Frontiers in Neuroendocrinology 36 (2015) 108–129

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review

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

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ARTICLE INFO

Article history:
Available online 16 September 2014

Keywords:
Backdoor pathway
Cholesterol
DHEA
Estradiol
Exosomes
GnRH
Neurosteroid
Songbird
Steroid profiling
Testosterone

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 pro-hormones (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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http://dx.doi.org/10.1016/j.yfrne.2014.08.005
0091-3022/

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

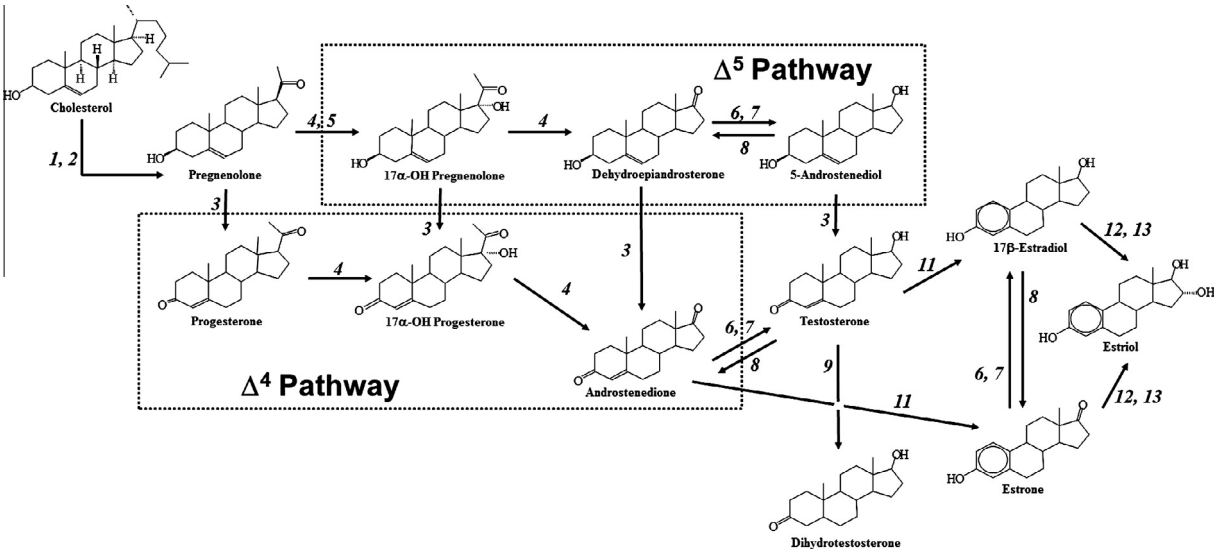

Fig. 1. Classic androgen and estrogen synthesis pathways with relevant numbered proteins and enzymes identified by their human gene names: (1) StAR, (2) CYP11A1, (3) HSD3B2, (4) CYP17A1, (5) CYB5A, (6) AKR1C3, (7) HSD17B3, (8) HSD17B2, (9) SRD5A1, (10) AKR1C2, (11) CYP19A1, (12) CYP1A2; and (13) CYP3A4.