggins, 1994). In addition, GCs promote morphological maturation of small intestine as well.

4.1.2. GCs and parturition

Fetal GCs secretion signals and initiates a complex hormonal cascades leading to parturition in many mammalian species (Challis et al., 2000, 2001; McLean and Smith, 1999, 2001;Renfree and Shaw, 1996; Thorburn and Liggins, 1994). Prior to birth, surges of ACTH, total and free fetal GCs are observed in sheep (Bassett and Thorburn, 1969; MacIsaac et al., 1985; Magyar et al., 1980; Norman et al., 1985), pigs (Heo et al., 2003), humans (Challis and Hooper, 1989; deM Fencl et al., 1980; Murphy, 1982; Murphy and Clifton, 2003; Yoon et al., 1998), and rodents (Martin et al., 1977; van Baelen et al., 1977). In addition, the followings may occur in concert: a decrease in fetal CBG (Martin et al., 1977) or maternal CRF binding protein (McLean et al., 1995), a positive feedback between placental CRF with fetal cortisol (Challis and Hooper, 1989), and/or decreased placental 11β-hydroxysteroid dehydrogenase activity (HSD) (Murphy and Clifton, 2003), all amplifying the elevation of GCs near term.

An unequivocal relationship between fetal cortisol and parturition was elegantly demonstrated in sheep. First, Dex infusion into fetus induced spontaneous delivery approximately 48 h after the infusion (Liggins, 1969). A similar Dex infusion to pregnant females, on the other hand, did not accelerate the parturition. Second, bilateral lesions of hypothalamic paraventricular nuclei, the site of CRF secretion, interfered with a normal preterm surge of fetal ACTH and cortisol and prolonged the gestational period (Gluckman et al., 1991; McDonald and Nathanielsz, 1991). Similarly, infusion of CRF receptor antagonist into fetus delayed parturition (Chan et al., 1998). Lastly, CRF infusion into fetus shortened the duration to parturition (Wintour et al., 1986). These lines of evidence strongly suggest that the fetal HPA axis is crucial for the onset of hormonal cascades in normal parturition.

4.1.3. GCs and hatching

Similarly to mammalian parturition, CORT peaks around hatching in birds (Carsia et al., 1987; Davis and Siopes, 1985; Frigerio et al., 2001; Jacobs, 1996; Mashaly, 1991; Scott et al., 1981; Wentworth and Hussein, 1985) and reptiles (Jennings et al., 2000; Medler and Lance, 1998). Is CORT required for hatching in oviparous species? Some data suggest so. CORT administrations in turkey embryos 2 days before hatching significantly increase hatching success and trend for shorter incubation period (Wentworth and Hussein, 1985; but also see Uller and Olsson, 2006). In tree lizards (*Urosaurus ornatus*), embryos hatch significantly faster after CORT administration (Weiss et al., 2007). Furthermore, an administration of RU486 (CORT and progesterone receptor blocker) results in low hatching success of otherwise healthy embryos in tree lizards (Jennings et al., 2000; Weiss et al., 2007) and chickens (Bordone et al., 1997; Nishigori et al., 2004). RU486 injection in late incubation also delays hatch date by 1 day in chickens (Bordone et al., 1997; Nishigori et al., 2004). Since RU486 specifically blocks CORT receptors in birds (Groyer et al., 1985), these data suggest endogenous CORT may control embryos' ability to hatch.

On the other hand, GC does not appear to be involved in hatching in fish with "small" eggs. Cortisol either stays low until hatching (Perez et al., 1999; Szisch et al., 2005) or decline from fertilization to hatching (expect for carp) (de Jesus et al., 1991; Hwang and Wu, 1993; Hwang et al., 1992; Sampath-Kumar et al., 1995; Stouthart et al., 1998). In "small"-egg tilapia (2.3 mm, Gunasekera et al., 1996), this decline is due to depletion of maternally-derived cortisol before the young's HPI axis is functional (Hwang et al., 1992). Conversely "large"-egg species like salmon increase ACTH and/or cortisol around hatchling (except for rainbow trout) (Barry et al., 1995a; de Jesus and Hirano, 1992; Feist and Schreck, 2001). Thus it is possible that fish with slow life history strategy (larger size, fewer offspring) have relatively mature HPI axis and the peak in cortisol is involved in initiation of hatching.

4.2. Fledging/dispersal

4.2.1. Fledging

Fledging refers to an ontogenetic transition where young birds leave their nest. In some species, fledglings cannot fly and are still fed by their parents. Regardless of fledglings' ability to fly, fledging exposes young to sudden metabolic demands. Hormonal control or correlates of fledging are still under debate. However, CORT is one of the promising candidates given its roles in mobilizing glucose, lipids, and amino acids from liver, adipose tissue, and muscle sources (Sapolsky et al., 2000). Observational studies show that CORT increases prior to fledging in American kestrels (*Falco sparverius*) (Heath, 1997; Sockman and Schwabl, 2001), pied flycatcher (*Ficedula hypoleuca*) (Kern et al., 2001), canaries (*Serinus canaria*) (Schwabl, 1999), thin-billed prion (*Pachyptila belcheri*) (Quillfeldt et al., 2007), and Laysan Albatross (*Phoebastria immutabilis*) (Seabury Sprague and Breuner, 2005). The latter coincides with a decline in CBG, elevating free CORT even

more. Furthermore, food supplementation to albatross chicks delays both elevations of total and free CORT as well as fledging (Seabury Sprague and Breuner, 2005). Although it is difficult to compare capital breeders (species which use energy reserve for reproduction; Jonsson, 1997) and income breeders (species which reproduce as they acquire energy) due to their diverse energetic demands in nestlings, CORT may be a common trigger for fledging.

Other species show heightened HPA activity during a fledgling period. In canaries, baseline CORT of 1-week fledglings is elevated compared to nestlings and adults (Schwabl, 1999). In American kestrels and zebra finches (*Taeniopygia guttata*), fledglings have significantly higher stress-induced CORT than adults (Love et al., 2003; Wada et al., 2008). In screech-owls (*Otus asio* and *O. kennicottii*), baseline CORT peaks before and during an activity period associated with dispersal (Belthoff and Dufty, 1998). Thus, these relatively high CORT levels may be related to increased locomotor and foraging activities, or changes in metabolism in preparations for fledging, dispersal, and independence.

Yet conflicting data exist in the roles of CORT in fledging. In these data, baseline CORT either does not change (Blas et al., 2005, 2006; Sims and Holberton, 2000) or decreases during the nestling period (Romero et al., 2006; Walker et al., 2005), or there is no difference between baseline CORT of fledged and non-fledged young (Love et al., 2003; Romero et al., 2006). Nesting location (ground or low brush vs. cavity or cliff) may contribute to the species variation seen in CORT near fledging since various location require different energetic demands at fledging (Heath, 1997; Romero et al., 2006). Fledglings of ground or brush nests (e.g. Northern mockingbirds and snowy owls) do not increase CORT at fledging but may not take the first flight until days/weeks after fledging. On the other hand, fledglings of cavity or cliff nesters (e.g. American kestrels, screech-owls, and pied flycatcher) take the first flight as they leave the nest and elevate plasma CORT at fledging. Experimental manipulations on CORT levels are needed to determine the causal relationship between CORT and fledging.

4.2.2. Dispersal

Natal dispersal can be influenced by multiple factors and CORT is one of the proximate factors affecting propensity for dispersal. In birds and mammals, CORT enhances dispersal behavior in juveniles (but also see Strier and Ziegler, 2000). Juvenile ground squirrels (*Spermophilus beldingi*), for example, have elevated cortisol levels during first days of emergence from their natal borrow (Mateo, 2006). In addition to GCs' role in metabolism, it is speculated that this increase in cortisol will promote learning alarm calls and enhance spatial memory which are critical for survival in this species. Similarly, baseline CORT surges before and during an activity period associated with dispersal in screech-owls (Belthoff and Dufty, 1998). In willow tits (*Parus montanus*), CORT implants in juveniles during flock establishment increase dispersal rates (Silverin, 1997). However, similar implants after flock establishment have no effect on dispersal, suggesting this effect of CORT on juvenile dispersal is limited to certain times of the year (Silverin, 1997).

In addition to seasons, the timing of CORT elevation may determine its effect as well. Prenatal CORT exposure decreases dispersal in common lizards (*Lacerta vivipara*) (de Fraipont et al., 2000; Meylan et al., 2002) while postnatal CORT elevation has no effect on dispersal (Meylan et al., 2002). Body conditions of mothers and juveniles also affect the dispersal behavior: CORT decreases offspring dispersal only in ones from large mothers while good body condition in juveniles increases dispersal (Meylan et al., 2002). This indicates that CORT modulates juveniles' dispersal behavior to one best adapted to the current environment, based on body condition and other factors.

4.3. Metamorphosis and smoltification

4.3.1. Metamorphosis

Thyroid hormones are known to be the main players of metamorphosis in amphibians and flatfishes. However, CORT acts in concert with thyroid hormones during the transformation of larvae. Triiodothyronine (T3) and/or thyroxine (T4) are elevated during metamorphosis in both taxa (de Jesus et al., 1991; Krain and Denver, 2004), and T3 or T4 alone can accelerate metamorphosis indicated by increased rate of tail resorption in tadpoles (Galton, 1990; Krug et al., 1983), dorsal fin ray resorption (de Jesus et al., 1990, 1998), and eye migration in flatfish larvae (de Jesus et al., 1990; Solbakken et al., 1999). Although CORT is also elevated in concert with metamorphosis (Krug et al., 1983; Glennemeier and Denver, 2002a; Krain and Denver, 2004; Szisch et al., 2005; Sakakura et al., 1998; de Jesus et al., 1991; but also see Yamano et al., 1991), CORT alone fails to speed up the metamorphosis (Galton, 1990, but also see de Jesus et al., 1990; Hayes et al., 1993). Yet, when tadpoles and fish larvae are treated with ACTH or CORT in addition to T3 or T4, combined treatments can elicit even faster metamorphosis than thyroid hormone alone (Brown and Kim, 1995; de Jesus et al., 1990; Galton, 1990; Krug et al., 1983), via further elevation of thyroid hormones (Galton, 1990) or increasing thyroid hormone receptors and conversions of T4 to T3 (Krain and Denver, 2004; Denver et al., 2002). In addition to presence/absence of the thyroid hormones, the dose and the timing of CORT administration are the key determinants for the effects of the hormone during metamorphosis (Denver et al., 2002).

In amphibians, studies indicate that both thyroid and interrenal axes are controlled by a common neurohormone, CRF. Injections of CRF-like peptide accelerate metamorphosis (Boorse and Denver, 2002; Denver, 1993, 1997; Miranda et al., 2000) while CRF antagonist delays metamorphosis (Denver, 1997). The current view for the hormonal control of metamorphosis in amphibians is that CRF induces secretions of T3, T4, and CORT (Denver,

1998; Denver et al., 2002; De Groef et al., 2006) and together orchestrate the transformations in metamorphosis. It is important to note that other hormones like aldosterone, prolactin, and growth hormone are also involved in this dramatic transition (Denver et al., 2002).

4.3.2. Smoltification

Smoltification in anadromous fish prepares the young for the transition from freshwater to saltwater which requires dramatic physiological, biochemical, and behavioral changes to adapt to the new salinity. Ontogeny of the seawater adaptation and its hormonal control (e.g. cortisol, prolactin, thyroid hormones, and growth hormone/insulin-like growth factor) are extensively studied and reviewed elsewhere (Mommsen et al., 1999; McCormick, 2001; Varsamos et al., 2005) thus this section briefly reviews the role of cortisol in this process.

Some of the main osmoregulatory physiology which cortisol regulates is the Na^+–K^+ ATPase activity and ion transport in gills and intestine. In salmonids, seawater tolerance, indicated by an increased Na^+–K^+ ATPase activity in the gills, is established while parrs are still in freshwater (Franklin et al., 1992; Ura et al., 1997). Around the same time, an increase in cortisol is observed (Barton et al., 1985; Young, 1986). Not only are cortisol levels highly correlated with the gills' Na^+–K^+ ATPase activity (Franklin et al., 1992), but cortisol administrations significantly (1) increase gill Na^+–K^+ ATPase activity, gill Na^+–K^+–$2Cl^-$ cotransporter number, and gill chloride cells, (2) decrease plasma osmolarity and Na^+ concentrations, and (3) increase survival in seawater (Bisbal and Specker, 1991; Hwang and Wu, 1993; Madsen, 1990a,b; Mancera et al., 2002; Pelis and McCormick, 2001; Redding et al., 1991). Growth hormone and cortisol have additive effects on the ion transport; a combined hormone treatment results in significantly higher gill Na^+–K^+–$2Cl^-$ cotransporter abundance and Na^+–K^+ ATPase activity than when each hormone is administered alone (Madsen, 1990b; Pelis and McCormick, 2001).

Kidney is another important organ for osmoregulation in fish and other vertebrates. In masu salmon (*Oncorhynchus masou*), juxtaglomerular cell number in the kidney increases during smoltification (Mizuno et al., 2001b) and is positively correlated with survival during freshwater to seawater transfer (Mizuno et al., 2002). Pre-smolts injected with cortisol for 5 days significantly increase juxtaglomerular cell size and number (Mizuno et al., 2001a). Furthermore, after 11 days of cortisol treatment, the cell size and number resemble those of smolt at the peak of seawater adaptability (Mizuno et al., 2001b).

5. Conclusion

Taken together, GCs have direct and permissive effects on various ontogenetic transitions in vertebrates (Table 2). GCs directly (1) promote maturation of critical organs before birth/hatch in mammals and birds, (2) initiate parturition events in mammals and possibly controls hatching in birds and reptiles, (3) facilitate acquisition of osmoregulatory ability in fish during smoltification, and (4) affect dispersal behavior in mammals, birds, and reptiles and are potential candidates for the timing of fledging in birds, although further studies are needed to determine the causal relationship. CORT also has a permissive action on thyroid hormones in amphibian and fish metamorphosis. However, cortisol does not appear to be involved in hatching in "small"-egg fish.

There is a wide range among taxa in the number of available studies concerning ontogeny of the HPA/HPI axes and the role of GCs in the ontogenetic transitions. Due to applications to medical and commercial practices, work has been mainly focused on mammals, cultured fish, and poultry. At the same time, relatively limited data are available in amphibians, reptiles, and free-living birds, fish, and mammals. Future studies should encompass these taxa and groups, particularly in (1) the ontogeny of the HPA/HPI axes and (2) the role of GCs in organ maturation (Table 2).

Overall, GCs prepare organisms and trigger transitions into the subsequent life history stage. At the same time, there are variations in the pattern of HPA/HPI axes development within and across taxa. As mentioned earlier, the developmental strategy of each taxon/species is likely the determinant for this variation, such as direct vs. indirect development and fast vs. slow life history strategy. Future research is needed to explore the common underlying mechanisms for GCs during development and evolution of these roles of GCs in vertebrate ontogeny.

Table 2
Summary of direct and permissive effects of GCs on various ontogenetic transitions in vertebrates

	Direct				Permissive
	Organ maturation	Parturition/hatch	Smoltification	Fledging/dispersal	Metamorphosis
Mammals	✓	✓		✓	
Birds	✓	?		?	
Fish	—	✗	✓		✓
Amphibians	—	—		—	✓
Reptiles	—	?		✓	

GCs have direct actions on organ maturation, parturition/hatch, smoltification, and fledging/dispersal, and permissive actions on metamorphosis. ✓ and ✗ denote the presence and absence of the effects, respectively. '—' and '?' denote a lack of studies and a possible role of GCs during the ontogenetic event, respectively.

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