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Cellular and Animal Studies: Insights into Pathophysiology and Therapy of PCOS

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Basic science studies have advanced our understanding of the role of key enzymes in the steroidogenesis pathway and those that affect the pathophysiology of PCOS. Studies with ovarian theca cells taken from women with PCOS have demonstrated increased androgen production due to increased CYP17A1 and HSD3B2 enzyme activities. Furthermore, overexpression of *DENND1A* variant 2 in normal theca cells resulted in a PCOS phenotype with increased androgen production. Notably, cellular steroidogenesis models have facilitated the understanding of the mechanistic effects of pharmacotherapies, including insulin sensitizers (e.g., pioglitazone and metformin) used for the treatment of insulin resistance in PCOS, on androgen production. In addition, animal models of PCOS have provided a critical platform to study the effects of therapeutic agents in a manner closer to the physiological state. Indeed, recent breakthroughs have demonstrated that natural derivatives such as the dietary medium-chain fatty acid decanoic acid (DA) can restore estrous cyclicity and lower androgen levels in an animal model of PCOS, thus laying the platform for novel therapeutic developments in PCOS. This chapter reviews the current understanding on the pathways modulating androgen biosynthesis, and the cellular and animal models that form the basis for preclinical research in PCOS, and sets the stage for clinical research.

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Introduction

Following on from the previous chapter, where the diagnostic criteria of PCOS and the difficulty of establishing a defined set of criteria is discussed, it is apparent that PCOS is not just a clinical conundrum but also one with a pathophysiological origin that remains unclear. Basic science studies based upon cellular models of steroidogenesis and animal models of PCOS have been fundamental to the current understanding of the PCOS pathophysiology. This chapter reviews the current understanding on the pathways modulating androgen biosynthesis and the cellular and animal models useful for preclinical research in PCOS.

Regulation of androgen production

Basic science studies have advanced our understanding of the mechanisms of androgen secretion, a process fundamental to the pathogenesis of PCOS. Androgens are produced by the adrenal and gonads and are involved in the regulation of numerous developmental and physiological processes in women. Two major axes control androgen production in women: the hypothalamic–pituitary–adrenal axis and the hypothalamic–pituitary–ovarian axis (Fig. 1).

In the hypothalamic–pituitary–adrenal axis, the hypothalamus secretes corticotrophin-releasing hormone (CRH), which stimulates the production of adrenocorticotropic hormone (ACTH) by the anterior pituitary [1] (Fig. 1, left panel). ACTH after being released into the systemic circulation binds to specific receptors on adrenocortical cells in the adrenal gland to stimulate the production of adrenal

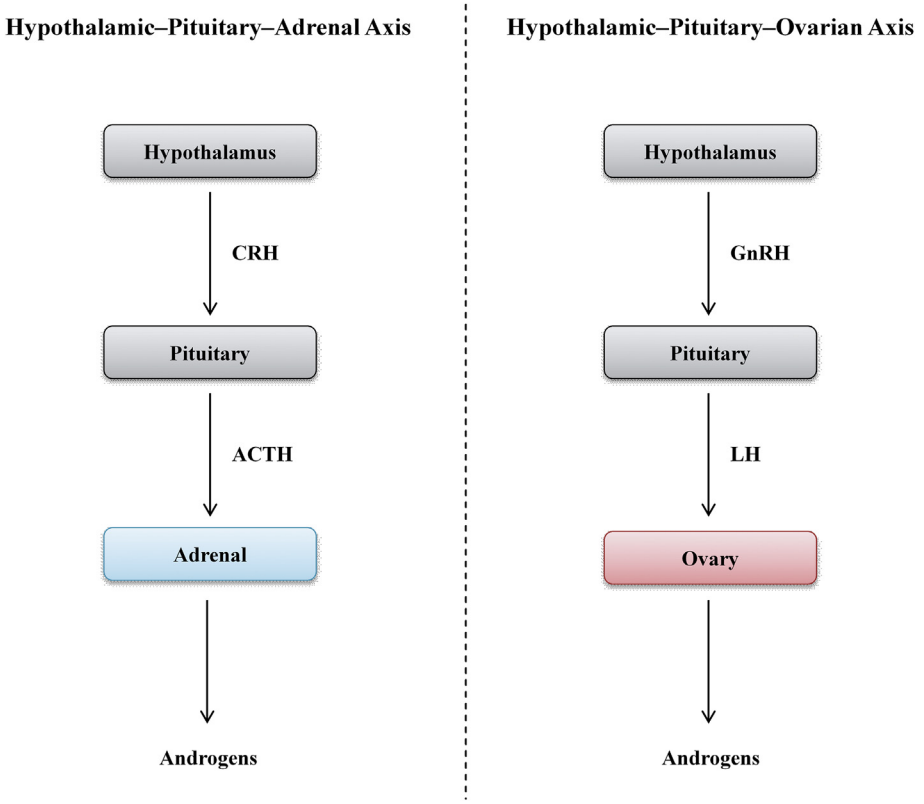

Fig. 1. Hypothalamic–pituitary–adrenal axis and hypothalamic–pituitary–ovarian axis. ACTH, adrenocorticotropic hormone; CRH, corticotrophin-releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.