EDITORIAL

Understanding the diversity of sex steroid action

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Steroidal estrogens are lipid-soluble compounds that are able to pass through the plasma membrane of cells by diffusion. According to the current knowledge, the three main naturally occurring estrogens are estrone (E_1), estradiol (E_2), and estriol. E_2 is the most active estrogen and the predominant female sex steroid during the reproductive years. In addition to these classical estrogens, there are various other steroidal and non-steroidal compounds that are able to interact with estrogen receptors (ERs), and thus at least partially act as estrogens. These include novel endogenous ligands (Saijo et al. 2011), pharmacological (McDonnell & Wardell 2010) and dietary compounds (Müller et al. 2004), as well as synthetic agents, such as pesticides and plasticizers (Craig et al. 2011).

Two nuclear ER subtypes have been well characterized, namely ESR1 (ERα) and ESR2 (ERβ). The nuclear ERs act as transcription factors, activated by ligand binding, and resulting in the recruitment of various receptor-interacting proteins and transcription factors of the general transcription machinery (Bulynko & O’Malley 2011, Hedengran Faulds et al. 2012). Several splice variants of both ERs have been found in normal and cancerous tissue, but their specific biological functions are still partially unclear. Despite the similarities between the two ERs, many studies have clearly demonstrated that there are subtype-specific actions, and, accordingly, the responses elicited by certain ligands differ depending on the receptor subtype. Furthermore, ERα and ERβ display partially overlapping tissue distribution, but they also possess receptor-specific expression patterns, and when expressed in the same tissue, the receptors often localize to different cell types. Several studies indicate that rapid estrogen signaling is not mediated via the nuclear ERs, but through the G-protein-coupled ER1 (GPER, also known as GPR30). GPER activates epidermal growth factor receptor (EGFR) by inducing a release of heparin-binding EGF, which activates EGFR leading to ERK1/2 activation (Prossnitz & Barton 2011). Moreover, E2-mediated activation of GPER induces cAMP production, intracellular calcium mobilization, and PI3K activation (for review, see Prossnitz & Barton (2011)). The distinct properties of ERα, ERβ and GPER have gained a lot of interest from the pharmaceutical industry, and there are several ongoing projects to develop selective ER modulators (Nilsson et al. 2011).

The structure and availability of the ligand is one of the key determinants in the regulation of ER-mediated actions. Intratissue estrogen concentrations are determined by circulating hormones, as well as by target tissue steroid metabolism, which enables a concentration gradient between the blood circulation and the target tissue. As an example, P450 aromatase (cytochrome P450, family 19, subfamily A, polypeptide (CYP19A1)), converting androgens (C-19 steroids) to estrogens (C-18 steroids), is widely expressed in peripheral tissues in humans, and P450 aromatase inhibitors are clinically used to inhibit estrogenic effects in various indications such as inhibiting the locally formed estrogens in post-menopausal breast cancer. More recently, the relevance of the hydroxysteroid (17β) dehydrogenases (HSD17Bs), converting the weak 17-keto steroids (e.g. E_1) to highly active 17β-steroids (e.g. E_2), and vice versa, has also become apparent, and the enzymes are expected to be involved in the local production of both classical and novel ligands for ERs in several normal and diseased tissues (for example, Chang et al. 2011, Mohler et al. 2011, Saijo et al. 2011, Saloniemi et al. 2012). It is thus likely that yet unknown endogenous small molecular compounds modulating ERs are to be discovered in the future.

In the three thematic reviews of the present issue of *Journal of Endocrinology*, the authors have summarized some of the recent advances in studies aimed at understanding the diversity in sex steroid action.

The regulation of the ligand availability for ERs by the family of HSD17B enzymes is discussed by Saloniemi et al. (2012) with special emphasis on novel findings obtained by using genetically modified mouse models. *In vivo* models have proven to be essential in defining the physiological processes where HSD17B enzymes are involved. The recent data indicate that these enzymes catalyze reactions also in other metabolic pathways in addition to those involved in sex steroid activation and inactivation and are likely to regulate ligand availability for numerous nuclear receptors.

The identification of ERβ was a fundamental milestone in the understanding of the mechanisms of estrogen signaling,
providing an explanation to a series of physiological actions of estrogens that are not mediated by ERα. Interestingly, in several organ systems, ERα and ERβ exert opposite effects, and the balance between the activation of the two ER subtypes regulates cell and tissue homeostasis. In this thematic review, Hedengran Faulds et al. (2012) have summarized the role of ERs in central metabolism, and the data provided indicate that in addition to their role in reproduction, ERs are centrally involved in the maintenance of metabolic control.

Endometrium is a classical estrogen target tissue, with marked morphological and physiological changes during the menstrual cycle. Furthermore, endometriosis (presence of endometrial tissue outside the uterine cavity) affects up to 10% of women at the reproductive age (Giudice 2010), and endometrial cancer is the most common malignancy of the genital tract in women in the western population (http://www.cancer.gov/cancertopics/types/endometrial). In this thematic review, Lam et al. (2012) have summarized the current knowledge on the molecular mechanism of sex steroid action in normal and diseased endometrium, with a special emphasis on the interaction of nuclear estrogen and progestin receptors with other transcription factors, such as FOXO proteins. Furthermore, they provide an outline of the novel mechanisms by which mRNA, small non-coding RNAs, and epigenetic mechanisms regulate steroid hormone responses in the endometrium.

Declaration of interest
The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received in final form 31 October 2011
Accepted 31 October 2011