How is the synthesis of testosterone regulated?

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The ability of a cell to make testosterone is defined by the presence of the steroidogenic machinery in an appropriate cellular environment able to respond in an optimal manner to the received stimuli. Testosterone, the major male sexual hormone, is synthesized and secreted primarily by Leydig cells of the testis. In these cells, testosterone synthesis is under the tight control of the pituitary gonadotrophin luteinizing hormone (LH), and also is influenced by local factors coming from other testicular cells or from external factors such as drugs and environmental chemicals.

There are a number of key points that are critical for the establishment and optimal function of the steroidogenic machinery responsible for testosterone synthesis in the Leydig cell (Figure 1). These include: (i) integrity of the plasma membrane LH receptor signal transduction cascade responsible for sensing and responding to the blood-borne LH; (ii) availability of sufficient amounts of the substrate cholesterol coming from the blood or synthesized de novo; storage or immediate availability of cholesterol for use in androgen production; (iii) de-esterification of cholesterol thus making available the stored cholesterol for androgen formation; (iv) integrity of the mechanism responsible for transporting cholesterol from intracellular stores into mitochondria; (v) availability of appropriate levels and combinations of the nuclear transcription factors controlling the expression of proteins involved in cholesterol transport and in testosterone biosynthesis; (vi) maintenance of appropriate organelle structures required for optimal testosterone formation; (vii) appropriate spatial and temporal expression of steroidogenic enzymes, mainly cytochrome P450 monooxygenases and dehydrogenases, responsible for metabolizing cholesterol to various intermediates leading to testosterone formation; and (viii) availability of the co-factors necessary for steroidogenic enzyme action. Steroids leave Leydig cells by passive transport. Steroids in the circulation exist as free or bound to extracellular proteins such as sex hormone binding globulin (SHBG), androgen binding protein (ABP) and/or albumin.

For Leydig cells to respond to LH and to function optimally, it is critical that the proteins involved in steroidogenesis, from the LH receptor to cholesterol transporting proteins and steroidogenic enzymes, are synthesized without any mistake in their amino acid sequences. Mutations of the involved proteins can be lethal or lead to disease states such as pseudohermaphroditism, hypogonadism, and infertility.

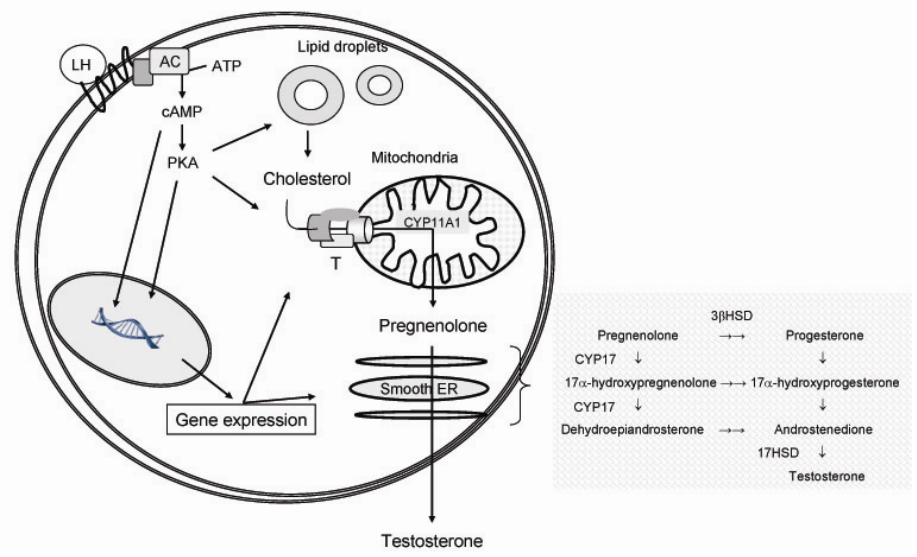

FIG. 1. Schematic representation of the steps involved in testosterone formation. Blood-borne luteinizing hormone (LH) binds to a G-protein coupled receptor leading to activation of adenylate cyclase (AC) that converts ATP to cAMP, the major second messenger of LH action in Leydig cells. cAMP subsequently activates the cAMP-dependent protein kinase (PKA), an event that triggers a series of reactions including the de-esterification of cholesterol from lipid droplets and activation of proteins, PKA substrates, involved in cholesterol transport into mitochondria. cAMP, as well as PKA act also in the nucleus activating steroidogenic protein and enzyme gene expression. Free cholesterol is transporter and imported into mitochondria via a multiprotein complex (T for transduceosome) formed to amplify the effect of LH and cAMP. This complex included proteins such as the A-kinase anchoring proteins PAP7 and AKAP121, steroidogenesis acute regulatory protein (StAR), translocator protein (18-kDa), and voltage-dependent anion channel. Imported cholesterol is metabolized to pregnenolone by the cytochrome P450 side chain cleavage (CYP11A1). Pregnenolone is subsequently metabolized in the smooth endoplasmic reticulum by a series of enzymes (CYP17, 3β-hydroxysteroid dehydrogenase and 17-hydroxysteroid dehydrogenase to form testosterone.

The amount of testosterone formed by the Leydig cells reflects specific needs of the body for cell growth, organ formation, masculinization and maintenance of androgen-dependent functions. During development, the differentiation of Leydig cell precursors leads to the establishment of specific

Leydig cell populations that are responsible for the formation of the amounts of testosterone needed at various ages. In the fetus, testosterone-forming fetal Leydig cells function in the prenatal masculinization of the male urogenital system. After birth this population disappears, and the adult Leydig cell population, evolving in an environment free of maternal factors, develops from a small pool of undifferentiated, self-renewing stem Leydig cells via a sequence of stages that include Leydig cell progenitors, immature Leydig cells and adult Leydig cells. These changes reflect the need for testosterone in the development of male characteristics, puberty and androgen-dependent functions. Changes in cell structure and gene expression are responsible for the morphological and functional differences among these various cell types; the basic components of the steroidogenic machinery are present but not used to the same extent. Thus, testosterone production changes during development are due to alterations in the cellular environment, and are designed for the optimal production of testosterone to accomplish specific needs. In aging, various components of the steroidogenic machinery fail to function at an optimal level, leading to a decline in androgen formation.

Although it seems that the pathway of testosterone formation and its regulation by LH are well established, there are many steps that have not been yet defined and questions have been raised about the adopted mechanisms leaving the field open for further investigation.

Suggested reading

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