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Sources of variation in plasma corticosterone and dehydroepiandrosterone in the male northern cardinal (*Cardinalis cardinalis*): I. Seasonal patterns and effects of stress and adrenocorticotropic hormone

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Highlights

- Restraint stress increases corticosterone (CORT), but decreases dehydroepiandrosterone (DHEA) levels in cardinals.
- Decreased DHEA levels with restraint stress only observed in jugular circulation.
- ACTH does not increase DHEA levels, but increases CORT.
- Both CORT and DHEA were generally lowest in the fall and highest during spring.

Abstract

The secretion of steroids from the adrenal gland is a classic endocrine response to perturbations that can affect homeostasis. During an acute stress response, glucocorticoids (GC), such as corticosterone (CORT), prepare the metabolic physiology and cognitive abilities of an animal in a manner that promotes survival during changing conditions. Although GC functions during stress are well established, much less is understood concerning how adrenal androgens, namely dehydroepiandrosterone (DHEA) are influenced by stress. I conducted three field studies (one experimental and two descriptive) aimed at identifying how both

CORT and DHEA secretion in free-living male northern cardinals (*Cardinalis cardinalis*), vary during acute stress; across different circulations (brachial vs. jugular); in response to ACTH challenge; and during the annual cycle. As predicted, restraint stress increased plasma CORT, but unexpectedly DHEA levels decreased, but the latter effect was only seen for blood sampled from the jugular vein, and not the brachial. The difference in DHEA between circulations may result from increased neural uptake of DHEA during stress. Injection with exogenous adrenocorticotropic hormone (ACTH) increased CORT concentrations, but failed to alter DHEA levels, thus suggesting ACTH is not a direct regulator of DHEA. Monthly field sampling revealed distinct seasonal patterns to both initial and restraint stress CORT and DHEA levels with distinct differences in the steroid milieu between breeding and non-breeding seasons. These data suggest that the CORT response to stress remains relatively consistent, but DHEA secretion is largely independent of the response by CORT. Although CORT functions have been well-studied in wild animals, little research exists for the role of DHEA and their variable relationship sets the stage for future experimental research addressing steroid stress responses.

Introduction

The hypothalamic–pituitary–adrenal (HPA) axis is an endocrine cascade in vertebrates that modulates key physiological and behavioral processes that promote survival during situations of stress (Wingfield and Sapolsky, 2003). The HPA axis initiates with the hypothalamic release of corticotropin-releasing hormone (CRH) into a specialized portal system, which binds to pituitary corticotropic cells resulting in secretion of adrenocorticotropic hormone (ACTH) into systemic circulation (Aguilera and Liu, 2012, Fokidis and Deviche, 2011). Acting on the adrenal cortex, ACTH promotes the synthesis and subsequent secretion of glucocorticoids (GCs) into the blood (Sapolsky et al., 2000). Specifically, ACTH interacts with a serpentine membrane bound G-protein coupled receptor on the adrenocortical cells found within the zona fasciculata (middle zone) where it rapidly encourages lipoprotein uptake and delivery to increase cholesterol bioavailability for steroidogenesis (Boyd and Trzeciak, 1973). Concurrently ACTH also initiates the transcription of GC synthesizing enzymes and mitochondrial oxidative phosphorylation systems that provide energy for enhanced cellular metabolism associated with increased steroid synthesis (Boyd and Trzeciak, 1973, Miller, 2013). The dominant bioactive GCs in vertebrate circulation are cortisol (the predominant GC in many mammals, including humans, and fish) and corticosterone (CORT: the dominant GC in birds and reptiles) (Sapolsky et al., 2000, Quinn et al., 2013). Both of these steroids induce a myriad of physiological effects that promote survival in the short-term, such as energy mobilization and vigilance behaviors, but can be detrimental with prolonged or chronic overstimulation, known as “allostatic load” (McEwen and Wingfield, 2003). In these situations, GCs can suppress immunity, interfere with reproductive physiology, and can influence the brain by impairing neuronal health and development (McEwen and Wingfield, 2003).

Circulating GC concentration is the typical endpoint measured to assess the acute stress response, usually by comparing a “baseline” level with that after a period of handling stress (Romero and Reed, 2008). This method is widely used and has garnered data concerning patterns of GC secretion and their various roles in wild animals (Deviche et al., 2010, Fokidis et al., 2011, French et al., 2008, Holding et al., 2014, Pereyra and Wingfield, 2003, Pravosudov et al., 2002, Refsnider et al., 2015). Many avian studies of seasonal patterns report higher CORT levels at the onset of breeding where it may serve to mobilize energy stores, and then levels declining post breeding when it may interfere with anabolic processes, such as feather molt (Foltz et al., 2015, Holding et al., 2014, Cornelius et al., 2011, DesRochers et al., 2009, Romero et al., 2009, Romero et al., 2005, Pereyra and Wingfield, 2003, Raja-aho et al., 2013). In some species, plasma CORT levels are reduced during breeding when stress might interfere with limited opportunities for reproduction (e.g., a short breeding season), and thus, yearly CORT patterns often align closely with specific life-history patterns and environmental conditions (Holberton and Wingfield, 2003, Romero et al., 1997).

During stress, the inner most adrenal cortical layer, the zona reticularis, also secretes the androgen precursor, dehydroepiandrosterone (DHEA) (Boonstra et al., 2008, Strous et al., 2006, Soma et al., 2015). In human circulation, DHEA is most prevalent in an inactive sulfated form (DHEAS), although the degree to which this form is present in other species is less understood (Soma et al., 2015). The secretion of DHEA in circulation appears directly regulated by ACTH based on studies in humans, hamsters, and squirrels (Kalimi et al., 1994, Boonstra et al., 2008, Soma et al., 2015), however the essentially undetectable DHEA levels in mice and rats do not change in response to ACTH (Van Weerden et al., 1992, Bélanger et al., 1990). Although no studies have tested DHEA responses to exogenous ACTH challenge in a non-mammalian model, in the song sparrow (*Melospiza melodia*) exposure to acute stress did not affect DHEA concentrations (Newman et al., 2008, Soma and Wingfield, 2001). Although, no specific receptor has been clearly identified (Labrie et al., 2001), significant evidence from ligand-binding assays suggests DHEA may interact with a specific membrane-receptor in both bovine aortic and human umbilical vein endothelial cells (Webb et al., 2006, Widstrom and Dillon, 2004). In humans, DHEA in circulation is found in its esterified sulfate form (DHEAS) which is both highly stable and largely thought to be incapable of exerting androgenic effects (Labrie et al., 2001). Data from *in vitro* studies in rats, suggests DHEA can protect neurons and neurogenesis from excessive GC exposure during stress (Kimonides et al., 1999, McNelis et al., 2013, Kalimi et al., 1994). Thus, DHEA may act as an anti-GC hormone within the nervous system however; the mechanisms of action are not clearly understood.

One possibility is that DHEA may be exerting its effects through enzymatic conversion to a bioactive steroid, such as testosterone (T) or estradiol (E_2), and both of these steroids are known to have neuroprotective qualities with the necessary enzymes being present within the brain (Duncan and Saldanha, 2013, Saldanha et al., 2009). This conversion of DHEA to T and E_2 within the brain can also promote territorial aggression in some birds and Siberian hamsters (*Phodopus sungorus*), especially when circulating sex steroids are low (e.g., nonbreeding season) (Schmidt et al., 2008, Soma et al., 2015). The conversion of circulating steroids by enzymes within the brain have prompted comparisons of CORT and DHEA levels between brachial and jugular circulations, particularly in response to handling stress (Newman and Soma, 2011, Newman et al., 2008). Brachial blood sampling may represent systemic hormone concentrations directly secreted by the adrenal gland, whereas jugular sampling may represent hormone levels after depletion and/or enrichment by the brain (Newman and Soma, 2011). Although several studies have compared both brachial and jugular DHEA levels in vertebrates between the breeding and nonbreeding condition (Boonstra et al., 2008, Hau et al., 2004, Soma and Wingfield, 2001), complete monthly-sampled profiles over the course of the year is limited in the literature (but see Hamlin et al., 2014). Furthermore, the secretory patterns of CORT and DHEA are not always congruent and their relationship can vary with seasonality (Newman and Soma, 2009).

Here, I investigated plasma CORT and DHEA concentrations in free-living adult male northern cardinals (*Cardinalis cardinalis*) during exposure to capture and handling stress across the course of the year. I also compared concentrations between the jugular and systemic circulations and in response to injection with exogenous ACTH. Northern cardinals are common, sedentary and sexually dimorphic songbirds that exhibit a substantial amount of behavioral similarity between the sexes (Nealen and Breitwisch, 1997, Jawor and MacDougall-Shackleton, 2008, Devries et al., 2014). The endocrine research on this species has largely focused on the regulation of gonadal T in both sexes (DeVries et al., 2011, DeVries and Jawor, 2013, DeVries et al., 2015, Jawor, 2007, Jawor et al., 2014). Artificial activation of the reproductive axis may increase CORT levels, however CORT does not appear to affect T levels in cardinals (DeVries et al., 2011). Levels of CORT have been examined in other studies of this species (Barron et al., 2012, Owen et al., 2012, DeVries and Jawor, 2013) and this research provides additional insight into the regulation of and relative associations between these adrenal steroids.

Section snippets

Ethics statement

All studies were conducted under United States Geological Survey Bird Banding Laboratory permit # 23847, Florida Fish, and Wildlife Commission scientific collecting permit #LSSC-13-00057, and with relevant access permits from the appropriate agencies. The Institutional Animal Care and Use Committee at Rollins College approved all experimental procedures (protocols # 2513B and 2514).…

Study 1: variation between jugular and systemic circulation

Blood sampled from the brachial vein represents systemic levels of steroids that are secreted from classic…

Brachial and jugular circulation

Based on data from a subset of birds collected in Oct 3, 2013, restraint stress increased jugular CORT and simultaneously decreased jugular DHEA (Fig. 2). Based on these data the 30min period for restraint was sufficient to induce a maximal change in both steroids (Fig. 2). Whether the brachial or jugular vein was sampled had a significant effect on both the CORT ($F_{2,12}=3.62$, $P=0.028$, Fig.3A) and DHEA ($F_{2,12}=3.04$, $P=0.035$, Fig.3B) response to capture restraint. Initial brachial samples had…

Discussion

I investigated how circulating concentrations of two adrenocortical steroids CORT and DHEA varied between circulation patterns, across the course of a year, and in response to both acute stress and exogenous ACTH challenge in free-living male northern cardinals. As predicted, restraint stress elevated CORT levels while simultaneously lowering DHEA concentrations, but this latter effect was only present in jugular (neutrally enhanced or depleted) than brachial (systemic) circulation. Jugular…

Conclusion

Clearly this study demonstrates that DHEA and CORT, although both presumably originating primarily from adrenocortical tissue, they each exhibit distinct patterns of secretion. In response to acute restraint stress, CORT increases and DHEA often decreases (though sometimes increase) particularly when sampling the jugular vein, which supports the uptake of DHEA by the brain, possibly for further metabolism to bioactive steroids. This decrease in DHEA with stress contradicts its potential role as …

Acknowledgments

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> …Thus CORT and DHEA secretion is uncoupled, suggesting they may be regulated by different secretogues. Supporting this hypothesis, injections of ACTH increased CORT, but not DHEA in cardinals (Fokidis, 2016). Future studies should aim to test CORT and DHEA responses to various exogenous secretogues to characterize the regulatory pathways that control DHEA secretion.…

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