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Editorial Focus: *Stressed tissue in a calm organism*. Comments on "Cortisol and corticosterone in the songbird immune and nervous systems: local vs. systemic levels during development," by Schmidt and Soma

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GONE ARE THE DAYS OF gland-limited hormone production. Estrogens and androgens only come from the gonad? No: neural and lipid tissue can produce estrogens; adrenals can produce androgens.

The story originally started in the 1970s, with the discovery of extra-gonadal aromatase (7, 12). In 1981, Corpechot et al. (2) coined the term "neurosteroid," indicating active steroids that were synthesized in the brain. However, studies focused primarily on in vitro studies, producing estrogens from precursors or labeling enzymes on tissue sections. A classic study in the early 1990s demonstrated the functional consequences of neural aromatase (in vivo) through injection of ^{3}H-labeled testosterone into the telencephalon and recovery of ^{3}H-labeled estradiol from the jugular (10).

Dr. Kiran Soma built his PhD work around the functional consequences of the neurosteroid hypothesis (13–15; for review, see 16, 17–21). High peripheral testosterone levels can be quite costly, increasing energy expenditure, injury, mortality, and oncogenic risk, while suppressing immune activity and interfering with pair bonds (23). Given these costs, it was assumed that any functional organismal output that required androgen activation would be absent in the nonbreeding season. However, many animals demonstrate apparent androgen-mediated behaviors, such as aggression outside of breeding. Through an elegant combination of neural, hormonal, behavioral, and field studies Dr. Soma demonstrated that neurosteroids can regulate nonbreeding season expression of androgen/estrogen-mediated behaviors, while avoiding the high costs of peripheral testosterone.

Now Dr. Soma and his graduate student, Kim Schmidt, have turned their focus towards glucocorticoids (GCs). GCs are thought to be integral to normal immune function (1, 8), with potentially profound effects on developing immune tissues (in birds: thymus, spleen, and bursa of fabricus). However, developing organisms are very sensitive to elevated circulating GCs, sensitive enough that neonates go through a "hyporesponsive period" to avoid the risk of elevated GCs interfering with growth and development (reviewed in Ref. 9). With the need for tissue-specific GC action independent of costly elevated peripheral levels, the possibility of extra-adrenal GC production arises. This question was examined in mice, with the identification of the enzymatic steps necessary for thymic GC production (22). In 2001, these same enzymes were identified in chicken thymus and bursa of fabricus (6). However, these studies again used in vitro methods to infer local GC production.

Schmidt and Soma (11) use an in vivo approach to examine the production of GCs in immune tissues. Through direct tissue measures of both cortisol and corticosterone, the authors demonstrate that immune tissues contain 16-fold higher GC levels than plasma. During development, plasma levels of cortisol and corticosterone range between 1 and 6 ng/ml. In the bursa of the neonate, however, GC levels reach near 50 ng/g (Figure 1). It is possible that endogenous levels are not locally produced but sequestered by immune tissues. However, I am unaware of any tissue that can sequester hormones at >10-fold plasma levels. Additionally, Schmidt and Soma have preliminary data, back in the dish, that these immune tissues produce cortisol and corticosterone in similar ratios as that found in vivo.

And surprisingly, the primary immunosteroid produced is cortisol. Each vertebrate class has a presumed primary GC (with few exceptions); in birds that GC is corticosterone. A Web of Science search using avian terms with corticosterone turned up ~1,200 references; the same search using "cortisol" found only five references.

Schmidt and Soma (11) have demonstrated not only the presence of cortisol in both immune tissues and plasma, but they clearly show that cortisol is the preferred GC for immune regulation during development. First, cortisol-to-corticosterone ratios are 10:1 in the postnatal bursa. Second, the effect is not limited to the bursa: later in development, the spleen and thymus have more than twofold greater cortisol compared to corticosterone. The authors propose that cortisol may be the more potent GC in regulation of immune tissue in birds. They suggest that elevated cortisol levels during development may suppress development of the adaptive arm of the immune system, therefore reserving energy available for growth. This suggestion is a bit premature for me, given the dose-specific effects of GCs on lymphocyte development. In the thymus low and high GC levels induce thymocyte apoptosis, but intermediate levels (in the presence of T cell receptor activation) will promote thymocyte survival. These data suggest that interaction of GCs and immune tissues will not be so easily summarized. However, given the data presented by Schmidt and Soma, it would behoove those of us studying avian GCs to consider inclusion of cortisol in future studies, looking for differential action of GCs based on GC type and tissue specificity.

The detail and precision Schmidt and Soma (11) use in their methods of hormone detection is impressive. It is common these days for labs to casually reference early Wingfield papers when discussing hormone assays. Schmidt and Soma take those papers to the mat, measuring GCs with precision and testing the validity of their results separately from the main focus of the manuscript.

In summary, Schmidt and Soma (11) suggest both local immunospecific production of GCs and cortisol-specific regu-

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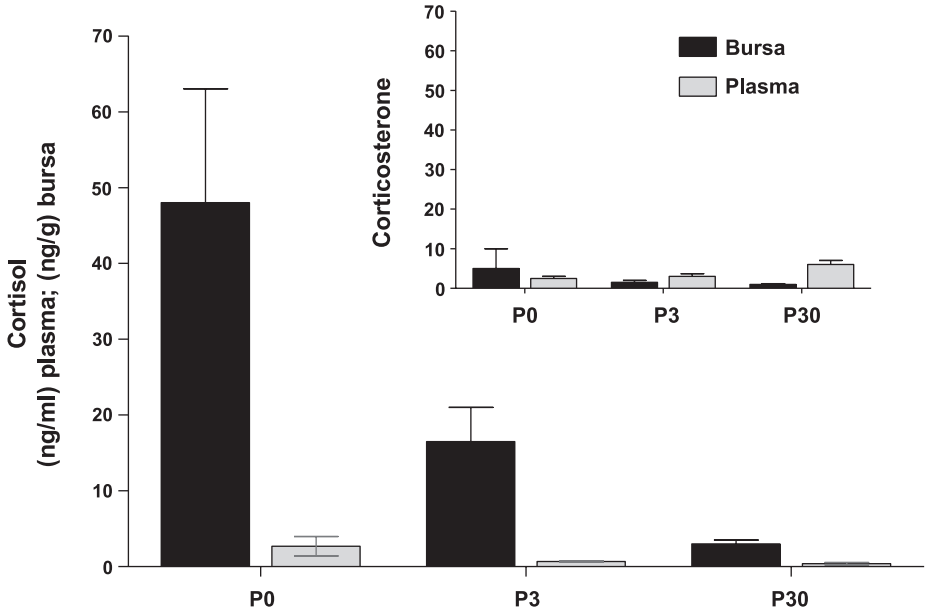

Fig. 1. Cortisol levels in immune tissue vs. circulating in the plasma over the first 30 days posthatch. Circulating cortisol levels (gray bars) are low to begin with (~3 ng/ml) and decline over development. Immune tissue (the bursa of fabricus: black bars) contains ~16-fold higher cortisol levels at hatch. *Inset*: in contrast, corticosterone levels in both immune and plasma remain comparatively low through development.

lation of immune function in birds. Once again, Soma is taking the field and turning it on its head.

Cortisol in birds? Immunosteroids? No way. Well, actually, yes.

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