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Minireview

Neurosteroids, immunosteroids, and the Balkanization of endocrinology

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ABSTRACT

Traditionally, the production and regulation of steroid hormones has been viewed as a multi-organ process involving the hypothalamic–pituitary–gonadal (HPG) axis for sex steroids and the hypothalamic–pituitary–adrenal (HPA) axis for glucocorticoids. However, active steroids can also be synthesized locally in target tissues, either from circulating inactive precursors or *de novo* from cholesterol. Here, we review recent work demonstrating local steroid synthesis, with an emphasis on steroids synthesized in the brain (neurosteroids) and steroids synthesized in the immune system (immunosteroids). Furthermore, recent evidence suggests that other components of the HPG axis (luteinizing hormone and gonadotropin-releasing hormone) and HPA axis (adrenocorticotropic hormone and corticotropin-releasing hormone) are expressed locally in target tissues, potentially providing a mechanism for local regulation of neurosteroid and immunosteroid synthesis. The balance between systemic and local steroid signals depends critically on life history stage, species adaptations, and the costs of systemic signals. During particular life history stages, there can be a shift from systemic to local steroid signals. We propose that the shift to local synthesis and regulation of steroids within target tissues represents a "Balkanization" of the endocrine system, whereby individual tissues and organs may become capable of autonomously synthesizing and modulating local steroid signals, perhaps independently of the HPG and HPA axes.

1. Introduction

1.1. HPG and HPA axes

Traditionally the hypothalamic–pituitary–gonadal (HPG) and hypothalamic–pituitary–adrenal (HPA) axes have been viewed as the sole sources of sex steroids and glucocorticoids (GCs), respectively. In the HPG axis, hypothalamic gonadotropin-releasing hormone (GnRH) stimulates the anterior pituitary to secrete gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), into the general circulation (Shally, 1978; Guillemin, 1978). In the gonads, gonadotropins stimulate synthesis of sex steroids such as testosterone (T), 17β-estradiol (E_2) and progesterone (PROG) (Fig. 1), which are secreted into the general circulation (Norris, 2007).

Similarly, in the HPA axis, hypothalamic corticotropin-releasing hormone (CRH) stimulates the anterior pituitary to release adrenocorticotropin hormone (ACTH) into the general circulation (Shally, 1978; Guillemin, 1978). In the adrenal glands, ACTH stimulates synthesis of GCs (e.g., cortisol, corticosterone) (Fig. 1), which are also secreted into the general circulation (Norris, 2007).

Thus, studies of sex steroids and GCs typically focus on levels in the blood (Newman et al., 2008a). Steroids are small, lipophilic molecules that can cross the plasma membrane and blood–brain barrier, and steroids in the blood reach cells throughout the body. Spatial specificity of steroid action has traditionally been thought to be determined by steroid receptor expression by target cells.

1.2. Local steroid synthesis

Steroids can also be synthesized locally, in at least three general ways. First, steroidogenic enzymes in target tissues can convert circulating hormones to more potent hormones locally (Fig. 2). For

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example, in the brain and other tissues, 5α-reduction of gonadal T produces a more potent androgen, 5α-dihydrotestosterone (Celotti et al., 1992). Gonadal T can also be converted to E_2 by aromatase in the brain (Naftolin et al., 1975; Cornil et al., 2006).

Second, steroids can be synthesized locally from circulating inactive precursors (prohormones) (Fig. 2). For example, dehydroepiandrosterone (DHEA) is a sex steroid precursor that does not bind with high-affinity to any intracellular steroid receptor (Widstrom and Dillon, 2004). DHEA can be secreted into the circulation by the gonads or adrenals and then converted to active sex steroids locally (Labrie et al., 2005; Schlinger et al., 2008). Similarly, deoxycorticosterone and deoxycortisol can be locally converted to corticosterone or cortisol, respectively, (Sippell et al., 1978; Chan and Phillips, 1973).

Third, steroids can be locally synthesized *de novo* from cholesterol (Fig. 2). For example, E_2 and cortisol may be synthesized *de novo* in the retina (Cascio et al., 2007; Zmijewski et al., 2007). All the GC-synthetic enzymes are also expressed in the skin (Slominski et al., 2007), lung (Provost and Tremblay, 2005), heart (Kayes-Wandover and White, 2000), and intestine (Cima et al., 2004). Here, we focus on two examples: (1) steroids synthesized in the nervous system (neurosteroids) (Corpechot et al., 1981; Tsutsui et al., 2006) and (2) steroids synthesized in the immune system (immunosteroids) (Vacchio et al., 1994; Matsuzaki et al., 2005).

2. Neurosteroids

2.1. Definition

Baulieu and colleagues detected high levels of DHEA and its esters in the brains of male rats, which have very low levels of DHEA in the blood (Corpechot et al., 1981). High levels of DHEA remained in the brain, even 15 days after gonadectomy and adrenalectomy (Corpechot et al., 1981). These results raised the hypothesis that DHEA is a "neurosteroid," synthesized locally in the brain (Corpechot et al., 1981). A strict definition of the term neurosteroid would require the steroid to be synthesized in the brain *de novo* from cholesterol. A less strict definition would also include steroids that are synthesized in the brain from circulating precursors (Mensah-Nayagan et al., 2001; Mellon and Vaudry, 2001).

2.2. Sex steroid synthesis in the brain: nonbreeding season

High circulating T levels are generally associated with aggression in the breeding season, particularly during social instability (Wingfield et al., 1990). However, some species are territorial year-round, even during the nonbreeding season when the gonads are regressed and plasma T levels are low (Demas et al., 2007; Soma and Wingfield, 1999; Soma et al., in press). For example, male song sparrows (*Melospiza melodia morphna*) display similar territorial behavior in response to simulated territorial intrusions during the breeding and nonbreeding seasons (Wingfield and Hahn, 1994). Castration has no effect on nonbreeding aggression (Wingfield, 1994). In contrast, aromatase inhibitors decrease nonbreeding aggression (Soma et al., 1999; Soma et al., 2000a,b). These results suggest that the steroids (particularly estrogens) regulating nonbreeding aggression are of non-gonadal origin (Soma et al., 2003, 2004a).

The prohormone DHEA is secreted by the adrenal glands in some vertebrates (Labrie et al., 2005). In nonbreeding song sparrows, circulating DHEA levels are elevated, and DHEA levels in the adrenals and gonads are very high (Soma and Wingfield 2001; Goodson et al., 2005a; Newman et al., 2008b). DHEA treatment during the nonbreeding season increases territorial singing behavior (Soma et al., 2002). Song sparrow and zebra finch *(Taeniopygia guttata)* brain tissue metabolize DHEA to active sex steroids

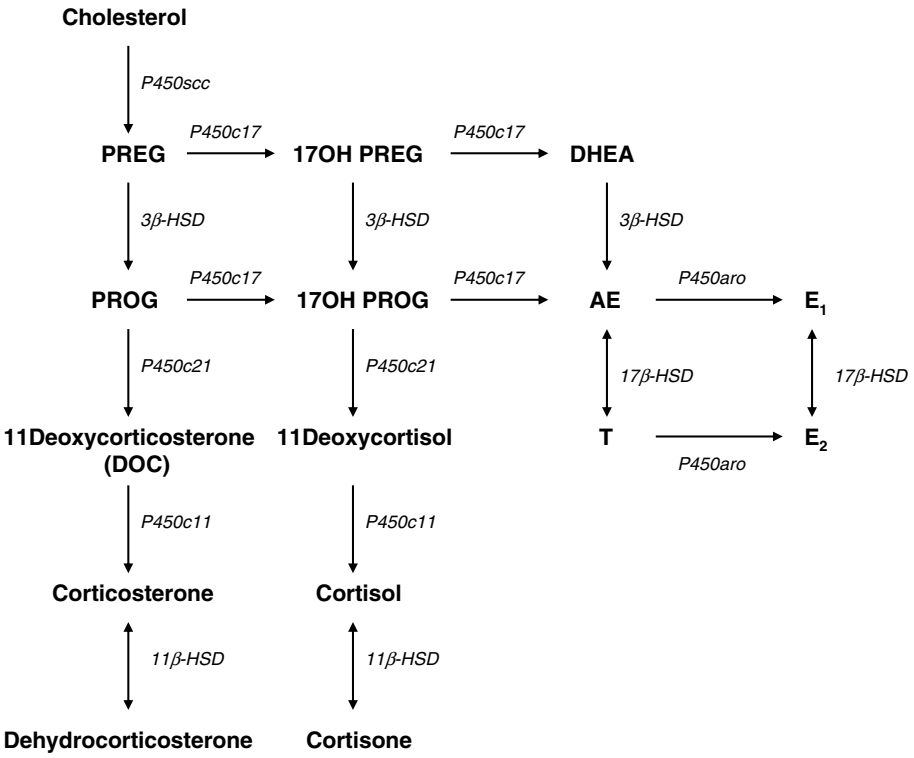

Fig. 1. Simplified diagram of steroid synthesis. Steroids are shown in bold and enzymes in italics. Steroids: PREG, pregnenolone; 17OH PREG, 17α-hydroxy-pregnenolone; DHEA, dehydroepiandrosterone; PROG, progesterone, 17OH PROG, 17α-hydroxy-progesterone; AE, androstenedione; T, testosterone; E_2, 17β-estradiol; E_1, estrone. Enzymes: P450scc, cytochrome P450 side chain cleavage; P450c17, cytochrome P450 17α-hydroxylase/17,20 lysase; 3β-HSD, 3β-hydroxysteroid dehydrogenase/isomerase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; P450aro, cytochrome P450 aromatase; P450c21, cytochrome P450 21α-hydroxylase; P450c11, cytochrome P450 11β-hydroxylase; 11β-HSD, 11β-hydroxysteroid dehydrogenase.