New Insights into Alternate Signaling Pathways Involved in Steroid Hormone Biosynthesis

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The biosynthesis of steroid hormones by steroidogenic tissues is regulated through the action of trophic hormones. It has long been known that this trophic hormone action is mediated through the cAMP signal transduction pathway. In addition, a number of observations have shown that steroid biosynthesis has an absolute requirement for the release of arachidonic acid (AA) from intracellular phospholipids. This talk will discuss the role of an additional signaling pathway, the AA metabolizing pathway, in the biosynthesis of steroid hormones in testicular Leydig cells. Data indicating that steroid biosynthesis has an absolute requirement for both increases in intracellular cAMP and for metabolites of AA that are formed in the lipoxygenase metabolic pathway will be shown. It will further be demonstrated that the same signaling pathways involved in the stimulation of steroid hormones induce the expression of the steroidogenic acute regulatory (StAR) protein, providing the likely mechanism for the observed increase in steroids. During the course of studies on the role of AA metabolites on steroidogenesis, it was observed that inhibition of one of the AA metabolizing enzymes, cyclooxygenase 2 (COX2), resulted in significant increases in steroid biosynthesis. Further observations indicated that in the aging male rat, COX2 levels in the testicular Leydig cells are greatly increased. A potential link between elevated COX2 levels and the observed decreases in testosterone levels during the course of normal aging in males will be discussed. (Supported by NIH grant HD 17481 and funds from the Robert A. Welch Foundation).