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Scientific and Clinical Aspects

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This work is dedicated to my good friend and mentor, the late Dr. Atko Viru, of Tartu University, Estonia.

Preface

In the late 1970s medical science was beginning to understand that exercise training, while normally an extremely positive physiological stimulus, could also have some drawbacks. Landmark research studies by scientists such as Dr. Barbara Drinkwater, Dr. Anne Loucks, and Dr. Michelle Warren, as well as others, demonstrated that exercise training could be a causative factor in disrupting the endocrine control of a woman's reproductive system leading to the development of "athletic amenorrhea" (secondary amenorrhea). This medical condition is now recognized as part of the conditions associated with the Female Athletic Triad.

The basic premise of the research work on the development of athletic amenorrhea in women can be conceptualized as follows:

Exercise → Female Reproductive Hormones → Physiologic Consequences (negative)

That is, aspects of exercise and exercise training modulate the functioning of the female reproductive hormones. This modulating influence can be highly negative, leading to low estrogen and progesterone states and disruption of normal ovary function and menstruation. Contemporary research has demonstrated that the critical aspects initiating the sequence of such events are energy availability (i.e., development of a low energy availability state; recently designated as part of the Reduced Energy Deficient in Sports conditions [REDS] by an International Olympic Committee medical commission).

As a young professional I found the research on athletic amenorrhea an exciting and fascinating aspect of exercise endocrinology. But my curiosity also caused me to think about the relationship in a different fashion and ask the question—If exercise affects reproductive hormones, could the reproductive hormones have physiological effects unrelated to reproduction that influences the capacity of women to exercise? This seemed a logical question to me as many hormones have more than

one physiological effect/impact, and structurally many reproductive hormones have chemical structures similar to many metabolic and water balance hormones. In other words I wondered:

Female Reproductive Hormones → Exercise → Physiologic Consequences
(negative/positive?)

After studying the research literature, it was apparent that animal researchers had been asking this question and seeing that the female reproductive hormones did affect physiological systems and processes that affected exercise capacity. At that time, nearly 30 years ago, the human-based literature was extremely sparse. With that, I and a number of other researchers began to pursue the question of whether the female reproductive hormones have physiological impacts on the bodily systems that are essential to the exercise capacity of women exercisers.

In asking this question, to myself, the underlying premise was not to examine women to see why in some activities men are better. But, more to understanding the unique physiology of women and whether female sex hormones might account for some of the variance in physiological performance between amenorrheic and eumenorrheic women, and within women across the age span as they experience menarche to menopause. That has been my interest in pursuing this absorbing topic and why I wanted to develop this book.

This book was developed with hope that the select group of professionals writing the various chapters could address this last question. Like nearly all written works, this one could be improved and be made better, but I am extremely proud and thankful to the authors who contributed and put forth so much hard work. Each discussed topic provides current insight into the state-of-the-art research in the respective topic area. It is hoped the reader will be as excited and fascinated after reading the individual topics as the authors were in writing them. I also hope the insights provided here will inspire new researchers to ask questions about the roles of female sex hormones in exercise and pursue investigations to seek answers to those questions.

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Chapter 1
The Hypothalamic–Pituitary–Ovarian Axis and Oral Contraceptives: Regulation and Function

Hope C. Davis and Anthony C. Hackney

Introduction

Over the past few generations female participation in sports has continued to increase, which has resulted in a greater need for research in the area of sports medicine, physiological effects, and consequences of exercise by women. Specific further work is still needed particularly in the area of reproductive endocrinology. The female reproductive system is a complex physiological system consisting of many hormonal and regulatory components. Thus, it is imperative for exercise scientists who wish to study the female reproductive system to have a strong knowledge base of the controlling regulatory axis of the system, referred to as the Hypothalamic–Pituitary–Ovarian (HPO) axis.

The intent of this chapter is to provide such background information about the neuroendocrine basics of the female reproductive system relative to: the hypothalamus, the pituitary, the ovary, and the uterus. The chapter focuses on providing a brief review of the essential endocrinology of the menstrual cycle in health females as well as providing information about oral contraceptive (OC) function and use. This context provides an essential framework for discussions provided in subsequent chapters in this book.

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Hypothalamic–Pituitary System

Proper functioning of the reproductive system is critical not only to reproductive health, but overall health in women. Abnormal reproductive health can sometimes be characterized by amenorrhea and, or other medical maladies (see later discussion, this chapter).

Regulation of the female reproductive system consists of complex interactions between endocrine feedback loops of the hypothalamus, pituitary, and ovary. Although there is debate whether the hypothalamus or pituitary is the most important regulator in the process, there is no denying that all three neuroendocrine glands must work together to ensure proper functioning (Sam and Frohman 2008).

The signaling process begins in the hypothalamus, where gonadotropin-releasing hormone (GnRH) is released into the blood stream and travels to the pituitary gland. The pituitary responds by releasing gonadotropin hormones, specifically luteinizing hormone (LH) and follicle stimulating hormone (FSH) in females. The anterior pituitary also releases growth hormone (GH), thyroid-stimulating hormone (TSH), prolactin, and adrenal corticotrophin hormone in response to a variety of other hypothalamic stimuli; these other hormones control primarily growth-development, metabolism, and responses to stress. The posterior pituitary produces hormones as well, namely oxytocin and antidiuretic hormone (ADH; also called vasopressin). Oxytocin controls lactation as opposed to growth and development, and ADH functions with aldosterone (released by adrenal cortex) to maintain fluid and electrolyte balance (Brooks et al. 2005). In healthy women GnRH is released in a pulsatile manner, and consequently FSH and LH are released in a similar pulsatile pattern from the anterior pituitary (Speroff and Fritz 2005).

Current research suggests that a set of brain peptides encoded by the *Kiss1* gene, known more commonly as kisspeptin, may be an important upstream regulator in GnRH release in humans as well as many other mammalian species (Lapatto et al. 2007). Kisspeptin neurons in the hypothalamus modulate the prepubescent LH surge that occurs in females as well as the actions of sex steroids on GnRH neurons (Gu and Simerly 1997). This regulation of the reproductive axis is illustrated by the reproductive defects that exist in mice and other mammals when the kisspeptin receptor gene is disrupted (Dungan et al. 2007). Additional physiological parameters, such as metabolic disruptions (e.g., under nutrition), can decrease kisspeptin expression, which in turn can suppress reproductive functioning (Castellano et al. 2005; Luque et al. 2007).

Sex Steroid Hormones

Estrogen

Estrogen is one of the two major reproductive hormones released as a result of the HPO axis activity. Estrogen refers to a group of similarly structured steroid hormones that are produced primarily in the ovaries of females. The estrogen group is made up of estrone, estriol, and estradiol-β-17, the latter of which

contributes primarily to reproductive function (Wierman 2007). These estrogens have physiological roles in both males and females, including soft tissue, skeletal muscle, and the epidermis (Wierman 2007). The estrogens (estrone and estriol) are essentially produced locally in target tissue (peripheral conversion) such as adipose cells. Estradiol-β-17, the estrogen primarily produced at the ovaries, is responsible for primary and secondary female sex characteristics and therefore is the main estrogen discussed in this chapter.

As previously stated, the HPO axis is the main regulator of estrogen production in women. The pituitary release of FSH and LH results in binding to the ovarian receptors for these hormones, which induces the production and secretion of both estrogen and progesterone (see later section; Ferin 1996).

Specifically within the ovary, LH binds to LH receptor cites on the thecal cells. When stimulated, they convert available cholesterol into androgens (McNatty et al. 1979). These androgens are then transported to the granulosa cells where FSH binds to FSH receptors, thus stimulating conversion of androgens into estradiol-β-17 via aromatase enzymes (Hillier 1987).

Estrogen gradually increases during the follicular phase of the menstrual cycle in order to support the developing oocyte (McNatty et al. 1979). Once the egg is released from the ovary, the follicle shifts from estrogen to progesterone production and estrogen levels slowly decrease throughout the luteal phase of the cycle. Although the ovary will still produce estradiol-β-17 during the cycle, it will be in conjunction with progesterone, thus decreasing the overall concentration and effectiveness of estrogen (see discussion later section).

Recent studies have found that natural mutation of estrogen receptors (ERs) or deficiency of aromatase (the enzyme that converts androgens to estradiol-β-17 in the ovary and some peripheral tissues) results in tissue specific deficits, including the vascular system, central nervous system, gastrointestinal tract, immune system, skin, kidney, and lungs (Couse and Korach 1999; Curtis and Korach 2000; Eddy et al. 1996; Hewitt and Korach 2003; Matsumoto et al. 2005; Robertson et al. 1999). Lastly, physiological estradiol-β-17 can increase lipolysis and inhibit glycogen utilization during rest and acute exercise (Hackney 1999). It is thought that estradiol-β-17 may directly alter enzymatic activity or indirectly affect insulin sensitivity thereby affecting glycogen usage (Bunt 1990). Estrogens not only control primary and secondary sex characteristics in females, but also regulate a number of functions throughout female and male target tissues in the body through its direct and indirect impacts on other neuroendocrine agents (Bunt 1990; see Fig. 1.1 and 1.2).

Progesterone

Progesterone is the second major reproductive hormone produced and regulated via the HPO axis. Progesterone is the major progestogen (steroid hormone classification) and is produced predominately by the ovaries, but it is also produced locally in some tissues. Similarly to estradiol-β-17, LH regulates progesterone production within the ovary. During the luteal phase of the menstrual cycle, LH