Published in final edited form as:

Nat Rev Endocrinol. 2015 November ; 11(11): 640–641. doi:10.1038/nrendo.2015.179.

Understanding reproductive endocrine disorders

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Abstract

The past decade has witnessed incredible advances in the field of reproductive endocrinology. The use of new genetic and genomic tools has had a particular impact, leading to advances in our understanding, diagnosis and treatment of reproductive endocrine disorders, particularly those related to the neuroendocrine control of reproduction and ovarian biology.

In the 10 years since *Nature Reviews Endocrinology* was first published, many important advances in the field of reproductive endocrinology have occurred. During this decade, incredible advances have been made in science and medicine in general as a result of new tools (such as genetics, epigenetics and big data) that are available in discovery research and can be applied to human biology and medicine. These advances have made the past decade an exciting time to be involved in translational research in reproductive biology. As the many advances in this field over the past decade could not all be included in this article, I have limited the scope to advances involving, directly or indirectly, hormones, neuroendocrine factors and paracrine factors.

I will start at the top of the reproductive axis, with advances in our understanding of the neuroendocrine control of reproduction (Figure 1). Hypothalamic gonadotropin-releasing hormone (GnRH) is at the top of the axis and has effects in the pituitary gland, where peripheral and central signals are integrated to control the output of gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In turn, LH and FSH act on the gonads to stimulate gametogenesis and the production of gonadal sex steroids and peptides, including estrogens, progesterone and testosterone, as well as inhibins. Although GnRH has historically been considered to be at the apex of the reproductive axis, the past decade has led to important advances in our understanding of upstream regulators of GnRH, heralded by two key publications.^{1,2} Two groups independently reported the identification of mutations in *GPR54* (now better known as *KISS1R*), which encodes a G protein-coupled receptor, in patients with hypogonadotropic hypogonadism, a disorder characterized by the absence of spontaneous pubertal maturation, infertility and low levels of sex steroid hormones in association with inappropriately low-normal levels of LH and FSH.

These two landmark papers reinvigorated the field of reproductive neuroendocrinology. Subsequently, a multitude of studies in animal models, as well as in humans, determined that

Competing interests

The author declares no competing interests.

the ligand for this receptor, kisspeptin, is a potent stimulator of GnRH secretion, is produced in specific hypothalamic neuronal populations and directly activates kisspeptin receptors in GnRH neurons. These findings confirm that kisspeptin is an upstream regulator of GnRH secretion. Four key roles of kisspeptin have been demonstrated by the >1,400 papers that have been published on this topic over the past decade. Firstly, the kisspeptin system is a gatekeeper of puberty and GnRH secretion. Secondly, kisspeptin is important for regulation of male and female fertility. Thirdly, kisspeptin-secreting neurons are important mediators of both negative and positive feedback of estrogen, thereby providing new insights into the regulation of ovulation and the menstrual or estrous cycle. Fourthly, kisspeptin is an important component of the link between metabolism and reproduction, as well as of other disruptors of reproductive control such as stress.

The identification of this new regulator of GnRH secretion using human genomics ushered in a new era of genetic discoveries in the control of puberty and reproduction, notably leading to the identification of loss-of-function mutations in the genes encoding neurokinin B (NKB) and its receptor, the neurokinin 3 receptor (NK3R), in patients with hypogonadotropic hypogonadism.³ This discovery took us further up the neuronal ladder of GnRH control, with demonstrations that both NKB and NK3R are expressed in kisspeptin neurons and that this system regulates kisspeptin secretion to control GnRH release. These discoveries are already affecting clinical care, with intense pharmaceutical interest in the development of kisspeptin agonists and antagonists and a clinical study demonstrating the potential utility of kisspeptin to effectively and safely trigger oocyte maturation in women undergoing *in vitro* fertilization, with a possible reduction in the risk of ovarian hyperstimulation syndrome.⁴ In the past few years, the application of genomic tools to study patients with central precocious puberty (CPP; characterized by premature activation of GnRH secretion and early onset of puberty) has led to the identification of mutations in *MKRN3* as a prevalent cause of CPP, confirming the genetic basis of this disorder and identifying the first inhibitor of GnRH secretion in humans.⁵ This discovery has already had clinical implications in the diagnosis of CPP, enabling genetic counselling of family members and early treatment of this disorder.⁵

These advances in our understanding of the neuroendocrine control of reproduction could improve the safety of fertility induction in patients at risk of ovarian hyperstimulation syndrome, such as those with polycystic ovary syndrome (PCOS). However, additional advances in the treatment of these patients have also been made in the past decade. The historical mainstay of treatment for women with PCOS has been an estrogen–progestin contraceptive and clomiphene citrate when fertility is desired. PCOS is also associated with metabolic disturbances such as obesity and insulin resistance. Therapy with the insulin sensitizer, metformin, ameliorates the metabolic disturbances seen in PCOS; however, despite reports of improved ovulation rates, metformin did not increase the rate of live births.⁶ Aromatase inhibitors (such as letrozole) have been proposed as a method to induce ovulation in women with PCOS (Figure 1). These drugs would also have stimulatory effects on the hypothalamic–pituitary–gonadal axis and might be better than clomiphene citrate, providing more physiologic hormonal stimulation of the endometrium, a lower rate of multiple pregnancies and a more favourable adverse effect profile. Indeed, a double-blind,

multicentre, randomized trial demonstrated superiority of letrozole over clomiphene citrate for fertility induction in women with PCOS.⁷ Genes associated with PCOS, most notably *DENNDIA*, have been identified in genome-wide association studies and could open up opportunities for the development of additional targets for the treatment of this disorder (Figure 1).⁸

The importance of anti-Müllerian hormone (AMH) in female reproduction has been revealed over the past decade. AMH was initially known as a ‘male’ hormone because of its role in male sexual differentiation; it is produced in the testes and causes regression of the Müllerian ducts during male fetal sexual differentiation. AMH was subsequently shown to be produced in granulosa cells of the ovary and identified as an inhibitor of primordial follicle recruitment. Now recognized as a biomarker of ovarian reserve, serum levels of AMH are being used in the clinic as reliable predictors of responsiveness to fertility induction therapy,⁹ of ovarian damage and effects on the ovarian reserve after chemotherapy or radiotherapy and of age at the start of menopause.¹⁰ Thus, AMH is now recognized as an important ‘female’ hormone that is crucial for maintaining the right tempo of folliculogenesis, and with important diagnostic implications that enable a personalized approach to fertility induction therapy.

As we reflect on the many advances in reproductive endocrinology that have occurred in the past decade, we likewise can look forward to the discoveries of the next decade; for example, the further development and application of selective progesterone receptor modulators, elucidation of the effects of endocrine disruptors on oogenesis and spermatogenesis and the translation of epigenetic discoveries into clinical care. It is with great anticipation and excitement that we can look ahead to the next wave of discoveries and advances to improve our understanding of the most fundamental of biologic processes—reproduction and the preservation of our species.

Acknowledgments

I would like to acknowledge my many colleagues who contributed ideas and suggestions for inclusion in this review, including L. Halvorson, W. Kuohung, E. Norwitz, H. Taylor and L. Heckert, among others. I would also like to acknowledge the support of the NIH (grant numbers: R01 HD019938, R01 HD 082314, U54 HD028138 and K12 HD051959).

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Figure 1.

Advances in reproductive endocrinology related to hypothalamic and ovarian control of reproduction. Neurokinin B, kisspeptin and MKRN3 have been identified as regulators of GnRH release in both male and female individuals that modulate the timing of puberty, fertility and feedback effects of estrogen and other sex steroids. Letrozole, an aromatase inhibitor, improves fertility induction in women with PCOS. DENND1A is involved in the pathogenesis of PCOS and might be a new target for treatment of PCOS. AMH is now recognized as a biomarker of ovarian reserve for fertility induction therapy. Abbreviations: AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PCOS, polycystic ovary syndrome.