The Beta-Adrenergic Receptors

The Receptors

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Preface

Prior to 1974, the β -adrenergic receptors were known only indirectly as entities that responded to drugs in a selective manner to mediate a variety of physiologically important responses. During the intervening years, our view of β -adrenergic receptors has changed dramatically. The availability of high affinity ^{125}I -labeled radioligands selective for these receptors presaged an explosion of experimentation utilizing direct binding assays to establish the biochemical properties of the receptor protein. In the opening chapter, Stadel and Lefkowitz describe this development and its impact on our understanding of the molecular basis of β -adrenergic receptor function.

The availability of well-characterized receptor ligands, coupled with the development of efficient methods for detergent solubilization, formed the basis of receptor purification using affinity chromatography. The related technique of photoaffinity labeling provided a means to estimate the molecular mass of these receptors. The availability of substantial amounts of purified β_2 -adrenergic receptor allowed determination of segments of its amino acid sequence. This information led to the production of polynucleotide probes and eventually to cloning of the receptor gene and determination of the complete primary sequence of the receptor protein. Caron and Lefkowitz review the investigations leading to this major development and discuss the methods involved. They analyze our current perception of the relation of receptor function to its structure and discuss the general features of the G protein-interacting receptor family, of which the β -adrenergic receptors are prototypes.

Perkins, Hausdorff, and Lefkowitz examine the current status of ligand-induced desensitization of β -adrenergic receptor function. The role of receptor phosphorylation is discussed in terms of the involvement of cyclic AMP-dependent protein kinase and the newly discovered β -adrenergic receptor kinase (β ARK). Receptor endocytosis is examined as a mechanism for ligand-induced β AR

sequestration and a novel mechanism of receptor down-regulation is considered.

Elliott Ross next discusses in detail the methods and theories of membrane protein solubilization, purification, and reconstitution in a functional state, in defined phospholipid vesicles. His treatment focuses on the β -adrenergic receptor, but provides general insight into this important methodology for the analysis of structure/function relationships of membrane proteins.

The intact β -adrenergic receptor has routinely been found to be a poor antigen. However, knowledge of the amino acid sequence of the receptor provided the means for production of sequence-specific antibodies. The early frustrations and eventual success of the search for antibodies to the β_2 -adrenergic receptor is next described by Malbon, Moxham, and Brandwein. They critically review the techniques involved and discuss the insights gained into receptor secondary structure using immunological methods.

Barry Wolfe analyzes the information gained about the localization of β -adrenergic receptors in tissues and on cells using autoradiographic techniques. He provides a critical analysis of the techniques and the limits to conclusions that can be drawn from such data.

The chapters by Stiles and Insel, respectively, review our understanding of the regulation of β -adrenergic receptor function and/or expression by other hormones and neurotransmitters and the involvement of altered receptor function or expression in disease states.

Many of the important new insights into the structure of β -adrenergic receptors and the molecular bases of their various modes of action are revealed to be generally applicable to other members of this class of receptor molecules.

John P. Perkins

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