POINT/COUNTERPOINT

Introduction

Steroidogenesis, StAR and PBR: Is There Light at the End of the Tunnel? (44213)

MICHAEL R. WATERMAN[1]

Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-0146

The biochemistry and physiology of steroidogenesis have been active areas of investigation for more than 30 years. Once the techniques of molecular biology were applied to this effort, the understanding of the regulation of steroidogenesis and the steroidogenic enzymes themselves moved forward at a rapid pace. While steroidogenesis is crucial for development and homeostasis in all animal species, the pattern of steroid hormone expression between different species is quite variable. However all steroidogenic pathways in all species begin in the mitochondrion with the conversion of cholesterol to pregnenolone. A mitochondrial steroid hydroxylase, cholesterol side-chain cleavage cytochrome P-450 (P-450scc), located in the inner mitochondrial membrane catalyzes this reaction. P-450scc activity is supported by a mini-electron transport chain located in the mitochondrial matrix, and it is presumed that P-450scc is an integral protein of the inner mitochondrial membrane that faces the matrix.

In addition to being a substrate for steroidogenesis, cholesterol is a component of membranes. Presumably the inner mitochondrial membrane in the steroidogenic factories (adrenal cortex, Leydig cells in testis, thecal and granulosa cells in ovary) contain two pools of cholesterol; one for maintenance of membrane structure, which is found in inner mitochondrial membranes in all tissues, and a steroidogenic pool found exclusively or most abundantly in the above tissues. Cholesterol is one of the most hydrophobic lipids, and its conversion to the more polar pregnenolone occurs very rapidly in steroidogenic cells in response to stimulus by peptide hormones from the anterior pituitary (ACTH, LH, FSH). It has long been a mystery how steroidogenic cholesterol is transported rapidly from lipid stores or the site of *de novo* synthesis to the mitochondrion and then across the double membranes of the mitochondrion to the vicinity of P-450scc. The movement of cholesterol to the mitochondrion remains unsolved, but the transport of cholesterol from outside the mitochondrion across the outer mitochondrial membrane and the hydrophilic intermembrane space to the inner mitochondrial membrane is becoming clearer. At least, as summarized in the minireviews by Stocco and Papadopoulos, key proteins required for this transport have been identified.

In studies carried out over 30 years or more, a variety of criteria have been established for proteins that participate in the regulated transport of cholesterol to P-450scc. In his minireview, Doug Stocco outlines these criteria and presents compelling arguments that the protein characterized in his laboratory, steroidogenic acute regulatory protein (StAR) meets these criteria. One of the key discoveries leading to the conclusion that StAR is essential in acute regulation of steroidogenesis is that the basis of all known examples of congenital lipoid adrenal hyperplasia are mutations in the primary amino acid sequence of StAR. This genetic disease results from a deficit or absence of steroid hormone biosynthesis and was originally thought to be due to mutations in P-450scc itself. As will be seen from the Stocco review, the pattern of StAR expression, StAR synthesis, and biochemical studies of this protein along with the genetic defect strongly argue that StAR is the key regulatory protein in the acute steroidogenic response to peptide hormones.

However, data obtained in the study of StAR leave one big question. How does StAR facilitate the movement of cholesterol to P-450scc? The minireview by Vassilios Papadopoulos describes a system that could provide the an-

[1] To whom requests for reprints should be addressed at Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, TN 37232-0146.

0037-9727/98/2172-0121$10.50/0

swer. The peripheral-type benzodiazapine receptor (PBR) is described as a multiprotein channel that allows movement of cholesterol through it. Thus by concentration of PBR at contact points between the inner and outer mitochondrial membranes in response to peptide hormones, cholesterol could move efficiently from outside the mitochondrion to the vicinity of P-450scc. PBR is widely or ubiquitously distributed and could be important in providing a path for cholesterol leading to oxysterol production in all cells, necessary for regulation of cholesterol biosynthesis. From studies outlined in the Papadopoulos review, it is apparent that PBR also has features that match certain of the criteria established for proteins involved in the acute events in steroidogenesis.

Thus the reader of these reviews will be faced with the challenge of trying to fit StAR and PBR together into a coherent model for rapid, regulated movement of cholesterol from outside the mitochondrion to P-450scc. The genetic evidence for the role of StAR is irrefutable. However, no compelling biochemical hypothesis of how cholesterol moves from one membrane to another across the hydrophilic intermembrane space arises from the study of StAR. If, in fact, PBR can serve as a channel through which cholesterol moves particularly as a result of its being concentrated at membrane contact points in response to peptide hormone action, perhaps common ground exists between Stocco and Papadopoulos. Each strongly touts their specific system as the key, and the reader of both reviews will come away with appreciation of a large amount of data supporting roles of both StAR and PBR in acute steroidogenesis. We seem left with a working hypothesis involving a requirement of StAR for regulation of cholesterol movement into steroidogenic mitochondria and of PBR as a means by which transport of cholesterol to the inner mitochondrial membrane could be accomplished. It can be anticipated that one fruitful avenue for future investigation of acute steroidogenesis will accommodate both proteins into the experimental scheme.