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Minireview Prologue

G Protein-coupled Receptors Minireview Series*

Martha Vaughan

From the Pulmonary-Critical Care Medicine Branch, NHLBI, National Institutes of Health, Bethesda, Maryland 20892

Several months ago the current understanding of some specific aspects of "Signaling by Heterotrimeric G Proteins" was summarized in a series of minireviews by some of those working most actively in the field. Although three quite different topics were addressed, there was an attempt to emphasize overall similarities of structure and function among the numerous α- and $\beta\gamma$-subunits and to provide an organizational framework within which subgroups of specific subunits could be considered and compared.

If the diversity and complexity of G protein interactions is daunting, the universe of G protein-coupled receptors, more than 1000 of which are known, could be considered overwhelming. Thanks to the efforts of a great many investigators, however, it is becoming possible to rationalize the enormous amount of available data in a way that is yielding a perception of underlying parallels (and differences) in their interactions with activating ligands, as well as with effectors and other molecules that modulate their activity or serve in a scaffolding/anchoring capacity. This issue of the Journal contains the first of a series of three minireviews on "Signaling by G Protein-coupled Receptors." It is hoped that they will provide an interesting and informative overview of these critical molecules.

The first G protein-coupled receptors to be purified and characterized were rhodopsin, the photon receptor from retinal rod outer segments, and the β-adrenergic receptor. They were the fruits of completely independent research efforts, directed on the one hand toward understanding the mechanism of light activation of cGMP phosphodiesterase and on the other toward the mechanism of activation of adenylyl cyclase by epinephrine. Differences in the agonists (catecholamines and photons) and effectors (adenylyl cyclase and cGMP phosphodiesterase) provided an early hint of the remarkable diversity of situations in which G protein-coupled receptors are employed to select, amplify, and transmit signals from the external environment to elicit cellular responses and modify functions. As a result of cDNA cloning, the structural resemblance of these two G protein-coupled receptors with seven membrane-spanning helices was established, and cloning made possible the subsequent extraordinarily rapid accumulation of information on other members of the family. More recently, notable advances in methodology and techniques of structural biology have facilitated studies in several laboratories that provide new details of mechanisms of agonist binding and initiation or transmission of signals, as well as the orientation and translocation of specific parts of the receptor molecule relative to the lipid bilayer membrane in which it resides.

The first minireview by Tae H. Ji, Mathis Grossmann, and Inhae Ji on "Diversity of Receptor-Ligand Interactions" summarizes briefly the overall three-dimensional structure of G protein-coupled receptors in cell membranes as background for the more detailed consideration of individual subfamilies. The latter are defined by differences in the kinds of agonist ligands with which they interact. The agonists range widely in size and structure from large glycoprotein hormones to relatively simple amines or nucleosides and even cations. Differences in receptor structure and mechanisms of ligand interaction then further characterize the subfamilies. This seems to be a useful (and enlightening) way of thinking about the multitude of G protein-coupled receptors.

Present knowledge of the conformational changes in G protein-coupled receptors that link agonist binding to G protein activation is described in the second minireview, "Mechanism of Agonist Activation," by Ulrik Gether and Brian K. Kobilka. They have focused on the rhodopsin-like receptors, which are the best known and appear to represent the largest family of G protein-coupled receptors. The model presented, along with the summary of experimental approaches employed to obtain data from which the three-dimensional molecular structure can be deduced, should facilitate understanding of current thinking about how these molecules transduce signals from the external environment to the G proteins that will, in turn, communicate with the effector.

The third minireview is an update on "New Roles for Receptor Kinases and β-Arrestins in Receptor Signaling and Desensitization." Phosphorylation of the receptor catalyzed by these specific kinases with resulting modification of its association with other proteins and its subcellular localization underlies the relatively rapid desensitization (as opposed to the slower down-regulation) or alteration of receptor function. Termination of activation and desensitization of receptors are, of course, as much a part of their regulatory function as the initiation and transmission of signals. An exciting product of the studies reviewed, however, is the realization that reactions hitherto viewed solely as parts of a mechanism for receptor desensitization may be equally important in signaling by G protein-coupled receptors, thereby increasing the potential scope and complexity of their physiological roles. The author, Robert J. Lefkowitz, continues to be a major contributor in this area, as he was in the purification and cloning of the β-adrenergic receptor in the 1980s.

* These minireviews will be reprinted in the 1998 Minireview Compendium, which will be available in December, 1998.