The Ionotropic Glutamate Receptors

The Receptors

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Preface

The field of the excitatory amino acids was born when L-glutamate and L-aspartate were found to be potent convulsants (Hayashi, 1954), and were subsequently found to excite neurons directly (Curtis, Phillis, and Watkins, 1959). Although these studies initiated the hypothesis of glutamate-mediated neurotransmission, it was noted that the ubiquitous actions of glutamate could also reflect a general, nonspecific property of glutamate on neuronal membranes. It was not until 20 years later that pharmacological, physiological, and biochemical studies provided convincing evidence for a neurotransmitter role for glutamate in the mammalian central nervous system (CNS). With the critical demonstration that the pharmacologically defined glutamate receptors mediate synaptic currents, glutamate rapidly became widely accepted as a major neurotransmitter by the mid-1980s. This breakthrough, together with the simultaneous findings that glutamate receptors are involved in many essential, as well as pathological, processes in the CNS, instantly transformed the study of glutamate receptors into one of the fastest-growing and most exciting areas of neuroscience.

With the cloning of numerous ionotropic glutamate receptor subunits over the last six years, the field has experienced another dramatic acceleration in the understanding of receptor action and in providing the first clear insights into the molecular bases underlying the wealth of pharmacological and physiological data on these receptors. The principal objective of *The Ionotropic Glutamate Receptors* is to present an overview of this most recent wave of information providing fresh understanding of glutamate receptor properties at the molecular level. In some ways the results from the cloning studies are not surprising. The functional separation of receptor types into NMDA, kainate, and AMPA receptors has been confirmed by the cloning results, even to the point that the function of kainate receptors remains a question, as it did for many years when they were detected by ligand binding studies, but rarely in functional analyses. Some findings could be anticipated by analogy to other ionotropic receptors, such as multiple subunits and splice variants, but some could not, such as mRNA editing and the novel topology of the receptor. In viewing the ionotropic glutamate receptors, it is striking to see the amazing range of functionally different receptors and receptor combinations that can be generated in the nervous system through the multiple subunits, splice variants,

RNA editing, and glycosylation. This functional diversity is compounded further by modulatory systems, such as phosphorylation, and by the combining of multiple ionotropic and metabotropic glutamate receptors within a synapse. Clearly this diversity evolved to meet the functional requirements of this important family of receptors in the nervous system. Understanding the function of this diversity and deciphering the mechanisms regulating these events remains an important area of current and future research.

In planning *The Ionotropic Glutamate Receptors,* we faced the challenge of covering a rapidly growing and changing field that is perhaps already too broad for complete coverage in a single volume. We wanted to provide the latest and most exciting aspects of the molecular properties of glutamate receptors, but to present them in such a way as to help explain the vast earlier (precloning) literature on these receptors. Thus, within the practical limits of a book, the following chapters cover the biochemical, physiological, and pharmacological properties of recombinant ionotropic glutamate receptors and, generally, compare these properties to those of native glutamate receptors expressed in the CNS. The first chapter presents a historical context and summary of ionotropic glutamate receptor characterization, the following five chapters describe molecular properties of glutamate receptor subunits with the last two of these concerned with receptor modulation by phosphorylation. The next three chapters present an overview of the anatomical localization of specific glutamate receptor subunits as determined by *in situ* hybridization and immunohistochemistry. The last five chapters describe the pharmacological and physiological properties of NMDA and non-NMDA receptors.

Working with the outstanding cohort of authoritative writers, and reading their chapters has proved an exciting and highly instructive experience, and we thank all our authors for their outstanding contributions.

Robert J. Wenthold
Daniel T. Monaghan

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