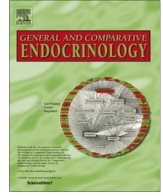




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Determinants and significance of corticosterone regulation in the songbird brain

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ABSTRACT

Songbirds exhibit significant adult neuroplasticity that, together with other neural specializations, makes them an important model system for neurobiological studies. A large body of work also points to the songbird brain as a significant target of steroid hormones, including corticosterone (CORT), the primary avian glucocorticoid. Whereas CORT positively signals the brain for many functions, excess CORT may interfere with natural neuroplasticity. Consequently, mechanisms may exist to locally regulate CORT levels in brain to ensure optimal concentrations. However, most studies in songbirds measure plasma CORT as a proxy for levels at target tissues. In this paper, we review literature concerning circulating CORT and its effects on behavior in songbirds, and discuss recent work suggesting that brain CORT levels are regulated independently of changes in adrenal secretion. We review possible mechanisms for CORT regulation in the avian brain, including corticosteroid-binding globulins, p-glycoprotein activity in the blood–brain barrier and CORT metabolism by the 11 β hydroxysteroid dehydrogenases. Data supporting a role for CORT regulation within the songbird brain have only recently begun to emerge, suggesting that this is an avenue for important future research.

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1. Introduction

Songbirds are increasingly recognized as powerful animal models for studies in developmental neurobiology, sensory processing, the neural control of learning and memory, and the control of complex behavior. They stand out for their extensive neuroplasticity that can be retained throughout adult life (Kirn, 2010; McDonald and Kirn, 2012; Tramontin and Brenowitz, 2000). Interestingly, many of the neural attributes that make songbirds unique are influenced by sex steroid hormones (Ball et al., 2002; Brenowitz, 2013; Brenowitz, 2015; Schlinger and Brenowitz, 2009; Soma et al., 2004; Tramontin et al., 2003). Songbirds also possess specializations of neural sex steroid synthesis and metabolism, notably a significant capacity to synthesize estrogens in brain (Ball and Balthazart, 2009; London et al., 2009; Schlinger et al., 2014). In addition, there is increasing evidence that songbirds also possess special properties governing neural glucocorticoid physiology.

In the traditional view, steroid hormones are synthesized and released from the peripheral steroidogenic glands, the gonads

and adrenals, and circulate in the bloodstream until reaching various target tissues. Steroids readily cross the blood–brain barrier (Pardridge, 1981) where they bind to receptors in the hypothalamus to initiate negative feedback control over the hypothalamo–pituitary–adrenal (HPA) and hypothalamo–pituitary–gonadal (HPG) axes, as well as receptors in numerous other brain regions important for cognition, behavior, and physiology. In songbirds, while a great deal of work has focused on the dynamics of sex-steroid availability to discrete neural circuits (see citations above), fewer studies have examined the nature of neural corticosterone (CORT) neurobiology and physiology. This is surprising, given the large amount of research devoted to understanding stress physiology, including the effects of chronic stress on CORT secretion (e.g., Cyr and Romero, 2007; Rich and Romero, 2005), behavioral effects of CORT (e.g., Breuner et al., 1998; Breuner and Wingfield, 2000; Busch et al., 2008; Loiseau et al., 2008; Pravosudov, 2003; Saldanha et al., 2000; Schoech et al., 2007, 2012; Spencer and Verhulst, 2007; Wada and Breuner, 2008), the role of developmental stress in the programming of the HPA axis (Crino et al., 2014; Schoech et al., 2011; Spencer et al., 2009), and the potential fitness consequences of glucocorticoid secretion over the lifespan of the individual (Bonier et al., 2009; Breuner et al., 2008; Brown et al., 2005; Cyr and Romero, 2007; Ouyang et al.,

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2011). For the most part, these studies utilize measures of plasma CORT (either free or total) as indicators of CORT activity, despite the fact that local CORT synthesis may occur independently of the adrenals (Taves et al., 2011) and several mechanisms exist that alter the availability of CORT to target tissues and receptors (see below).

The purpose of this mini-review is to discuss the dynamics of CORT synthesis, release, and regulation in the songbird, with an emphasis on CORT levels and function in the songbird brain. To this end, we provide a synopsis of studies that have addressed these topics and discuss future avenues for research. Our principal goal is to outline the multiple pathways by which CORT gains access to its receptors within neural circuits in the brain and to discuss whether neural CORT levels are subject to regulation. These findings may point out ways in which the measurement of plasma CORT provides an incomplete picture of functional CORT activity in the brain. Accordingly, we first address what is known about effects of circulating CORT on songbird behavior. We then describe studies that have sought to determine the relationship between CORT levels in brain and blood. Next we discuss three sets of mechanisms for regulation of CORT access and/or activity in the songbird brain: corticosteroid-binding globulins in the periphery, p-glycoprotein-mediated transport at the blood–brain barrier, and local CORT metabolism by the 11 β hydroxysteroid dehydrogenases. As the latter mechanisms have only recently been addressed in songbirds, this stands as an exciting field for discovery. Finally, we examine the hypothesis that the adult songbird brain may retain considerable control over neural CORT levels in part to limit potentially deleterious effects of CORT on the extensive neuroplasticity that is retained in adulthood. Note that while differential expression of CORT receptors is unquestionably a primary mechanism for regulating neural effects of CORT, the focus of this paper is on less-studied CORT regulatory mechanisms in the songbird brain.

2. Plasma CORT and behavior

Many studies utilize measures of circulating CORT as a proxy for CORT availability to target tissues and as an indicator of overall functioning of the HPA axis. This is particularly useful for field-based studies wherein the relatively non-invasive taking of a small blood sample permits release of the subject for relatively naturalistic study, as well as the possibility of subsequent recapture and sampling. Circulating CORT levels have been correlated with traits such as aggression (Charlier et al., 2009; Newman and Soma, 2011; Van Duyse et al., 2004) and measures of personality, such as exploratory behavior and risk-taking (Atwell et al., 2012; Carere et al., 2010; Liebl and Martin, 2012; Martins et al., 2007; Schoech et al., 2012). In addition, manipulation of CORT profiles through use of implants, patches, and oral dosing has established a causal role for CORT in the expression of various behaviors (Breuner et al., 1998; Pravosudov, 2003; Saldanha et al., 2000; Schoech et al., 2007; Spencer and Verhulst, 2007; Wada and Breuner, 2008; Wingfield and Silverin, 1986). The intracellular CORT receptors (glucocorticoid receptor (GR) and mineralocorticoid receptor (MR)) are also differentially expressed in the songbird brain (Dickens et al., 2009; Hodgson et al., 2007; Shahbazi et al., 2011) and a membrane CORT receptor has been characterized (Breuner and Orchinik, 2009). Taken together, studies documenting CORT receptor expression in brain, as well as behavioral effects of CORT, make it clear that CORT is present in and acts on the songbird brain. An important question remains, however: do CORT levels in all regions of the brain mirror levels in the circulation – i.e., are plasma CORT measures a reliable proxy for levels of CORT acting on discrete neural circuits?

The adult songbird brain exhibits remarkable plasticity that may be sensitive to the effects of CORT. Our lab and others have previously shown that excess CORT exposure inhibits neurogenesis in songbirds (Katz et al., 2008b; Newman et al., 2010), and CORT can be cytotoxic to neurons in rodents (Behl et al., 1997; Magarinos and McEwen, 1995; Sapolsky et al., 1988) and birds (Newman et al., 2010). In addition, CORT can inhibit reproduction in times of chronic or extreme stress (Wingfield et al., 1983). One could therefore readily imagine that CORT levels in the songbird brain should be regulated to prevent over-exposure, and thus not all fluctuations in the songbird brain might be a mirror of the circulation. Indeed, local optimization of brain CORT levels is likely critical; even though chronic or over-exposure to CORT is detrimental, some level of CORT is necessary and permissive for many physiological and behavioral processes (Sapolsky et al., 2000). What then do we know about CORT levels in the brains of songbirds, and do they suggest that the brain is a passive recipient of fluctuations originating in the periphery?

3. Does brain CORT mirror plasma CORT?

Studies designed to assess CORT levels in the songbird brain have to date utilized one of two techniques to measure CORT: direct steroid extraction from brain tissue, or measurement of extracellular CORT using in vivo microdialysis.

3.1. Direct steroid extraction from brain tissue

Steroid extraction from whole, discrete regions of the songbird brain is gaining interest as a technique, and our lab and others have validated this method for measures of brain estradiol, CORT, and dehydroepiandrosterone (DHEA; Chao et al., 2011; Newman et al., 2008; Taves et al., 2011). Brain CORT levels have been successfully measured in developing songbirds, notably European starlings (*Sturnus vulgaris*; Schmidt et al., 2009) and zebra finches (*Taeniopygia guttata*; Schmidt and Soma, 2008), as well as in adult song sparrow brain (*Melospiza melodia*; Newman and Soma, 2011).

One of the goals of studies measuring brain CORT is to determine whether or not levels are determined solely by changes in the circulation. While several studies have found no evidence for brain-specific regulation of CORT (i.e., plasma and brain CORT fluctuations were similar; Newman and Soma, 2011; Schmidt et al., 2009), a recent study found support for the hypothesis that the songbird brain regulates CORT access to discrete neural circuits. Newman and Soma (2009) investigated seasonal and stress-induced changes in plasma and brain CORT levels (as well as levels of DHEA) in adult male song sparrows. Fluctuations in multiple brain regions generally matched those in blood, with one exception. During molt, CORT levels in the hippocampus (HP) were undetectable after, but not before stress, producing a “mismatch” between the HP and the plasma. This result suggests that under certain conditions, the songbird HP is protected from exposure to acute stress-induced CORT, although the mechanism producing this effect was not investigated.

3.2. In vivo microdialysis to measure brain CORT

The studies discussed above have utilized a solid-phase extraction method to extract hormone from brain tissue. Unfortunately, measuring CORT from brain tissue as described above requires sacrifice of the animal, providing only one data point per individual. While this is certainly an informative and useful method, we have developed the use of in vivo microdialysis in the songbird brain to obtain repeated, pseudo real-time measures of extracellular steroid hormones as measured in dialysates collected from discrete brain

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