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Review

Regulation of local steroidogenesis in the brain and in prostate cancer: Lessons learned from interdisciplinary collaboration

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ABSTRACT

Sex steroids play critical roles in the regulation of the brain and many other organs. Traditionally, researchers have focused on sex steroid signaling that involves travel from the gonads via the circulation to intracellular receptors in target tissues. This classic concept has been challenged, however, by the growing number of cases in which steroids are synthesized locally and act locally within diverse tissues. For example, the brain and prostate carcinoma were previously considered targets of gonadal sex steroids, but under certain circumstances, these tissues can upregulate their steroidogenic potential, particularly when circulating sex steroid concentrations are low. We review some of the similarities and differences between local sex steroid synthesis in the brain and prostate cancer. We also share five lessons that we have learned during the course of our interdisciplinary collaboration, which brought together neuroendocrinologists and cancer biologists. These lessons have important implications for future research in both fields.

1. Introduction

Sex steroids, such as androgens, estrogens and progestins, play vital roles in regulating numerous physiological processes and behaviors, and they are implicated in a wide variety of diseases of the brain and reproductive system. The traditional view of sex steroid signaling involves their synthesis by classic steroidogenic organs (e.g., testes, ovaries) and their secretion into the systemic circulation to act on intracellular receptors in target organs, such as the brain, prostate gland and breasts (Schmidt et al., 2008; de Kloet et al., 1990). Emerging evidence, however, has demonstrated that organs previously thought of solely as targets of sex steroids are capable of local steroidogenesis, either from blood-borne prohormones (Schlinger and Arnold, 1991; Pradhan et al., 2008; George et al., 1991; Long et al., 2000) or *de novo* biosynthesis from cholesterol (Fig. 1) (Bennett et al., 2012; Cheng et al., 2010; Locke et al., 2008; Mellon and Deschepper, 1993). The relative importance of these locally-produced steroids is being increasingly recognized in a variety of disciplines, including neuroscience, reproductive physiology and oncology (Locke et al., 2008; Soma, 2006). As new functions are attributed to these local steroids, there is a greater need to understand their synthesis, regulation, and mechanisms of action. Interdisciplinary collaborations offer tremendous opportunities to address these large gaps in our knowledge.

1.1. Steroid synthesis in the brain

Insight into local steroidogenesis can be garnered from situations where target organs upregulate their steroidogenic capacity, particularly when the steroid supply from a peripheral source becomes limited. In the brain, "neurosteroids" were first described by Dr. Etienne-Emile Baulieu and colleagues (Corpechot et al., 1985; Zong et al., 1987; Jungtestas et al., 1989; Baulieu and Robel, 1990) and are now known to exhibit autocrine and

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paracrine effects on neural function, and these effects may be especially important when systemic steroid levels are low (Baulieu, 1998; Labrie, 1991).

For example, neural androgens and estrogens can be synthesized *de novo* from cholesterol or from systemic prohormones, such as dehydroepiandrosterone (DHEA) (Pradhan et al., 2008; Labrie et al., 2001; Labrie, 2003). Neural androgens and estrogens protect against neurodegeneration (Behl et al., 1995; Green et al., 1997; Sawada et al., 1998). In addition, neural androgens and estrogens might decrease the risk of Alzheimer's disease (Harkany et al., 1999; Butler et al., 2010), and some studies have shown lower circulating DHEA levels in patients with Alzheimer's disease (Aldred and Mecocci, 2010; Hillen et al., 2000). Both *in vivo* studies (Aly et al., 2011; Bastianetto et al., 1999) and *in vitro* studies (Danenberg et al., 1996) have demonstrated a neuroprotective role for DHEA. Circulating DHEA can maintain, at least partially, neural estrogen levels, even after systemic declines in ovarian estrogen synthesis with menopause. Similarly, neuroprotective roles have also been documented for other neurosteroids, such as allopregnanolone (Haraguchi et al., 2012). The transition from reliance on systemic steroids to local steroidogenesis is observed in both natural contexts and experimental manipulations, and might also be important following clinical interventions aimed at treating steroid-dependent diseases.

1.2. Steroid synthesis in the prostate gland and prostate cancer

In steroid-dependent cancers, the proliferation, survival, and metastasis of cancer cells require the activation of steroid signaling pathways (Risbridger et al., 2010; Jozwik and Carroll, 2012; Huggins and Hodges, 1941). These are typically cancers of the reproductive system: prostate and testicular cancer in men; and breast, ovarian and endometrial cancer in women. In these cancers, gonadal secretion of androgens, estrogens, and progestins can promote tumor development (Jozwik and Carroll, 2012; Huggins and Hodges, 1941). Common courses of treatment involve reducing systemic sex steroid levels via surgical gonadectomy, pharmacological suppression of the HPG axis, or pharmacological inhibition of steroidogenic enzymes. In addition, steroid receptor antagonists are commonly employed. These treatments often reduce tumor growth and metastatic potential (Kirby et al., 2009; Sharifi et al., 2010). However, as a rule in all advanced cancers, gonadectomy and HPG axis suppression are only effective in the short-term, because "resistance" to systemic steroid deprivation develops, with tumor advancement continuing until metastasis (Sharifi et al., 2005; Isbarn et al., 2009). In prostate cancer (PCa), tumor advancement is dependent upon the activation of the androgen receptor (AR), usually through the actions of the enzyme 5α-reductase, which converts systemic testosterone (T) to 5α-dihydrotestosterone (5α-DHT) (Andriole et al., 2004). Gonadotropin-releasing hormone (GnRH) receptor agonists and antagonists are regularly employed in androgen deprivation therapies (ADT) to reduce pituitary secretion of gonadotropins and thus reduce systemic T levels, resulting in remission (Wolff, 2009; Johnson et al., 2010; Labrie et al., 1985, 1986). Despite these treatments, an eventual resurgence of tumor growth ensues, which initially led to the idea of an "androgen-independent" PCa (Garde et al., 1993; Furuya et al., 1997). However, research has demonstrated that tumor growth following ADT is still highly androgen-dependent (Chen et al., 2008) and that tumor resurgence is, in part, the result of increased intratumoral steroidogenesis (from circulating cholesterol or DHEA) (Locke et al., 2008; Lubik et al., 2011; Pinski et al., 2011; Chang et al., 2013). Now referred to as "castration-resistant" PCa (CRPC), the tumor is capable of converting systemic DHEA to 5α-DHT (Chang et al., 2013) or capable of *de novo* steroidogenesis, including uptake of circulating cholesterols (Leon et al., 2010; Mostaghel et al., 2012). This increased capacity of PCa tumors to self-generate androgens in response to ADT has many similarities to neural steroidogenesis.

1.3. Neuroendocrinologists and Cancer Biologists can address the same question

Recently, our two research groups (the Soma laboratory and the Guns laboratory) have been working together on studies of local steroid production. During the course of our collaboration, we have learned a great deal about differences in the conceptual approaches and technical methodologies that our fields employ to address the same question: *"How does an organ or tissue decrease its reliance on systemic steroids and increase its reliance on locally-produced steroids?"* Here, we review (a) sex steroid synthesis in the brain, with an emphasis on its behavioral roles, and (b) sex steroid synthesis in the healthy prostate and prostate carcinoma. We highlight similarities and differences between steroidogenesis in

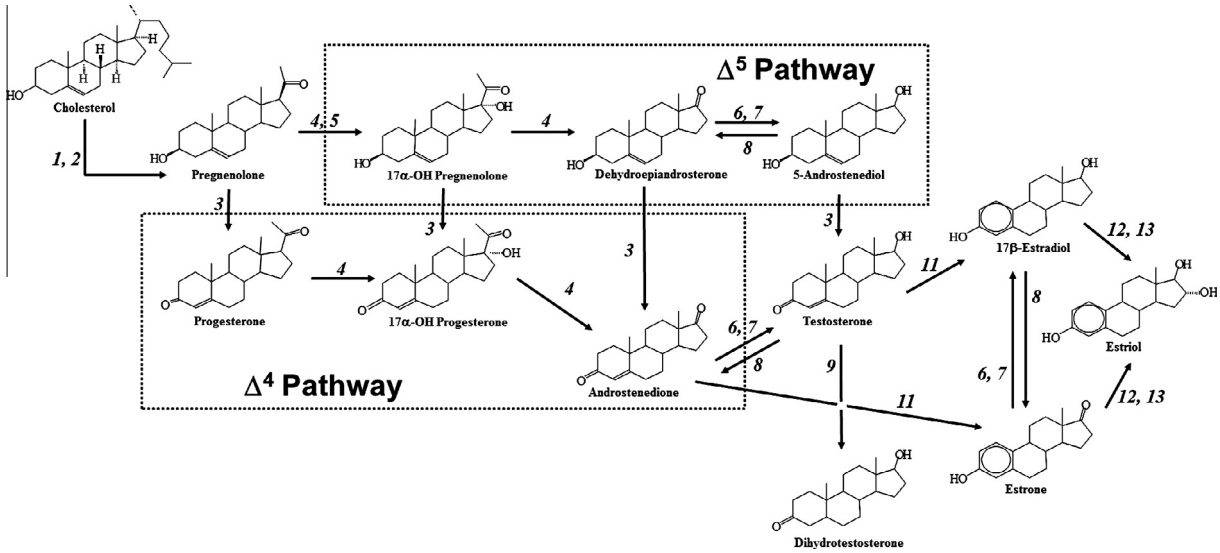

Fig. 1. Classic androgen and estrogen synthesis pathways with relevant numbered proteins and enzymes identified by their human gene names: (1) StAR, (2) CYP11A1, (3) HSD3B2, (4) CYP17A1, (5) CYB5A, (6) AKR1C3, (7) HSD17B3, (8) HSD17B2, (9) SRD5A1, (10) AKR1C2, (11) CYP19A1, (12) CYP1A2; and (13) CYP3A4.

the brain and prostate. We also identify several key lessons that neuroendocrinologists and cancer biologists can learn from each other, which have great potential to influence their respective research programs. By identifying common mechanisms that enable different tissues to shift the balance between the roles of systemic steroids and locally-produced steroids, we can begin to develop a broad framework for understanding steroid signaling at the organismal level.

2. Steroidogenesis in the brain

2.1. Evidence for local steroid synthesis in the brain

Sex steroids are essential for the development and function of the central nervous system in all vertebrates (Micevych and Hammer, 1995; Adkins-Regan, 2005). Traditionally, the brain was viewed as a recipient of circulating sex steroids that came primarily from the gonads. This view was supported by a large body of evidence, beginning with the castration experiments in chickens conducted by Arnold Berthold in 1849, who is considered one of the founders of endocrinology (Soma, 2006). The identification of the enzyme cytochrome P450 aromatase (AROM) in the brain in 1975 demonstrated that the brain is capable of converting T to estradiol (E_2) (Naftolin et al., 1975). The identification of 5α-reductase (and 5β-reductase) in the brain indicated alternate pathways for T metabolism within the brain (Celotti et al., 1992). Mapping of the distributions of both AROM and 5α-reductase within evolutionarily-conserved brain regions suggest fundamental roles for these enzymes. These observations no longer portrayed the brain as a simple recipient of gonadal sex steroids, but still suggested that the brain can only metabolize T that was synthesized within the gonads.

Later studies demonstrated that the androgen precursor DHEA can be secreted from the adrenal glands and metabolized to active sex steroids (T, 5α-DHT, and E_2) within specific brain regions (e.g., hypothalamus, hippocampus) that possess the necessary steroidogenic enzymes, a phenomenon known as "intracrinology" (Labrie, 1991; Labrie et al., 2005, 1988). In humans, DHEA and its sulfated ester (DHEAS) are synthesized in abundance by adrenocortical cells (Labrie et al., 2005; Rainey et al., 2002; Thijssen and Nieuwenhuyse, 1999; Beck and Handa, 2004). Although DHEA can bind with very low affinity to AR or estrogen receptors (ER) (Mo et al., 2004, 2006; Widstrom and Dillon, 2004), DHEA appears to lack a specific high-affinity intracellular steroid receptor (Labrie et al., 2005). However, DHEA can be readily converted to androgens or estrogens locally and thus influence neural activity. For such reasons, sex steroid levels in the blood do not always reflect levels in the brain (Taves et al., 2011; Hojo et al., 2011) and gonadectomy does not always eliminate sex steroids from some brain regions (Okamoto et al., 2012; Fester et al., 2011). Indeed, gonadectomy may lead to compensatory increases in neurosteroid synthesis to maintain local steroid levels (Ye et al., 2008).

In addition, the brain is capable of *de novo* steroidogenesis from cholesterol (Fig. 1) (Corpechot et al., 1985; Mellon and Griffin, 2002; Do Rego et al., 2009a; Compagnone et al., 2000). The brain is the most cholesterol-rich organ, containing about 20% of the body's total cholesterol (Orth and Bellosta, 2012), and the brain also expresses all the steroidogenic enzymes necessary for *de novo* steroid production (Corpechot et al., 1985; Mellon and Griffin, 2002; Do Rego et al., 2009a). There are two possible sources of cholesterol for neurosteroidogenesis: cholesterol esters bound to circulating lipoproteins, and unesterified cholesterol within myelin and plasma membranes (Korade and Kenworthy, 2008). As cholesterol bound to circulating lipoproteins cannot cross the blood–brain barrier (Mortaud and Degrelle, 1996; Moutafis, 2002), neurosteroidogenesis is thought to rely on the latter source, although further studies are required. The rate-limiting step in steroid biosynthesis is regulated by the steroidogenic acute regulatory protein (StAR), which mediates the transport of cholesterol to the inner mitochondrial membrane, where it can be converted to pregnenolone by cytochrome P450 side-chain cleavage (P450scc or CYP11A1) (Fig. 1) (Stocco, 2000). Within the brain, StAR is expressed by both neurons and glia (King et al., 2004; Samson, 2003) in specific regions (King et al., 2002).

These discoveries have fundamentally altered our perspective on steroid regulation of behavior, as they shift the focus from systemic steroid levels in the blood to local steroid levels within specific brain regions and circuits. Furthermore, these discoveries have helped to understand some novel roles for sex steroids, such as the rapid effects of brain E_2 (Charalampopoulos et al., 2008; Chen et al., 2007; Veiga et al., 2004). Note that a few studies have demonstrated that the brain is also capable of synthesizing glucocorticoids and aldosterone (Taves et al., 2011). Many studies have examined the distributions of steroidogenic enzymes (mRNA, protein or activity) within the brains of diverse vertebrates: teleost fish (Arukwe, 2005; Diotel et al., 2011; Hinfray et al., 2006; Mathieu et al., 2001; Nagarajan et al., 2013; Tomy et al., 2007); amphibians (Bruzzone et al., 2010; Do Rego et al., 2009b; Vaudry et al., 2005; Inai et al., 2003); reptiles (Dias et al., 2009; Endo et al., 2008; Willingham et al., 2000); birds (Soma et al., 2003; London and Clayton, 2010; London and Schlinger, 2007; Tam and Schlinger, 2007), and mammals (Yan et al., 2010; Zwain and Yen, 1999; Gottfried-Blackmore et al., 2008; Stromstedt and Waterman, 1995; Petratos et al., 2000), including humans (Pezzi et al., 2003; Stoffel-Wagner, 2001; Yu et al., 2002). Overall, the expression of steroidogenic enzymes in the brain appears to be higher in non-mammalian species than the mammalian species examined (primarily rats, mice, and humans). Higher expression levels facilitate studies of neurosteroidogenic enzymes in non-mammalian animal models. In general, the neural distributions of these enzymes suggest diverse roles, including the regulation of social behavior, sensory processing, neurogenesis, and learning and memory. However, we still have a limited understanding of the relative importance of steroids produced from circulating precursors vs. steroids synthesized *de novo* within the brain. Moreover, many important questions remain regarding how neurosteroid synthesis is influenced by physiological, environmental, and social cues.

2.2. Neuroendocrine regulation of neurosteroid sysnthesis

Neurosteroids are synthesized in the central and peripheral nervous systems not only by neurons, but also by astrocytes, radial glia, microglia, and oligodendrocytes (Zwain and Yen, 1999; Jung-Testas and Baulieu, 1998; Jung-Testas et al., 1999; Guennoun et al., 1995; Robel and Baulieu, 1995; Sanne and Krueger, 1995; Furukawa et al., 1998; Kohchi et al., 1998; Ukena et al., 1998; Sinchak et al., 2003; Garcia-Ovejero et al., 2005; Rune and Frotscher, 2005; Micevych et al., 2007; Forlano et al., 2001; Menuet et al., 2003; Diotel et al., 2011a,b; Mensah-Nyagan et al., 1996a,b). These different cell types may show some specificity in the steroidogenic enzymes that they express; however, there is wide variation across species and contexts (e.g., *in vivo* vs. *in vitro*; uninjured vs. injured brain; young vs. old animals) (Zwain and Yen, 1999; Jung-Testas et al., 1999; Guennoun et al., 1995; Sanne and Krueger, 1995; Sinchak et al., 2003; Micevych et al., 2007; Robel and Baulieu, 1994).

The regulation of neurosteroid synthesis within these different cell types is not well understood. There is evidence for multiple feedback systems, including feedback by gonadal sex steroids, pituitary gonadotropins, and GnRH (Meethal et al., 2009). For

example, in adult female mice, ovariectomy regulates the processing of StAR in the extrahypothalamic brain, in a manner consistent with greater transport of cholesterol into mitochondria. That is, ovariectomy appears to increase StAR activity and the capacity for *de novo* steroidogenesis in the brain. Furthermore, treating ovariectomized mice with E_2 or progesterone appears to reduce StAR activity in the extrahypothalamic brain (Meethal et al., 2009). These and other data (see Sections 2.4 and 2.5) indicate that in many cases, gonadal sex steroids downregulate neurosteroid synthesis. Thus, neurosteroid synthesis is typically higher when circulating sex steroid levels are low (e.g., after castration, before reproductive maturity, during aging, and outside of the breeding season in seasonally-breeding animals). In this way, neural production of sex steroids can potentially compensate for, or at least partially offset, reductions in gonadal production of sex steroids.

In the same mouse study described above, suppressing high gonadotropin levels in ovariectomized mice with leuprolide acetate, a long-acting GnRH receptor agonist, also appears to decrease StAR activity in the brain (Meethal et al., 2009). These data raise the interesting question of whether gonadotropins or GnRH also regulate neurosteroid synthesis, in a similar or complementary manner to how these hormones regulate gonadal steroid synthesis. There is increasing support for this possibility. First, there are some extrahypothalamic neurons that express GnRH (Kubek et al., 1979; Powell et al., 1987; Chieffi et al., 1991; Muske et al., 1994; Kim et al., 2007; Stevenson et al., 2007; Zhao and Wayne, 2012; McGuire et al., 2013), GnRH receptors (Wilson et al., 2006), or LH receptors (Liu et al., 2007). Second, *in vitro* studies have demonstrated that administering GnRH or LH upregulates expression of StAR (Liu et al., 2007; Rosati et al., 2011) and steroidogenic enzymes in neural cells (Rosati et al., 2011). Third, some GnRH neurons project to areas of the brain that are not part of the HPG axis (Merchenthaler et al., 1984; Merchenthaler and Petrusz, 1982). Fourth, other mediators of the HPG axis are present in brain regions that produce neurosteroids, including gonadotropin-inhibitory hormone (GnIH) (Ukena et al., 2003; Bentley et al., 2007; McGuire et al., 2013), kisspeptin (Franceschini et al., 2006; Estrada et al., 2006; Shimizu et al., 2012; Cao and Patisaul, 2013), and vasoactive intestinal peptide (VIP) (Gerhold and Wise, 2006).

Several other neuropeptides also modulate neurosteroid synthesis within the frog hypothalamus, including vasotocin and mesotocin (Do-Rego et al., 2006) as well as triakontatetraneuropeptide (TTN) and octadecaneuropeptide (ODN) (Do-Rego et al., 1998, 2001). Furthermore, studies of frog hypothalamic explants have demonstrated that several steroidogenic enzymes are directly inhibited by the neurotransmitter γ-aminobutyric acid (GABA) (Do-Rego et al., 2000).

2.3. Stress and DHEA

Much remains to be understood regarding the regulation of *de novo* neurosteroid synthesis. In contrast, more research has examined the production of circulating sex steroid precursors (or prohormones) that can be converted to active steroids within the brain. Among the best-studied of such prohormones is DHEA. In humans, the main source of circulating DHEA and DHEA-sulfate is the zona reticularis of the adrenal cortex, with much smaller amounts secreted from the testes (Alesci and Bornstein, 2001) or ovary (Labrie et al., 2011). In humans, circulating DHEA concentrations increase in response to acute stress (Lennartsson et al., 2012; Sugaya et al., 2012; Oberbeck et al., 1998), adrenocorticotropin hormone (ACTH) challenge (Lanfranco et al., 2004; Lombardi et al., 2004; Maccario et al., 2000; Arvat et al., 2000) and corticotropin-releasing hormone (CRH) challenge (Ibanez et al., 1999). Furthermore, CRH increases DHEA synthesis by human adrenal cells *in vitro* (Parker et al., 1999). Similarly, in a field study, red squirrels (*Tamiasciurus hudsonicus*) demonstrated a rapid increase in plasma DHEA levels in response to ACTH challenge (Boonstra et al., 2008). In rats, DHEA levels in the plasma are low, but acute restraint stress or ACTH challenge increase DHEA levels in the brain (Corpechot et al., 1981; Torres and Ortega, 2003). In song sparrows (*Melospiza melodia*), acute restraint stress has season-specific effects on plasma DHEA concentrations, indicating a strong seasonal component to stress responsivity (Newman et al., 2008). Interestingly, these effects of restraint stress were seen when DHEA concentrations were measured from the jugular vein but not from the brachial vein (Newman et al., 2008). In songbirds, plasma from the jugular vein is enriched with neurally-synthesized steroids (Schlinger and Arnold, 1991; Saldanha and Schlinger, 1997).

Generally, DHEA has anti-glucocorticoid effects (Muller et al., 2006) and ameliorates several of the negative effects of chronically high glucocorticoids on the brain (Bastianetto et al., 1999; Muller et al., 2006; Boudarene et al., 2002; Yotsuyanagi et al., 2006; Wolf et al., 1998; Newman et al., 2010; Karishma and Herbert, 2002; Kimonides et al., 1998, 1999). This neuroprotective role is highlighted by considering that in humans, systemic DHEA(S) concentrations follow a complex age-related profile, including an increase just before puberty ("adrenarche") (Nawata et al., 2004; Auchus, 2004; Miller, 2009) and a decline that starts at about 30 years (Alesci and Bornstein, 2001; Nawata et al., 2004; Labrie et al., 1997). This DHEA secretion profile parallels many neural changes, such as adrenarche coinciding with rapid maturation of the cerebral cortex (Gogtay et al., 2004). During aging, the decline in circulating DHEA levels and the concomitant rise in circulating glucocorticoid levels may contribute to age-related changes in cognition and neural structure, including neurodegeneration. The anti-glucocorticoid and neuroprotective effects of DHEA likely involve its conversion to active sex steroids within the brain, although this remains to be directly tested.

2.4. Energy balance and DHEA

DHEA is also considered an anti-obesity agent (Berdanier et al., 1993; Clore, 1995) and studies in both humans and rodents have shown that DHEA protects against various aspects of metabolic syndrome, including cardiovascular disease (Yorek et al., 2002a,b), atherosclerosis (Alexandersen et al., 1999; Kanazawa et al., 2008; Nestler et al., 1992; Slowinskasrzednicka et al., 1995; Yamakawa et al., 2009), insulin resistance (Roberge et al., 2007; Aragno et al., 1999; Perez-de-Heredia et al., 2008; Ishizuka et al., 2007; de Heredia et al., 2009; Hansen et al., 1997), and diabetes mellitus (Yorek et al., 2002a; Pesaresi et al., 2010). Exogenous DHEA can lower circulating levels of glucose (Ishizuka et al., 2007; Mukasa et al., 1998; McIntosh and Berdanier, 1991), insulin (Nestler et al., 1992; de Heredia et al., 2009; Mukasa et al., 1998), and lipids (Clore, 1995; de Heredia et al., 2009). Rodent studies have also shown that exogenous DHEA can both increase (Flatt and Faircloth, 1998) and, more often, decrease food intake (Wright et al., 1995; Navar et al., 2006; Reddy and Kulkarni, 1998; Pham et al., 2000), as well as affect food preferences (Pham et al., 2000; Svec et al., 1995; Wright et al., 1994).

Energetic status influences both peripheral and central DHEA concentrations. Circulating DHEA concentrations are increased by caloric restriction. For example, in zebra finches (*Taeniopygia guttata*), an acute 6 h fast decreases body mass by 8% and increases systemic DHEA levels in plasma from the brachial vein (Fig. 2A) (Fokidis et al., 2013). Refeeding (for only 15 min) causes DHEA levels to normalize (i.e., to resemble those of a control group fed *ad libitum*) (Fokidis et al., 2013). Long-term caloric restriction increases circulating DHEA levels in rhesus macaques (Lane et al., 1997) and may increase lifespan in this species (Lane et al., 1997; Abbott and Bird, 2009; Goncharova and Lapin, 2004;

Sorwell et al., 2012). Although the adrenal glands are the likely source for this increase in DHEA, the contributions of other organs remain understudied. In particular, during prolonged fasting in mice, several steps in DHEA synthesis are upregulated within the liver. Hepatic cholesterol uptake and hepatic expression of CYP17A1 (the enzyme that synthesizes DHEA from pregnenolone) are increased during fasting (Grasfeder et al., 2009; Bauer et al., 2004). Concurrently, hepatic enzymes involved in cholesterol conversion to bile acids are downregulated (Bauer et al., 2004). The overall result is an increase in hepatic DHEA synthesis, and DHEA can exert intracrine effects within the liver or potentially be secreted into the general circulation. In zebra finches, an acute fast increases DHEA levels in both the adrenals and the liver (Fig. 2A). Refeeding lowers DHEA levels in the adrenals and liver back to baseline levels (Fokidis et al., 2013). These data raise the possibility that hepatic DHEA secretion during fasting contributes to the circulating and neural steroidal milieu (Fig. 2B), with potential effects on the brain and behavior. Energy expenditure can also affect DHEA levels. Exercise increases circulating DHEA(S) in humans (Copeland et al., 2004; Copeland and Tremblay, 2005; Filaire et al., 1998) and increases DHEA synthesis by skeletal muscle in humans and rats (Aizawa et al., 2010; Sato et al., 2011). Thus, DHEA levels are sensitive to shifts in energy balance, and this may have implications for its role as a neurosteroid.

The energetic and metabolic effects of DHEA suggest interactions with metabolic hormones within the brain. Hydroxysteroid sulfotransferase (HST) is the enzyme that transfers a sulfonate moiety onto the acceptor site of DHEA or pregnenolone, to form DHEAS or pregnenolone-S, respectively (Vaudry et al., 2005). In hypothalamic explants from European green frogs (*Rana ridibunda*), administration of neuropeptide Y (NPY), an orexigenic peptide, acts via the Y_1 receptor to inhibit HST activity, thus reducing neural DHEAS and pregnenolone-S synthesis (Beaujean et al., 2002). This observation is consistent with the neuroanatomical distribution of NPY and HST in this species, where substantial overlap is seen in the anterior preoptic area and the dorsal magnocellular nucleus, areas involved in social behavior (Beaujean et al., 1999; Danger et al., 1985). Recent evidence suggests that GnRH has the opposite effect and stimulates neural DHEAS and pregnenolone-S synthesis (Burel et al., 2013), thus providing a potential link between energy balance and reproduction.

In Zucker rats, NPY promotes over-eating but this effect is blocked by co-administration of DHEA (Navar et al., 2006). This inhibitory effect of DHEA is complex, but may involve actions on serotonergic signaling in the arcuate nucleus or ventromedial hypothalamus (VMH). Administering DHEA increases the firing rate of serotonergic neurons in the dorsal raphe nucleus (Robichaud and Debonnel, 2004) and increases hypothalamic serotonin levels in obese Zucker rats (Abadie et al., 1993; Porter et al., 1995). These effects of DHEA on NPY and serotonin signaling are likely mediated through its conversion to an active sex steroid such as T or E_2. These interactions among serotonin, NPY and DHEA may have implications for behaviors other than food intake, including aggression.

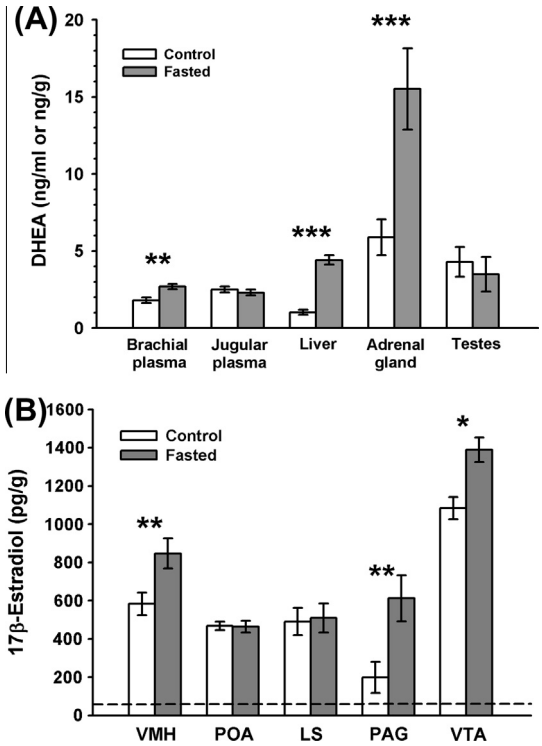

Fig. 2. (A) DHEA concentrations in plasma from the brachial vein and jugular vein, as well as in liver, adrenal glands, and testes of adult male zebra finches. (B) E_2 concentrations in microdissected brain regions of the social behavior network in adult male zebra finches. These brain regions include the ventromedial hypothalamus (VMH); medial preoptic area (POA); lateral septum (LS); periaqueductal gray (PAG); and the ventral tegmental area (VTA). The dashed line shows the E_2 level in the plasma. Control subjects received food *ad libitum*, and fasted subjects did not receive food for 6 h. Data shown as mean ± standard error, with $* \; p < 0.05$, $** \; p < 0.01$, and $*** \; p < 0.001$. Modified from Fokidis et al. (2013).

2.5. Territorial aggression: a natural transition from systemic to local steroid signaling

The neuroendocrine regulation of aggression (or aggressivity) has been a major focus of research. In particular, the regulation of male aggression in reproductive contexts by gonadal T is well-established, as is the aromatization of T to E_2 within the relevant neural circuits. Most research on the neuroendocrine regulation of aggression has been done using inbred laboratory rodents (Barkley and Goldman, 1978; Hammour et al., 1985; Haug et al., 1986; Albert et al., 1992; Bonson and Winter, 1992; Clark and Barber, 1994; Bonson et al., 1994; McGinnis, 2004). Despite the invaluable contributions of such studies, complementary and critical insights have been gained through comparative research on other vertebrates. In particular, birds (especially songbirds) have emerged as major model systems for investigating the behavioral functions of steroids synthesized within the brain, due in part to higher levels of neurosteroidogenesis in birds compared to mammals (Charlier et al., 2010b, 2011; Taves et al., 2010; Overk et al., 2013; Hojo et al., 2004), robust seasonal changes and species differences in aggressive behavior, and the extensive neuroplasticity of androgen- and estrogen-sensitive brain regions that regulate social behavior (Bernard et al., 1999; Tramontin and Brenowitz, 2000; Smith et al., 1997, 1995; Wacker et al., 2010).

A series of studies has examined neural steroid synthesis and territorial aggression in male song sparrows (*Melospiza melodia*) of the Pacific coast of North America. In these animals, territorial aggression toward conspecifics during a simulated territorial intrusion (STI) is qualitatively and quantitatively similar in the spring breeding season (when circulating T is high) and the winter non-breeding season (when circulating T is low) (Wingfield and Hahn, 1994; Mukai et al., 2009; Newman and Soma, 2011). Circulating E_2 levels are very low throughout the year in male song sparrows. Nonetheless, year-round aggression in this species is dependent on E_2 signaling within relevant brain circuits. Treatment with the steroidal aromatase inhibitor ATD in combination with the AR antagonist flutamide reduces aggression in the non-breeding season (Soma et al., 1999), but treatment with flutamide alone has no effect on this species (Sperry et al., 2010) or another songbird species (Schwabl and Kriner, 1991). Acute or chronic administration of

a potent non-steroidal aromatase inhibitor, fadrozole, also reduces aggression in the non-breeding season (Soma et al., 2000a,b), and E_2 replacement rescues the effects of fadrozole (Soma et al., 2000a). Furthermore, E_2 treatment of non-breeding male sparrows increases the size of a brain region associated with song production, HVC (abbreviation used as proper name), to a size typical of breeding males (Soma et al., 2004a).

There is no seasonal variation in mRNA for ERα or ERβ in multiple brain regions that regulate aggression, including the preoptic area, nucleus taeniae of the amygdala, and the ventromedial hypothalamus (VMH) (Wacker et al., 2010). These data suggest that non-breeding animals are not simply more sensitive to neurally-synthesized E_2. Gonadal T is the obvious substrate for brain aromatase during the breeding season, but in the non-breeding season, the regressed testes and very low circulating T and androstenedione levels suggest an alternate mechanism. One possible mechanism is neural metabolism of circulating DHEA. In the non-breeding season, DHEA circulates in the plasma at levels much higher than those of T or androstenedione, and further, plasma DHEA levels are specifically reduced during the annual molt, when aggression is also reduced (Soma and Wingfield, 2001). The source(s) of circulating DHEA in non-breeding song sparrows might be the regressed testes, adrenal glands and/or the liver, which all have substantial DHEA content (Newman and Soma, 2011, 2009; Soma and Wingfield, 2001).

Chronic DHEA administration to non-breeding song sparrows increases both aggressive singing in response to STI (Soma et al., 2002) and HVC size (Soma et al., 2002; Newman et al., 2010), similar to the effects of T and E_2 administration. The enzyme 3β-hydroxysteroid dehydrogenase/isomerase (3β-HSD), which converts DHEA to androstenedione, is abundant in the songbird brain (Schlinger et al., 2008; Soma et al., 2004b) and its activity is upregulated during the non-breeding season compared to the breeding season (Pradhan et al., 2010a). Interestingly, this seasonal change is observed in some of the same brain regions where aromatase activity is also high in the non-breeding season (Soma et al., 2003). Further studies in non-breeding song sparrows demonstrate that 3β-HSD activity in portions of the telencephalon rapidly (within 30 min) increases in response to STI and is positively correlated with one measure of aggressive behavior (Pradhan et al., 2010a). Importantly, this effect of STI on 3β-HSD activity is only observed if exogenous NAD^+ (the cofactor for 3β-HSD) is not added during the assay, whereas if NAD^+ is added at saturating levels, then no effect of STI is observed (Pradhan et al., 2010a). This result suggests that cofactors such as NAD^+ may play important roles in the rapid modulation of neural steroidogenic enzymes, or that STI may only influence 3β-HSD in NAD^+ rich subcellular compartments such as the mitochondria (Pradhan et al., 2010a,b). Thus, in this species, the neural metabolism of DHEA appears important in the maintenance of aggression outside of a breeding context.

DHEA may maintain non-breeding aggression in other species, including Siberian hamsters (*Phodopus sungorus*) (Scotti et al., 2009), spotted antbirds (*Hylophylax naevioides*) (Hau and Beebe, 2011; Hau et al., 2004), and alligators (*Alligator mississippiensis*) (Hamlin et al., 2011). Furthermore, recent studies on zebra finches have used a fasting and refeeding paradigm to elicit aggression over access to food. In these studies, increases in circulating DHEA levels with fasting are accompanied by increases in E_2 levels in specific brain nuclei (VMH, VTA, periaqueductal gray (PAG)) that regulate both social behavior and energy balance (Fig. 2B; Fokidis et al., 2013). These data suggest that aggression in different contexts may involve DHEA and its neural metabolism to E_2. Future studies should also examine the role of *de novo* neurosteroidogenesis, since the avian brain expresses all the enzymes for the synthesis of androgens and estrogens (Tsutsui et al., 2006; Schlinger and Remage-Healey, 2011).

Shifting from a reliance on gonadal steroid synthesis during the breeding season to an increased reliance on neural steroid synthesis during the non-breeding season may have evolved to avoid the costs of high circulating T levels during the winter (Wingfield et al., 2001), including immunosuppression (Owen-Ashley et al., 2004), maintenance of energetically costly (and inappropriate) secondary sexual characteristics and sexual behaviors, and depletion of energy reserves required to survive low ambient temperatures and limited food availability (Ketterson et al., 1991; Wikelski et al., 1999). The last factor may explain why unpredictable food availability (e.g., fasting), which increases glucocorticoids (Fokidis et al., 2011, 2012) and decreases T in the blood (Deviche et al., 2010), nonetheless increases circulating DHEA levels (Berdanier et al., 1993). DHEA is a relatively inactive prohormone in the general circulation that can be rapidly converted, and thus activated, within specific brain regions to influence behavior.

3. Steroidogenesis in the prostate gland

3.1. Steroid signaling in the normal prostate gland

As the principal circulating androgen in mammalian males, T is found at concentrations of 10–30 nmol/L in human serum. In contrast, 5α-DHT circulates at much lower concentrations (0.5–2.5 nmol/L), and yet it is the most potent ligand of AR in the prostate (Isaacs, 1994; Cunha et al., 2004). Androgen target tissues, such as the prostate and brain, accomplish the local biotransformation of T to 5α-DHT via the 5α-reductase enzymes (Hayward and Cunha, 2000), and other tissues able to perform this conversion include the lungs, adipose tissue, blood cells, skin, mammary glands, endometrium and hair. Still other tissues see a predominance of T due to the fact that they lack 5α-reductase.

Both T and 5α-DHT are required for normal prostate development and function in humans. They are the natural ligands for the AR, which recognizes 5α-DHT with a 10-fold higher affinity than T. The prostate is a male sex gland that has an exocrine secretory role, supporting sperm function and motility during reproduction. Prostate development *in utero* is initiated upon androgen stimulation of the AR in the urogenital sinus mesenchyme (UGM), supporting the differentiation of stem cells in the UGM. At birth, the human prostate is 1–2 g, and after puberty, when further androgen action matures the organ for reproduction, it is approximately 20 g (Tysnes and Bjerkvig, 2007; Moltzahn et al., 2008). It is located at the base of the penis and internally envelops the urethra. Its secretions are combined with sperm from the testes to form semen ejaculate, and these secretions support semen gelation, coagulation and liquefaction, which are required to fertilize an ovum. AR-mediated signaling events brought about by T and 5α-DHT action promote the secretion of various growth factors, including keratinocyte growth factor (KGF) and fibroblast growth factor (FGF), in the UGM where they act on stem cells to specifically impact epithelial cell proliferation. Thereafter, during both development and pubertal maturation, through a series of androgen-dependent epithelial–mesenchymal interactions (Cunha, 1996; Thomson, 2001; Condon, 2005), the prostate organ's glandular structure is formed and subsequently grows (during puberty) via proliferation of distinct cellular subsets including fibroblasts, smooth muscle and endothelial mesenchymal stromal cells as well as luminal secretory, basal and neuroendocrine epithelial cells (Moltzahn et al., 2008; Hayward et al., 1997; Cunha et al., 2002; Cunha, 2008).

In the mature adult male, T is bound in the circulation to albumin, sex hormone binding globulin or other binding proteins (Cunha, 1996). Unbound free T enters cells of the prostate and is then converted to 5α-DHT, which binds to the AR and activates the transcription of hundreds of genes involved in the regulation

of the cell cycle and the production of proteins necessary for survival, growth, proliferation and function of the normal prostate gland (Long et al., 2005; Isaacs, 1996).

3.2. Steroid signaling in prostate cancer

Malignancy occurs as the result of a series of irregular cell growth cues that cause abnormal cell cycling and cell growth dysregulation, wherein an apparently 'normal' cell starts to grow uncontrollably and invade surrounding tissues, establishing a potential for distant metastases (Hanahan and Weinberg, 2000). An abundance of growth factors that act to disrupt the mesenchymal–epithelial equilibrium, along with an acquired loss or 'silencing' of tumor suppressor proteins, causes a shift in cellular growth homeostasis and ultimately contributes to prostate cancer (PCa) emergence (Moltzahn et al., 2008; Isaacs et al., 1982; Isaacs, 1995).

Activation of AR by T and/or 5α-DHT within an abnormal stromal microenvironment ultimately drives a malignant phenotype. Extraordinarily, from a single epithelial stem cell, a heterogeneous tumor population can arise. This stem cell characteristically is present within the stromal microenvironment, having ordinarily been destined for differentiation into a basal or luminal secretory cell (Cunha, 2008; Long et al., 2005; Cunha et al., 2003). The contribution of unchecked AR to cell growth signaling in a predisposed stromal microenvironment is likely to be a factor that continues to drive PCa, evoking a forced path of transiency with respect to growth regulation, leading to an instability that evades normal checkpoints and fuels cancer progression as a frenzied pro-survival status within a tumor population.

For many years, we have known that reducing circulating androgens can cause regression in prostate tumor growth, which varies for individual patients with respect to the length of sustained response (Huggins and Hodges, 1941; Huggins, 1967). Eventually, the emergence of resistance to castration and the development of castration-resistant prostate cancer (CRPC) is inevitable and almost without exception lethal. Surgery or radiation are therefore 'standard of care' for organ-confined PCa, and the use of androgen deprivation therapies is generally applied only in advanced cases of PCa in an attempt to control androgen-sensitive metastatic cancer. Importantly, the development of CRPC is, in part, the result of increased intraprostatic androgen synthesis within the tumor tissue itself, including increased conversion of circulating DHEA(S) to androgens as well as *de novo* androgen synthesis (Locke et al., 2008; Fung et al., 2006; Penning et al., 2007; Bauman et al., 2006; Chang et al., 2013). Studies of responses to castration, in both human tissues and mice bearing human tumor xenografts, demonstrate a distinct upregulation of steroid synthesis machinery with increased androgenic steroid profiles in prostate tumor tissues (Locke et al., 2008). Several lines of evidence support this point: increased 5α-DHT content within the tumor relative to the circulation (Locke et al., 2008; Leon et al., 2010); upregulation of steroidogenic enzymes within the tumor in LNCaP xenograft mouse models (Locke et al., 2008); re-expression of androgen-dependent genes in the absence of testicular androgens (Locke et al., 2008); and radiotracing evidence indicating a capacity of CRPC tumor tissue to convert acetic acid to 5α-DHT in a mouse model (Locke et al., 2008). These observations are consistent with an increase in *de novo* steroid production during CRPC in a mouse model.

In men with CRPC, as a response to attenuated AR signaling, there is a diversion of steroidogenesis from the testes to the local prostate tissue, as a castration resistance mechanism (Mostaghel et al., 2011). Upon further treatment of these men with drugs targeting local prostatic steroidogenesis, such as the CYP17A1 inhibitor Abiraterone, evasion of 'androgen blockade' advances in tumors, and the seemingly relentless formation of androgens continues via alternate steroid synthesis pathways that we are only now starting to decipher (see Section 4.3). Maintenance of local AR signaling as a result of the cancer being able to provide an independent androgen supply is therefore likely to be a key tactic that PCa tumors employ to overcome typical androgen deprivation therapies.

In addition, there are acquired changes in AR co-regulatory factors that sensitize AR activation (Mostaghel et al., 2011). It has also been suggested that, in response to androgen deprivation therapy, AR splice variants arise that no longer require androgen binding for transactivation (Mostaghel et al., 2011).

3.3. Factors influencing prostate cancer risk and progression

Cholesterol can serve as a substrate for intratumoral androgen synthesis in mice (Leon et al., 2010; Mostaghel et al., 2012). Several studies suggest that high dietary cholesterol is a predisposing factor for PCa and that loss of cholesterol regulatory factors is a risk factor for PCa progression in men (Wu et al., 2006; Iso et al., 2009; Mondul et al., 2010; Platz et al., 2008, 2009). It has been shown that elements of cholesterol regulation are in fact androgen-sensitive and that a negative feedback loop supports intratumoral androgen synthesis in AR-dependent CRPC tumors (Leon et al., 2010; Mostaghel et al., 2012; Dillard et al., 2008). Cholesterol has, therefore, also been suggested as a potential target in CRPC treatment (Twiddy et al., 2011). The use of statins and patterns of PCa incidence and aggressiveness have also been examined, and some studies suggest that cholesterol is an underlying predisposing factor for PCa and disease progression (Farwell et al., 2011; Hamilton et al., 2010). Other factors have been examined as risk factors for the development of PCa, and recently obesity has been determined to increase the risk for aggressive disease as well as CRPC progression (Keto et al., 2012; Allott et al., 2013).

3.4. Current pharmacological treatments for PCa and CRPC

Current strategies for the treatment of advanced PCa are based on pioneering studies of the effectiveness of a chemical castration using an LHRH/GnRH agonist given alongside a pure AR antagonist (e.g., Casodex or X-tandi (MDV3100)) (Cai and Balk, 2011; Crawford et al., 1989; Labrie et al., 1985). Since it is now well-established that AR remains active in the majority of CRPC cases, the most recent clinical trials have been evaluating combinations of drugs to combat castration resistance mechanisms, such as intratumoral androgen production. Steroidogenesis inhibitors used in conjunction with AR targeting approaches that are appropriate for CRPC include: Abiraterone (inhibits CYP17A1) and Finasteride or Dutasteride (inhibit 5α-reductases) (Cai and Balk, 2011; Sharifi et al., 2008). However, these treatment strategies are currently unable to combat AR splicing (i.e., elimination of the ligand binding domain, which can lead to constitutive AR activation) or androgen-independent PCa (Mostaghel et al., 2011). Chemotherapeutic regimens are therefore also used and include taxanes such Docetaxel or Cabazitaxel, which target tubulin and spindle formation. However, extension in life for men undergoing chemotherapy is relatively modest, and current clinical trials are geared toward the development of drugs that can be individually tailored to patients and combined with current strategies to target distinct CRPC resistance mechanisms (Abidi, 2013; Choudhury and Kantoff, 2012).

4. Lessons learned from an interdisciplinary collaboration

4.1. Prostate cancer biologists can examine local regulation of steroid synthesis by GnRH

The regulation of gonadal sex steroid secretion by hypothalamic GnRH is well-understood. Several forms of GnRH have been identi-

fied in the mammalian brain (White et al., 1998; Yahalom et al., 1999; Dees et al., 1999). GnRH1 regulates LH and FSH secretion from the anterior pituitary and is the primary driver of the HPG axis (Guillemin, 2005; Densmore and Urbanski, 2003; Gault et al., 2003). Discovered in chicken, GnRH2 is highly evolutionarily conserved and expressed in the brain and other tissues (Densmore and Urbanski, 2003), but the primary function of GnRH2 does not appear to be stimulation of pituitary gonadotropin secretion (Gault et al., 2003). Instead, GnRH2 appears to act within the brain to regulate reproductive behaviors (Temple et al., 2003; Kauffman and Rissman, 2004; Maney et al., 1997). Another form of GnRH (lamprey GnRH-III) was first identified in the sea lamprey, *Petromyzon marinus* (Calvin et al., 1993; Sower et al., 1993; Deragon and Sower, 1994), and has since been detected in several mammals, including humans (Yahalom et al., 1999). Lamprey GnRH-III might regulate pituitary gonadatropin secretion, but its primary neural function remains unclear (Montaner et al., 2001; Dees et al., 2001; Kovacs et al., 2002; Kauffold et al., 2005; Proudman et al., 2006; Brussow et al., 2010). GnRH receptors are expressed in the brain, with high levels in the hippocampus (Wilson et al., 2006; Fester et al., 2012), as well as in peripheral tissues (Limonta et al., 2003). Very interestingly, *in vitro* studies show that GnRH administration stimulates E_2 synthesis by neuronal cells and hippocampal or hypothalamic slices (Prange-Kiel et al., 2008; Rosati et al., 2011; Burel et al., 2013). Thus, GnRH may play a role in the control of the classic HPG axis, as well as a local paracrine/autocrine loop in some brain regions such as the hippocampus. Similarly, local feedback loops including CRH have been described for the regulation of local glucocorticoid synthesis in the skin (reviewed in Taves et al. (2011)).

GnRH is commonly targeted for the treatment of prostate cancer. To suppress testicular androgen secretion, (1) long-acting GnRH receptor agonists are used to cause GnRH receptor down-regulation in the pituitary, or (2) GnRH receptor antagonists are used for direct inhibition of pituitary gonadotropin secretion (Armer and Smelt, 2004; d'Ancona and Debruyne, 2005; Labrie, 2010; Leurs et al., 2012). Intriguingly, GnRH1 and GnRH2 and their respective receptors (mRNA or immunoreactivity) have been detected in PCa cells, and also specific binding of lamprey GnRH-III to PCa cell membranes has been reported (Limonta et al., 2003; Kakar et al., 1994; Bahk et al., 1998; Lovas et al., 1998; Eicke et al., 2005; Maiti et al., 2005; Marelli et al., 2009; Qayum et al., 1990; Dondi et al., 1994; Azad et al., 1993; Harrison et al., 2004). In PCa, GnRH1 receptors have an identical mRNA sequence to those in the pituitary, and GnRH1 promotes cell growth and proliferation in androgen-dependent PCa cell lines (Fekete et al., 1989). In contrast, other forms of GnRH might have anti-proliferative effects on PCa cells (Lovas et al., 1998; Limonta and Manea, 2013). Thus, different forms of GnRH may exert varying effects on the tumor. In a study of rats, treatment with a GnRH receptor agonist decreased GnRH receptors in the pituitary, but increased GnRH receptors in the ventral prostate (Tieva et al., 2003). Furthermore, tumors from PCa and CRPC patients that underwent androgen deprivation therapy (including GnRH receptor agonist treatment) had higher GnRH receptor levels than those from patients without treatment, with highest levels in the CRPC tumors (Liu et al., 2010). Prostate cancer cells may also express gonadotropins (LH and FSH) as well as their receptors (Pinski et al., 2011; Dirnhofer et al., 1998). Thus, the components for a localized HPG axis might exist within the prostate or PCa and might regulate intratumoral steroidogenesis during the development of CRPC. Although speculative, future studies can test this possibility.

4.2. Prostate cancer biologists can examine the effects of locally-synthesized E_2

In the brain, aromatase has been well-studied, and its products (estrogens) play many vital roles. The traditional view is that E_2 binds to intracellular estrogen receptors (ERα and ERβ), which then modulate gene transcription, thus affecting neural processes over the course of hours to days. The discovery of a membrane-bound G-protein-coupled receptor (O'Dowd et al., 1998), which binds E_2 with high specificity and affinity (Revankar et al., 2005; Feng and Gregor, 1997; Thomas et al., 2005), provided a non-genomic mechanism by which E_2 could act within seconds to minutes, via intracellular signaling cascades (Woolley, 2007; Kelly and Qiu, 2010; Kelly and Ronnekleiv, 2012). This G-protein-coupled estrogen receptor 1 (GPER-1), formerly G protein-coupled receptor 30, might mediate some of the rapid neural and behavioral effects of E_2 (i.e., within 30 min) (Woolley, 2007; Cornil and Charlier, 2010; Srivastava et al., 2011; Vasudevan and Pfaff, 2008; Mhyre and Dorsa, 2006). For example, in male song sparrows, E_2 treatment (within 15 min) alters the phosphorylation of signaling proteins in several brain regions that regulate social behavior (Heimovics et al., 2012). E_2 treatment also rapidly increases aggression in non-breeding male song sparrows (Heimovics et al., submitted for publication). In many cases, to see rapid effects of E_2, high doses are required, and these doses may surpass E_2 levels found in plasma (Pradhan et al., 2008; Trainor et al., 2008; Cornil et al., 2006). However, neural levels of E_2 are far higher than plasma levels (Charlier et al., 2010b, 2011; Taves et al., 2010; Overk et al., 2013; Hojo et al., 2004). Thus, the high E_2 doses necessary to see rapid neural effects may be considered "physiological" rather than "pharmacological" in this context. Furthermore, there is some evidence that membrane-associated ER in the brain might have a lower affinity for E_2, and thus are activated by high neural E_2 levels but not by lower systemic E_2 levels (Woolley, 2007; Ramirez et al., 1996).

Neural E_2 levels can be rapidly increased above baseline values, because aromatase and other steroidogenic enzymes in the brain are rapidly regulated (Charlier et al., 2011; Soma et al., 2004b). Within the brain, aromatase is rapidly regulated by calcium-dependent phosphorylation and by neurotransmitters such as dopamine, glutamate, and GABA (Charlier et al., 2010a). Further, aromatase is present in presynaptic boutons (Saldanha et al., 2011) and E_2 levels at these synapses might be quite high. Thus, neurally-synthesized E_2 may act more like a neurotransmitter or neuromodulator than a classical hormone (Saldanha et al., 2011; Balthazart and Ball, 2006; Remage-Healey et al., 2010). Similarly, glucocorticoids have rapid effects on the brain (Schmidt et al., 2008, 2010; Orchinik et al., 1991) via non-genomic mechanisms (Charlier et al., 2009; Mikics et al., 2004), which can require high doses (Stahn and Buttgereit, 2008). In general, locally-synthesized steroids can be produced quickly, reach high local concentrations, and rapidly bind to nearby receptors, without the need to enter the blood and travel to distant targets. Taken together, these data suggest that locally-produced estrogens can act via non-genomic mechanisms (Schmidt et al., 2008), and this point may be relevant for PCa research.

Research on the steroid regulation of PCa has historically focused on androgens, namely T and 5α-DHT. The normal prostate and PCa both express aromatase (Dowsett, 1990; Harada et al., 1993) but the role of E_2 in the etiology of PCa is not clear. The ratio of androgens to estrogens may be an important factor regulating the growth of prostatic tissue (Risbridger et al., 2003; Ellem and Risbridger, 2010). Aromatase knockout mice with a targeted disruption of the CYP19A1 gene show higher plasma androgen levels, which promote growth but not malignancy of prostatic tissue (McPherson et al., 2001). Prostate tissue is composed of glands and surrounding stromal cells that are separated by a basal lamina containing epithelial cells (Abate-Shen and Shen, 2002). In benign tissue, aromatase is found largely in the stromal cells, but in malignant tissue, other cell types also express aromatase (Ellem et al., 2004). Thus, the prostate has the necessary enzyme for local E_2 synthesis, and PCa might display changes in aromatase expression.

Other studies of the prostate have identified differential roles for ERα and ERβ, with the former inducing cell proliferation and the development of premalignant lesions, and the latter maintaining normal stromal–epithelial cell signaling and counteracting the proliferative actions of androgens (McPherson et al., 2007, 2010; Ricke et al., 2008; Ellem and Risbridger, 2009). Thus, E_2 can have different effects on prostate health, depending on which receptor is activated. Studies of breast (ERα-negative), endometrial, and ovarian cancer cells demonstrate that GPER-1 activation can stimulate cell proliferation (Thomas et al., 2005; Filardo et al., 2000; Vivacqua et al., 2006; Albanito et al., 2007), whereas GPER-1 activation reduces proliferation of bladder urothelial cells (Teng et al., 2008). To date, few PCa studies have examined GPER-1. A GPER-1 agonist inhibits cell growth in two androgen-independent PCa cell lines (PC-3 and DU145) and an androgen-dependent PCa cell line (LNCaP) (Chan et al., 2010). Further, a GPER-1 agonist suppresses tumor growth in nude mice with a PC-3 xenograft (Chan et al., 2010). Taken together, these initial studies suggest that GPER-1 might play a role in PCa, although more studies are required to test this possibility. Future studies can clarify the localization, regulation and functions of GPER-1 in the normal prostate and in PCa. In addition, future studies can examine aromatase expression and local E_2 synthesis in the normal prostate and in PCa.

4.3. Neuroendocrinologists can examine alternative steroidogenic pathways in the brain

Our knowledge of steroidogenic pathways is constantly evolving, as new enzymes and new steroid intermediates are uncovered, especially with the recent increased use of mass spectrometry. For example, the "backdoor" pathway to 5α-DHT was recently identified in studies of the pouch young of the tammar wallaby (*Macropus eugenii*) (Auchus, 2004) (Fig. 3A). Previously, androgen synthesis was thought to occur through either the Δ^5 or Δ^4 pathway, with androstenediol or androstenedione as precursors to T, respectively; the T is converted to 5α-DHT by 5α-reductase type 2 in peripheral tissues (Auchus, 2004; Labrie et al., 2000; Wilson et al., 2002) and the brain (Soma et al., 2003; Mo et al., 2009; Freking et al., 1998). However, in developing male tammar wallabies, the testes primarily secrete androstanediol (Adiol or 3α-diol), which is then locally converted to 5α-DHT in the male reproductive tract (Shaw et al., 2000; Wilson et al., 2002). Adiol is also produced in the testes of neonatal rodents (Sheffield and O'Shaughnessy, 1988; Hardy et al., 2000) and perhaps in some tissues of humans during early infancy and in several disorders (Kamrath et al., 2013; Fukami et al., 2013; Biason-Lauber et al., 2013; Miller, 2012; Kamrath et al., 2012a,b; Penning, 2010), even though the Δ^5 pathway is highly dominant in humans (Fluck et al., 2003). Thus, the backdoor pathway might bypass T on the route to 5α-DHT. In addition, 5α-DHT can be converted to Adiol, as this reaction is reversible. This example is another illustration of the utility of comparative endocrinology, as the original observation was made in tammar wallabies but might be of broad relevance.

This backdoor pathway might be involved in PCa and hence targeted for treatment (Mohler et al., 2011). In response to castration, there is some evidence for an upregulation of the backdoor pathway in PCa tumors, and this might support AR activation and cancer cell survival in CRPC (Locke et al., 2008). Pharmacological inhibition of both CYP17A1 and 5α-reductase altered, but did not eliminate, 5α-DHT production (from progesterone) in steroid-starved LNCaP cells, as well as in castrated nude mice with LNCaP

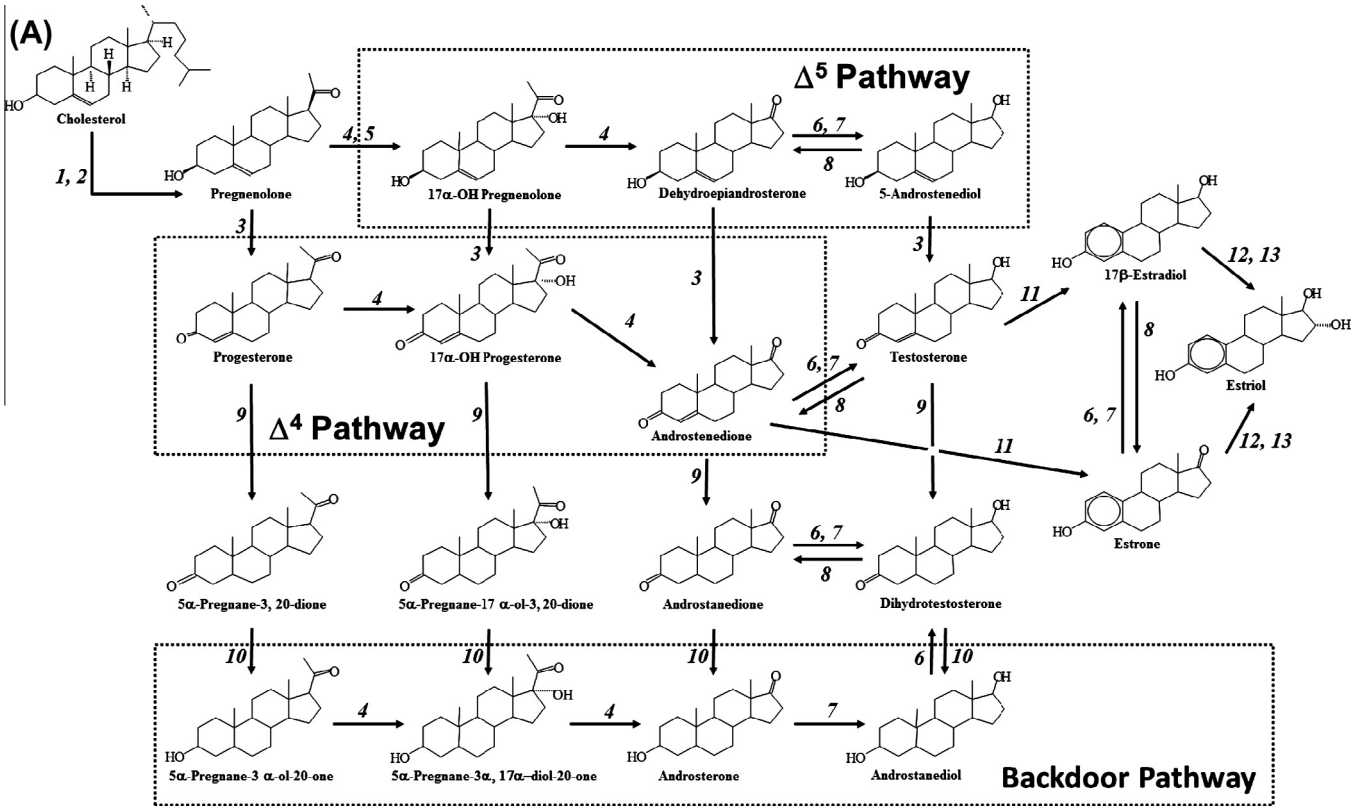

Fig. 3. (A) Androgen and estrogen synthesis indicating both classic and "backdoor" pathways to 5α-dihydrotestosterone (5α-DHT). Numbers indicate proteins and enzymes identified by their human gene names: (1) StAR, (2) CYP11A1, (3) HSD3B2, (4) CYP17A1, (5) CYB5A, (6) AKR1C3, (7) HSD17B3, (8) HSD17B2, (9) SRD5A1, (10) AKR1C2, (11) CYP19A1, (12) CYP1A2; and (13) CYP3A4. (B) Chromatograms depicting steroids in both classic and backdoor pathways from internal standards (S) or from adult male zebra finch diencephalon tissue (T). Steroids were analyzed using liquid chromatography-tandem mass spectrometry after derivatization to methylpyridinium or oxime derivatives. See Locke et al. (2008) for detailed methods.

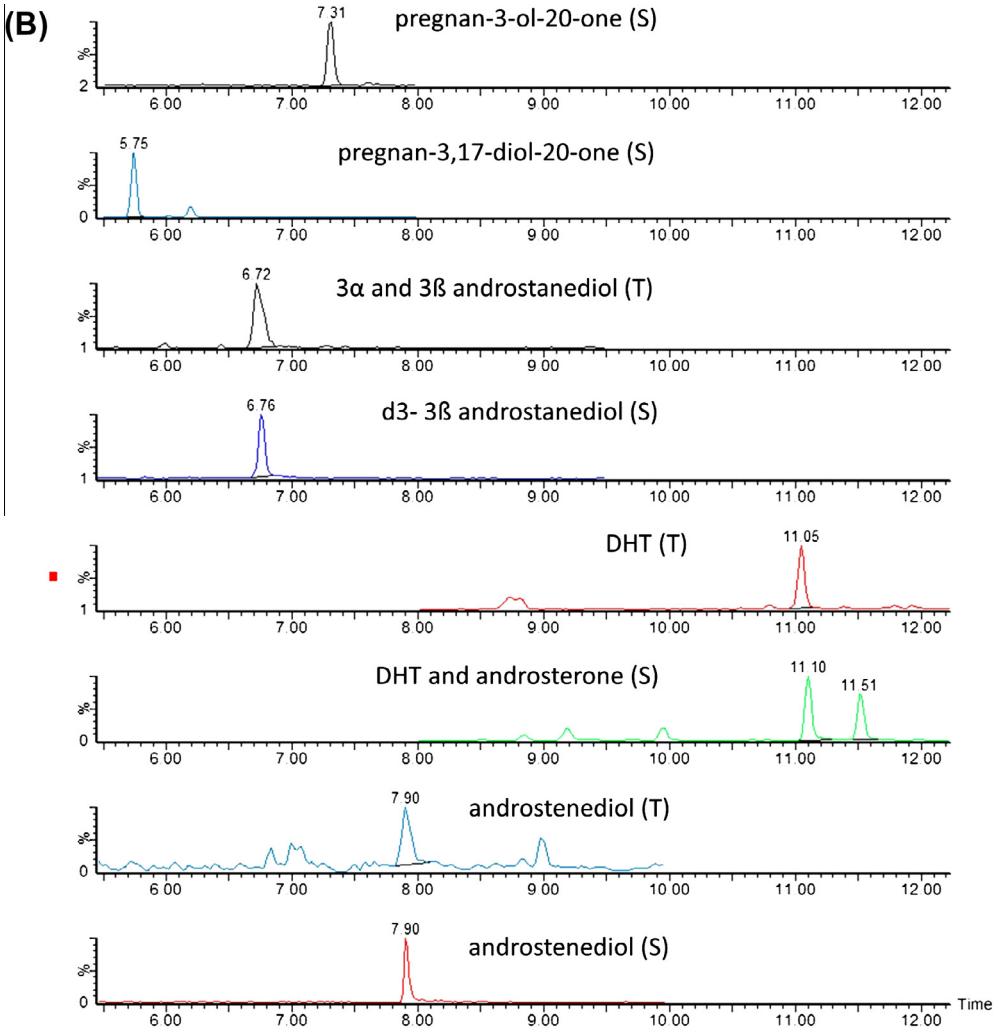

Fig. 3 (*continued*)

xenografts (Locke et al., 2009). These data suggest that the backdoor pathway might act as a compensatory mechanism for local 5α-DHT synthesis, which can take advantage of the high concentrations of precursors (e.g., progesterone) that are still present after castration or treatment with Abiraterone (CYP17A1 inhibitor). An ability of tissues to adapt and compensate for disruptions to steroidogenic pathways may have important implications for the design of both patient treatments and experimental manipulations in all fields, including neuroendocrinology.

The conversion of T to 5α-DHT has a well-established role in the physiology of peripheral androgen-dependent tissues, including development and function of the prostate. However, within the brain, aromatase has generally received more attention than 5α-reductase, and the degree to which T must be locally transformed to 5α-DHT prior to AR binding remains unclear. Nonetheless, 5α-reductase (type 2 isozyme) is widely distributed in the mammalian (Castelli et al., 2013; Celotti et al., 1997; Lauber and Lichtensteiger, 1996), avian (Soma et al., 2003; Schlinger et al., 1995), and amphibian brains (Bruzzone et al., 2010; Vallarino et al., 2005). To date, there are no published reports of the backdoor pathway to 5α-DHT in the brain. The presence of a backdoor pathway in the brain might help explain the maintenance of androgen-dependent behaviors, such as sexual or aggressive behaviors, after castration or during the non-breeding season in some species (Demas et al., 1999; Pinxten et al., 2003). This pathway might also be upregulated in the brain during aging, as gonadal T secretion naturally declines. Moreover, to our knowledge, the backdoor pathway has not been examined in any non-mammalian species.

Furthermore, 5α-DHT can be metabolized to 5α-androstane-3β,17β-diol (3β-diol) (Adinolfi et al., 1975). Interestingly, 3β-diol binds to ERβ (Chen et al., 2013; Frye et al., 2008; Handa et al., 2011; Hiroi et al., 2013; Huang et al., 2008; Osborne et al., 2009) and can affect prostate function (Horst et al., 1975; Krieg et al., 1975; Ahmad et al., 1978; Oliveira et al., 2007) and brain function, including neuropeptide expression (Hiroi et al., 2013; Huang et al., 2008; Pak et al., 2009) and behavior (Frye et al., 2008), via activation of ERβ (Chen et al., 2013). Such alternative steroidogenic pathways are generally understudied, but might prove to be important in a broad array of contexts and tissues.

4.4. Neuroendocrinologists can examine the role of cholesterol availability in neurosteroid synthesis

In a classic study, Japanese men experienced a 4- to 6-fold increase in the risk of developing PCa upon relocation to the United States, and this was irrespective of whether the move took place early or later in life (Muir et al., 1991; Wynder et al., 1991; Haenszel and Kurihara, 1968; Shimizu et al., 1991). Furthermore, the immigrants' PCa risk was comparable to that of US-born men of Japanese ethnicity (Shimizu et al., 1991; Severson et al., 1989).

Since then, the results have been replicated in Japanese migrants to Brazil (Tsugane et al., 1990). These studies highlight how environment can strongly influence PCa etiology, and the high sugar/high saturated fat/high cholesterol diet of Westerners (i.e., the Western diet) is an important environmental variable. As a steroid-dependent cancer, PCa might use cholesterol for intratumoral *de novo* steroidogenesis, and early studies demonstrated that cholesterol is synthesized and taken up by the rat prostate (Schaffner, 1981). In addition, tumor cholesterol content increases with PCa development and progression (Schaffner, 1981). Cholesterol has many cellular functions, including maintaining the structural integrity of plasma membranes and lipid rafts, and serving as a precursor to bile acids and steroids (Korade and Kenworthy, 2008; Miller and Bose, 2011). Thus, adequate cholesterol availability is necessary to support both cell growth and signaling, and it is perhaps not surprising that high cholesterol levels have been linked to the uncontrolled cell growth of PCa (Brown, 2007).

Steroidogenic cells can use four potential sources of cholesterol: (1) free cholesterol synthesized intracellularly within the endoplasmic reticulum, (2) intracellular stores of cholesteryl esters within cytosolic lipid droplets that can be liberated by hormone-sensitive lipases (HSL), (3) uptake of circulating high-density lipoproteins (HDL) via the scavenger receptor B1 (SRB1); and (4) uptake of circulating low-density lipoproteins (LDL) via receptor-mediated endocytosis (Miller and Bose, 2011; Hu et al., 2010). During PCa, local cholesterol uptake mechanisms (e.g., SRB1 and LDL receptors) are upregulated (Dillard et al., 2008; Chen and Hughes-Fulford, 2001; Krycer et al., 2012), thereby increasing cholesterol levels in PCa cancer cells, possibly to support both rapid cell proliferation and *de novo* steroid synthesis (Krycer and Brown, 2013). Surprisingly, in a mouse xenograft model, progression to CRPC is also associated with an increase in cholesterol efflux (i.e., removal of free cholesterol), perhaps to avoid the toxic effects of free cholesterol within the cell (Leon et al., 2010). The regulation of cholesterol homeostasis may involve AR signaling, and PCa cells respond to an AR agonist (R1881) by increasing the activity of HMG-CoA reductase, which is the rate-limiting enzyme in the mevalonate pathway of cholesterol synthesis (Locke et al., 2008). Similarly, others report that AR activation increases the activities of both sterol-regulatory element binding proteins 1 and 2 (SREBP-1 and SREBP-2); these are transcription factors that regulate expression of steroidogenic enzymes (Heemers et al., 2001, 2003, 2005; Swinnen et al., 2004; Krycer and Brown, 2011). Thus, the increase in local steroidogenesis in CRPC involves a substantial reorganization of the cellular machinery for cholesterol synthesis and import.

The brain is the most cholesterol-rich organ. Unlike the peripheral organs, neural cholesterol is thought to be primarily derived by *de novo* synthesis, because the blood–brain barrier limits the uptake of circulating lipoproteins (Orth and Bellosta, 2012; Mortaud and Degrelle, 1996; Moutafis, 2002; Turley et al., 1996; Bjorkhem and Meaney, 2004). Also unlike the peripheral organs, almost all cholesterol in the nervous system is present in an unesterified form in two major pools: (1) the myelin sheaths of oligodendrocytes; and (2) the plasma membranes of astrocytes and neurons (Bjorkhem and Meaney, 2004). Rates of *de novo* cholesterol synthesis in the brain are very high during development and early childhood, but decline substantially with age, perhaps due to an efficient ability to recycle neural cholesterol (Bjorkhem and Meaney, 2004), which can have a long half-life (Björkhem et al., 1998). Indeed, the brain may even export cholesterol into the peripheral circulation (Bjorkhem and Meaney, 2004). Nonetheless, neuroendocrinologists still know very little about how central and circulating cholesterol levels and dietary cholesterol affect neurosteroid synthesis. It is generally accepted that the rate-limiting step in steroid synthesis is the translocation by StAR of free cholesterol from the outer mitochondrial membrane to the inner mitochondrial membrane, where cytochrome P450 side-chain cleavage (P450scc, or CYP11A1) is located (Sierra, 2004). The distribution of StAR within the brain is extensive and includes many regions that produce neurosteroids (e.g., hippocampus, hypothalamus) (King et al., 2004, 2002; London and Clayton, 2010; Furukawa et al., 1998; Kimoto et al., 2002; London et al., 2006). Furthermore, many regions involved in steroid-dependent behaviors (e.g., sexual behavior), such as the medial preoptic area, have high concentrations of StAR, suggesting a potential for *de novo* steroid synthesis (King et al., 2002).

Few studies of neurosteroids examine central or circulating cholesterol levels. In song sparrows caught in their natural environment (i.e., not given *ad libitum* food in captivity), we measured circulating cholesterol concentrations via liquid chromatography-tandem mass spectrometry (Fig. 4). The data reveal higher levels of esterified cholesteryls in the non-breeding season than the breeding season. While speculative, these data raise the hypothesis that higher circulating cholesterol levels in the non-breeding season might, at least in part, support higher levels of *de novo* neurosteroidogenesis at this time of year. Despite the prevailing notion that the brain cannot take up circulating cholesterol, there is some evidence for SRB1 expression in the mammalian brain (Srivastava, 2003; Srivastava and Jain, 2002). SRB1 is involved in uptake of circulating high-density lipoproteins that transport cholesterol. Interestingly, treatment with E_2, but not with cholesterol, increases SRB1 expression in mouse brain (Srivastava, 2003). Thus, cholesterol uptake by the brain could be under endocrine control. Such mechanisms might be important when cholesterol cannot be rapidly mobilized from myelin sheaths or plasma membranes.

4.5. Neuroendocrinologists can examine extracellular vesicular transfer of RNA and proteins

A recent development in cancer biology is the expansion of our understanding of intercellular communication beyond direct cell–cell contact and secreted molecules (i.e., hormones) to include the transfer of extracellular vesicles (Raposo and Stoorvogel, 2013). Cells release vesicles into the extracellular environment, which may originate from endosomes or the plasma membrane (known as exosomes and microvesicles/membrane particles, respectively) (Raposo and Stoorvogel, 2013). Extracellular vesicles are classified based on intracellular origin, size, density, and protein and lipid markers. For example, exosomes are endosomal cholesterol-rich nanovesicles that are released from cells upon fusion of multivesicular endosomes with plasma membrane. Exosomes have been found in semen (Ronquist, 2012; Babiker et al., 2007; Jones et al., 2010), blood (Ajit, 2012; Orozco and Lewis, 2010; Vincenzo et al., 2009), urine (Pisitkun et al., 2012, 2006), saliva (Berckmans et al., 2011), breast milk (Admyre et al., 2008), and cerebrospinal fluid

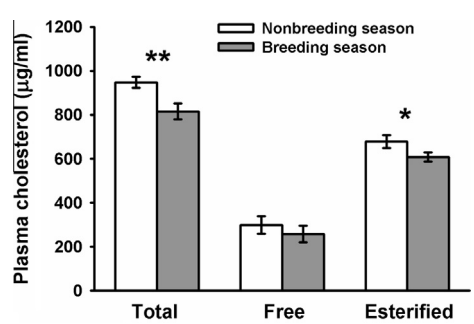

Fig. 4. Total, free and esterified cholesterol concentrations in the plasma of free-living male song sparrows during the non-breeding and breeding seasons. Measurements were made via liquid chromatography-tandem mass spectrometry. Data shown as mean ± standard error, with $* \ p < 0.05$, and $** \ p < 0.01$.

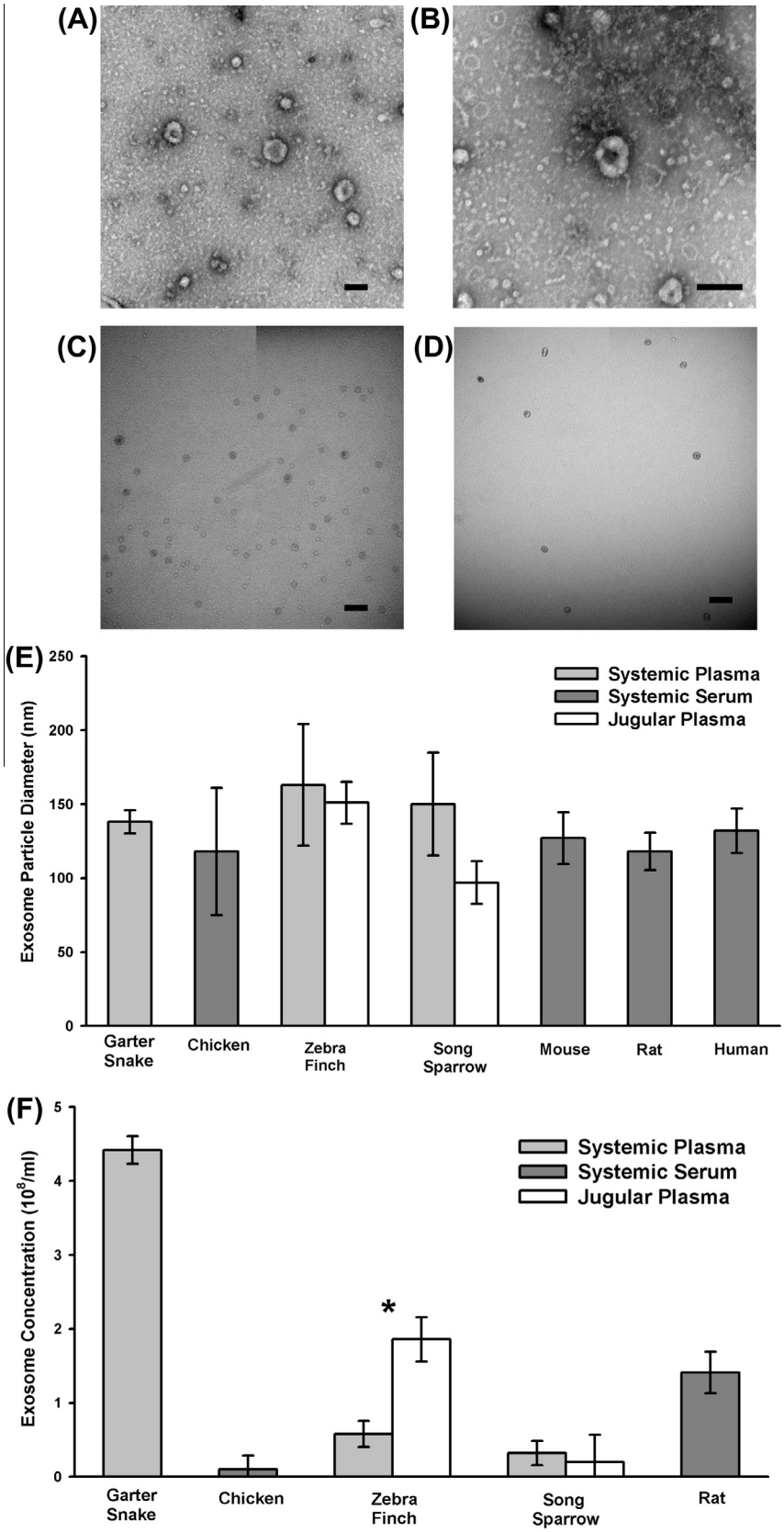

Fig. 5. Transmission Electron Microscopy (TEM) photomicrographs of exosomes isolated from (A) prostate cancer cells *in vitro* (PC3 cell line), (B) benign epithelial cells *in vitro* (RWPE-1 cell line), (C) serum from a mouse and (D) serum from a man. Scale bars represent 100 nm, 150 nm, 500 nm, and 500 nm, respectively. Exosomes were identified as cup-shaped structures after negative staining with 2% uracyl acetate. (E) Diameters and (F) concentrations of exosome particles visualized and quantified using Nanosight nanoparticle tracking analysis software, version 2.3 (Nanosight Ltd. Wiltshire, UK), from serum or plasma of various reptile, bird and mammal species, including humans. All data shown as mean ± standard error, with $* \; p < 0.05$. Exosomes were isolated prior to analysis via sequential (ultra)centrifugation using a sucrose gradient.

(Saman et al., 2012; Vella et al., 2007, 2008). Extracellular vesicles can be isolated using centrifugation (Locke et al., 2009; Taylor and Gercel-Taylor, 2005), and size classes are separated on the basis of flotation velocity (Aalberts et al., 2012). The contents of these vesicles can be characterized using immunoblotting, PCR, or mass spectrometry (Raposo and Stoorvogel, 2013). Vesicle contents can include a variety of proteins and RNA species (Bellingham et al., 2012; Nolte-'t Hoen et al., 2012). Thus, cells are capable of transporting proteins and mRNA across long distances (e.g., via the blood) to target cells, to alter the function of the target cells.

Cancer biologists are investigating how extracellular vesicles enhance the invasiveness of cancer cells. Tumor-derived exosomes can stimulate angiogenesis, modulate stromal cells, remodel extracellular matrix, and suppress local anti-tumor immune responses, and thus they can establish a suitable premetastatic microenvironment in distant sites (Peinado et al., 2012, 2011; Poutsiaka et al., 1985; Yang and Robbins, 2011). Both PCa and BPH cell lines and tumors release exosomes (Fig. 5A, B) (Locke et al., 2009; Hosseini-Beheshti et al., 2012; Hessvik et al., 1819; Bryant et al., 2012; Nilsson et al., 2009; Lehmann et al., 2008; Abusamra et al., 2005). Exosomes have been identified in the blood of rodent models (Fig. 5C) and humans (Fig. 5D). Interestingly, exosomes can contain steroidogenic enzymes, such as CYP17A1 (Locke et al., 2009). CYP17A1 is a key enzyme in androgen synthesis. Exosomal CYP17A1 protein levels, isolated from serum, are higher in patients with PCa compared to healthy controls, and they also increase after initial androgen deprivation with progression to CRPC (Locke et al., 2009). While speculative, the presence of CYP17A1 in tumor exosomes raises the possibility that tumor exosomes might promote nearby and distant cells to produce androgens (Locke et al., 2009). Recent work characterized the protein, lipid and cholesterol content of exosomes from five PCa cell lines and one benign prostate cell line. Exosomes from the PCa cells had more cholesterol than exosomes from the benign cells (Hosseini-Beheshti et al., 2012), consistent with a role for cholesterol in CRPC (Locke et al., 2008). However, initial analyses revealed few differences in protein profiles (Hosseini-Beheshti et al., 2012). Exosome biology is still in its early stages but might elucidate novel aspects of androgen physiology in PCa.

The identification of exosomes and their ability to regulate cellular processes at distant targets through protein and RNA trafficking has implications for neuroendocrinology. First, exosomal protein transfer means that steroidogenic enzymes do not have to be transcribed locally. In a cell or group of cells, the absence of a steroidogenic enzyme transcript does not necessarily mean the absence of the corresponding protein. Steroidogenesis in one brain region might be influenced by the transport of steroidogenic enzymes from another brain region or the blood. Second, exosomes and microvesicles might be useful for drug delivery to the brain (El Andaloussi et al., 2013; El-Andaloussi et al., 2012; Lakhal and Wood, 2011; O'Loughlin et al., 2012; Wood et al., 2011). Drug delivery to the brain is greatly limited by the blood–brain barrier, but exploiting naturally-occurring vesicular transport may ameliorate this obstacle. Vesicular delivery of siRNA or microRNA into the brain has also generated interest (O'Loughlin et al., 2012; Zhang et al., 2012). Third, intercellular transport via exosomes expands how we view cell–cell communication in the brain. Both neurons and glia release exosomes into the extracellular space (Faure et al., 2006; Bakhti et al., 2011; Chivet et al., 2012, 2013; Hooper et al., 2012) and cerebrospinal fluid (Saman et al., 2012; Vella et al., 2007, 2008) in a tightly regulated manner (Ghidoni et al., 2011; Putz et al., 2008; Arantes and Andrews, 2006; Lachenal et al., 2011). One study has shown that exosomes become internalized by neurons and impact neurite growth (Xin et al., 2012). We examined exosomes in the plasma and serum of several animal taxa, including reptiles, birds and mammals (Fig. 5E, 5F). Our preliminary data suggest that the diameter of the exosome particles does not vary widely among species, as expected (Fig. 5E). However, there appears to be variation in the concentration of exosomes among species. In addition, in zebra finches, the concentration of exosomes is higher in plasma from the jugular vein (exiting the brain) than plasma from the brachial vein (reflecting systemic levels) (Fig. 5F). Future studies will examine whether steroidogenic enzyme transcripts and/or proteins are present in these exosomes. Clearly, much more research is necessary to understand the functions of these extracellular vesicles, especially in the brain.

5. Conclusions

Sex steroids, such as androgens and estrogens, are extremely potent signaling molecules that affect many cells in the body, including cells of the nervous system and the reproductive system. Natural and synthetic androgens are widely used illegally (e.g., by athletes) and legally (e.g., for hypogonadism). Prescriptions for T are rapidly increasing worldwide (Handelsman, 2013). The use of natural and synthetic estrogens is also commonplace, for contraception and hormone replacement. Despite the widespread usage of steroids, steroid synthesis inhibitors and steroid receptor antagonists, much is still unknown about how sex steroids act on the brain, prostate, and other tissues.

Multiple lines of evidence demonstrate that androgen and estrogen synthesis can occur in the brain and in prostate cancer, in addition to classical synthesis in the testes and ovaries. Thus, we hypothesize that in some important contexts, circulating levels of sex steroids are not accurate indicators of local levels within the brain, the prostate, or a prostate tumor. Compared with gonadal sex steroids, locally-produced sex steroids may be synthesized by different enzymes, produced from alternate precursors, and potentially regulated by different factors. Locally-synthesized sex steroids may differ in mechanisms of action and functions from systemic, gonad-synthesized androgens, but as yet this remains understudied.

Interdisciplinary collaborations such as ours, while uncommon, can generate novel questions and approaches by both neuroendocrinologists and cancer biologists. For example, in the brain and in prostate tumors, local androgen synthesis is upregulated after a decrease in systemic androgen levels (e.g., termination of the breeding season, or following surgical castration). In prostate cancer patients, pharmacological interventions (e.g., long-lasting GnRH receptor agonists) that decrease testicular androgen synthesis and systemic androgen levels might also affect local androgen synthesis in the brain, but this issue remains unclear and is an important topic for future studies. This is just one example of a novel question raised during our collaboration.

Clinically, local administration of sex steroids or steroid receptor antagonists might be advantageous over systemic administration, which can have unwanted side effects throughout the body. Basic research on local sex steroid synthesis can inform therapies that target exogenous androgens or estrogens to specific tissues or that stimulate endogenous local steroid synthesis at specific sites. It is equally important to understand how steroid synthesis or action can be inhibited at specific sites (e.g., prostate tumor cells), to avoid the side effects of systemic steroid deprivation on the brain and other organs.

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