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New Developments in the Rapid Actions of Steroids and their Receptors

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Steroid hormones and their effects as mediators of physiology and disease have been recognized for about a century. In most areas, research into estrogen, its biology and its receptors has led that of other steroids, both chronologically and mechanistically. Estrogen (actually estrone) was first purified and crystallized in 1929, followed soon thereafter by other steroid hormones including progesterone, androsterone, testosterone, estradiol and estriol. The first evidence for steroid receptors appeared in the 1950s, with their signaling properties (both rapid and transcriptional) and purification beginning to be described in the 1960s. Cloning of the first steroid receptor (for estrogen) occurred in the mid 1980s. Although some of the earliest effects of steroids to be described would be what we today refer to as rapid signaling (cAMP production, Ca^{++} mobilization), their transcriptional/genomic effects dominated the field for decades. In the 1990s, however, under the auspices of Martin Wehling and others, there began a resurgence in the recognition of the rapid signaling effects of steroids via membrane-associated receptors. In the late 1990s, the genes for ER β and GPR30 were cloned, the latter as an orphan receptor. Over the last ~15 years, the roles of GPR30 (now termed GPER) have begun to be elucidated, revealing it to be a receptor that mediates or contributes to many of the rapid effects of estrogen. This special issue of the *Journal of Steroid Biochemistry and Molecular Biology* is focused on the novel effects of steroids and their receptors, with an emphasis on what we have learned over the last ~15 years regarding the actions, both rapid and genomic (see Figure 1), of the best-studied steroid hormone estrogen.

The first article in this special issue (Barton et al., Twenty years of the G protein-coupled estrogen receptor GPER: historical and personal perspectives) recaps the field of GPER biology from a historical viewpoint, and the personal perspectives of six individuals who made particularly important contributions to this field, describing how they came to work on

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COMPETING INTERESTS

E.R.P. is an inventor on U.S. patents 7,875,721 and 8,487,100 for GPER-selective ligands and imaging agents and applications for the therapeutic use of compounds targeting GPER.

GPER and each other, often by circuitous paths. The article summarizes the history of estrogen biology, including the early critical work of Clara Szego beginning in the 1940s, studies of the rapid effects of estrogen in the human vascular system beginning in 1990 (Barton), the first reported cloning of GPR30 in 1996 (Lolait), discovery of rapid signaling events mediated by estrogen via GPR30 in 2000 (Filardo), characterization of binding and signaling properties of GPR30 in 2005 (Thomas), identification of binding and signaling properties of GPR30 as well as selective GPR30/GPER ligands (beginning in 2005, Prossnitz), and transcriptional effects of GPR30 beginning in 2004 (Maggiolini). The authors conclude with an outlook for the next twenty years of research in the GPER field. The second article in this special issue by Nadal and colleagues (Extranuclear-initiated estrogenic action of endocrine disrupting chemicals: is there toxicology beyond Paracelsus?) examines the genomic (nuclear) and non-genomic (extra-nuclear) roles of the endocrine disrupting chemicals (EDCs) bisphenol-A (BPA), and its more recently employed alternative, bisphenol-S (BPS), particularly in obesity and diabetes, via both classical estrogen receptors (ER α and ER β) and GPER. They discuss the biphasic/U-shaped dose responses (hormesis) often observed with such compounds, emphasizing the fact that despite effects sometimes not being observed at high doses of EDCs, one cannot conclude that effects at low doses will not be observed and potentially detrimental, particularly under conditions of chronic exposure.

The third article in this special issue by Thomas (Role of G protein-coupled estrogen receptor GPER/GPR30 in maintenance of meiotic arrest in fish oocytes) focuses on the mechanisms of estrogen-mediated oocyte meiotic arrest in teleost fishes, which occurs via GPER-mediated activation of Gs protein and cAMP production, in an EGFR-dependent pathway that further involves regulation of EGFR expression on the oocyte membrane by progesterone component 1 (PCRM1). These effects of estrogen are similarly initiated by the GPER-selective agonist G-1, therapeutic nuclear ER antagonists (ICI 182,780 and tamoxifen) as well as the EDC discussed by Nadal, BPA. In the fourth article by Sharma et al. (Roles of G protein-coupled estrogen receptor GPER in metabolic regulation), the sexual dichotomy of obesity and its associated risk factors (metabolic syndrome) are discussed with respect to the beneficial roles of estrogen in metabolic regulation. In addition to established roles for ER α in these mechanisms, GPER has more recently become recognized as an important mediator of metabolic processes, including adiposity, energy balance, insulin sensitivity and glucose tolerance as well as islet function and survival, suggesting therapeutic opportunities for GPER-targeted drugs.

The next two articles in this special issue by Filardo (A role for G protein-coupled estrogen receptor (GPER) in estrogen-induced carcinogenesis: dysregulated glandular homeostasis, survival and metastasis) and Lappano and Maggiolini (GPER is involved in the functional liaison between breast tumor cells and cancer-associated fibroblasts (CAFs)) focus on the roles of estrogen, via GPER activity, in breast (and gynecological) carcinogenesis. Filardo discusses how GPER is becoming recognized for its roles in a wide array of systems that contribute to estrogen-induced effects associated with carcinogenesis, such as tumor cell proliferation, invasion and migration, but more broadly, obesity, vascular physiology, immune regulation and wound healing. These effects are particularly important as they regulate the tumor microenvironment, either facilitating or inhibiting the progression of

cancers, in the case of GPER via the activation of production of proteinases, growth factors and integrins. Lappano and Maggiolini build on these ideas with a focus on the roles of GPER in cancer-associated fibroblasts and the interaction with the tumor microenvironment, which play important roles in the initiation, progression, metastasis and recurrence of cancers. In particular, GPER is involved in the estrogen-mediated upregulation and secretion of paracrine factors that stimulate tumor cell proliferation and migration and angiogenesis, such as connective tissue growth factor and vascular endothelial growth factor.

In the seventh article, Hadjimarkou and Vasudevan discuss the effects of estrogen receptors (both classical and GPER) on behavior (GPER/GPR30 in the brain: Crosstalk with classical estrogen receptors and implications for behavior). The effects of estrogen in the brain are widespread and diverse, as is the expression of individual estrogen receptors, leading to complex effects on social behaviors, memory, and state anxiety. Although effects of GPER expression and activation on these behaviors have been demonstrated, little is known regarding how these multiple estrogen receptors interact to drive final outputs. The authors address, with examples, multiple potential mechanisms of cross-talk between these receptor systems, including synergistic and additive activation of common signaling pathways, activation of parallel unique signaling pathways leading to a common output, sequential activation within the same pathway, antagonistic actions of GPER on classical ERs and complete independence, where one receptor type alone is sufficient to elicit a behavioral response. These concepts provide a framework to understand the complex roles of multiple estrogen receptors, not only in the nervous system, but throughout the body.

The next three articles focus to a large extent on the roles of GPER in various aspects of vascular function and disease. Fredette et al. examine the role of GPER and mechanisms involved in estrogen-mediated nitric oxide production in endothelial cells that yield vasodilatory responses (Role of GPER in estrogen-dependent nitric oxide formation and vasodilation). Not only does GPER mediate eNOS phosphorylation and nitric oxide production in response to estrogen and G-1, it also stimulates nitric oxide production in response to the SERMs tamoxifen and raloxifene as well as the SERD ICI 182,780 (Fulvestrant). In addition, the vasodilatory responses to estrogen in the aortae of GPER-deficient mice are substantially reduced and those to G-1 completely absent. In the next article, I discuss the beneficial yet sometimes paradoxical effects of GPER-selective ligands (GPER modulators: Opportunity Nox on the heels of a class Akt). The salutary effects of the GPER-selective agonist G-1 in murine models of multiple sclerosis, cardiovascular diseases (e.g. atherosclerosis, myocardial infarct, hypertension), stroke and neurological injury are complex but often appear to involve direct effects via the activation of Akt (as well as Erk1/2 and other intracellular pathways) as well as indirect effects via immune modulation. Cancer represents a complex scenario where both GPER-selective agonists and antagonists have shown benefit, depending on the cancer, via distinct mechanisms. Most recently, however, an unexpected role for GPER in the maintenance of NADPH oxidase expression has been described, wherein GPER deficiency or inhibition (with the GPER-selective antagonist G36) reduces Nox1 expression and superoxide production, in turn leading to improved vascular and cardiac function with age, as well as prevention of hypertension in a more acute model. The novel role of GPER in the maintenance of NADPH oxidase expression is addressed in greater detail by Barton and Meyer in the next article (GPER blockers as Nox

downregulators: a new drug class to target chronic non-communicable diseases) that reviews recent work on the role of GPER, and specifically GPER antagonists (blockers) as Nox downregulators, in regulating oxidative stress, a hallmark of many chronic non-communicable and fibrotic diseases.

The final two articles in this special issue take us away from estrogen signaling to focus on progesterone and aldosterone. Leehy et al. (Progesterone Receptors (PR) Mediate STAT Actions: PR and Prolactin Receptor Signaling Crosstalk in Breast Cancer Models) discuss the role of progesterone and its receptor(s), through their induction of the prolactin receptor, in downstream signaling via JAKs and STATs to facilitate alveolar morphogenesis in the breast during pregnancy. Cross-talk between the pathways stimulated by progesterone and prolactin, as well as those of the estrogen receptors, is an important factor in breast carcinogenesis and progression. The effect of these hormones on mammographic density, an important indicator of breast cancer risk, is also discussed with a goal of reducing breast cancer development in high-risk women. In the last article, Wehling discusses our understanding of both the rapid and genomic actions of aldosterone and the receptors involved (Rapid actions of aldosterone revisited: receptors in the limelight), particularly under the Mannheim classification of non-genomically initiated steroid effects. Recent work has associated GPER with the rapid effects of aldosterone, leading to the conclusion, somewhat premature, that GPER is also an aldosterone-binding receptor, given the inability to demonstrate aldosterone binding to GPER under the conditions of estrogen binding. This article provides a beautiful synopsis of the challenges that have faced those studying the rapid effects of steroids over the last decades. Nevertheless, we can perhaps find solace in the introductory statement by Wehling: “Mission accomplished – it is now no longer a matter of debate whether rapid actions of steroid hormones do exist or do not exist.”

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Figure 1.

Steroid hormones mediate their effects on cells through multiple receptor types (SR, steroid receptor), including classical nuclear steroid hormone receptors (e.g. ER α), located in the cytoplasm (green), nucleus (red) or tethered to the plasma membrane (yellow), and transmembrane receptors (e.g. GPER), localized either to the plasma membrane (dark purple), intracellular membranes (light purple) or possibly the nucleus (not shown). Steroid receptors can either directly (red arrow) or indirectly (via other transcription factors, purple arrow) regulate gene expression; they also stimulate multiple "rapid" signaling pathways, such as Src, MAPK, PI3K, NOS and Ca⁺⁺ mobilization, which can also modulate the activity of classical steroid receptors, including independently of steroid binding (blue arrow). The interactions of these multiple receptors and pathways for a single steroid hormone are clearly complex and complicated further by interactions with other steroid and non-steroid receptors and signaling pathways.