Current and future applications of GnRH, kisspeptin and neurokinin B analogues

Robert P. Millar and Claire L. Newton

Abstract | Reproductive hormones affect all stages of life from gamete production, fertilization, fetal development and parturition, neonatal development and puberty through to adulthood and senescence. The reproductive hormone cascade has, therefore, been the target for the development of numerous drugs that modulate its activity at many levels. As the central regulator of the cascade, gonadotropin-releasing hormone (GnRH) agonists and antagonists have found extensive applications in treating a wide range of hormone-dependent diseases, such as precocious puberty, prostate cancer, benign prostatic hyperplasia, endometriosis and uterine fibroids, as well as being an essential component of *in vitro* fertilization protocols. The neuroendocrine peptides that regulate GnRH neurons, kisspeptin and neurokinin B, have also been identified as therapeutic targets, and novel agonists and antagonists are being developed as modulators of the cascade upstream of GnRH. Here, we review the development and applications of analogues of the major neuroendocrine peptide regulators of the reproductive hormone cascade: GnRH, kisspeptin and neurokinin B.

Millar, R. P. & Newton, C. L. *Nat. Rev. Endocrinol.* **9**, 451–466 (2013); published online 2 July 2013; doi:10.1038/nrendo.2013.120

Introduction

The development of synthetic molecules that modulate reproductive hormone levels has had a major effect on our lives. Arguably, the development of the female contraceptive pill was the single most important contribution to the empowerment of women and their increased participation in professional and public life. On the other hand, anabolic steroids are the most utilized enhancer of competitive athletic performance, whilst estrogen and androgen antagonists, and inhibitors of their synthesis and bioconversion, are extensively employed as therapeutics for breast and prostate cancers—two of the most prevalent cancers in men and women. A wide range of tissues are stimulated by sex steroid hormones, and a large number of hormone-dependent diseases arise from dysfunctional sex hormone stimulation. These diseases include benign prostatic hyperplasia, bone loss, endometriosis, polycystic ovary syndrome (PCOS), uterine fibroids, ovarian cancer, muscle wasting and various aspects of metabolic and cognitive dysfunction (Box 1).

Regulation of the reproductive system is initiated by an array of external and internal inputs, such as photoperiod, metabolic products and nutrients, growth factors, stress, infection and inflammation, as well as many central and peripheral growth factors and hormones. These inputs are integrated in the brain and hypothalamus to regulate the biosynthesis and secretion of gonadotropin-releasing hormone (GnRH; Figure 1). GnRH is conducted by portal vessels to the anterior pituitary where it engages the GnRH receptor (GnRH-R) in gonadotrope cells to recruit intracellular signalling machinery that stimulates the biosynthesis and secretion of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[1,2] LH and FSH then act on the ovary and testis to stimulate the production of gametes and steroid and peptide hormones. These hormones feed back in a positive and negative manner at the hypothalamus and pituitary to regulate the reproductive hormone cascade.[1,3]

The diverse external and internal factors regulating GnRH do so through a complex network of neurotransmitters and neuropeptides in the central nervous system (CNS) and hypothalamus.[3–5] In humans, inactivating mutations of two of these neuropeptides, kisspeptin and neurokinin B, or their cognate receptors results in a failure to progress through puberty and in adult infertility, highlighting the crucial role of these neuropeptides in GnRH neuron activation.[6–11] In addition to these major modulators of GnRH secretion, neuropeptide Y, products of the pro-opiomelanocortin protein, gonadotropin-inhibitory hormone (GnIH) and neurotransmitters (such as γ-amino butyric acid and glutamate) also regulate GnRH neuron activity.[12,13] All of the hormones in the cascade from the brain to the pituitary, gonads and peripheral tissues are potential targets for the development of analogues that modulate the production of gametes and sex steroid hormones that have an effect on diverse target tissues. The sites of current and potential intervention in the reproductive hormone cascade are indicated in Figure 1.

Sex steroid agonists, antagonists and inhibitors of their synthesis have been extensively employed for

Competing interests
R. P. Millar declares associations with the following companies: Euroscreen, Ferring. See the article online for full details of the relationships. C. L. Newton declares no competing interests.

Mammal Research Institute, Department of Zoology and Entomology, Faculty of Natural and Agricultural Sciences, University of Pretoria, Lynnwood Road, Hatfield 0028, Pretoria, South Africa (**R. P. Millar**). UCT/MRC Receptor Biology Research Unit, Institute of Infectious Diseases and Molecular Medicine and Division of Medical Biochemistry, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory 7925, Cape Town, South Africa (**R. P. Millar, C. L. Newton**).

Correspondence to: R. P. Millar robertpetermillar@gmail.com

© 2013 Macmillan Publishers Limited. All rights reserved