CHAPTER 3

Ionotropic Glutamate Receptors

Heterogeneity by Posttranscriptional Modifications

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1. Introduction

Glutamate is the major mediator of fast excitatory transmission in the mammalian central nervous system (CNS). It plays an important role in processes controlling synaptic plasticity, memory formation, and learning. The release of excess glutamate and overexcitation are the causes of neuronal damage and cell death in pathological conditions, such as ischemia (Bliss and Collingridge, 1993; Choi, 1992; Mayer and Westbrook 1987). Consequently, the glutamatergic system has been a primary target of biomedical research. Glutamatergic transmission acts through specific receptors, which are pharmacologically classified into three distinct, cation selective, ligand-gated ion channels based on their preferred agonists, N-methyl-d-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole acid (AMPA), and kainate. Expression cloning of AMPA (Hollmann et al., 1989) and NMDA (Moriyoshi et al., 1991) identified the molecular entities of these major receptor classes and triggered numerous cloning approaches based on sequence similarity. These efforts resulted in an explosive increase in our knowledge of ionotropic GluR molecular biology. To date, 16 individual ionotropic GluR genes have been identified. Their degree of molecular relationship largely matches the previous pharmacological classification (for review, see Hollmann and Heinemann, 1994).

In other families of ligand-gated ion channels (e.g., nicotinic acetylcholine receptors, GABA$\_A$-receptors), receptor heterogeneity is largely generated by hetero-oligomeric assembly of various subunits into the multisubunit complex. Further diversification by alternative splicing of the mRNA encoding individual subunits appears to be the exception rather than the rule. In contrast,
multiple incidents of posttranscriptional modifications have been described for GluRs, where alternative splicing is found frequently. It is, in some cases, highly cell-type specific and subserves defined functional properties. Furthermore, a curious phenomenon of posttranscriptional processing has been assigned to GluRs: selective nuclear RNA editing. This chapter summarizes the events and underlying mechanisms of posttranscriptional modifications in GluRs known to date. Physiological consequences and spatial heterogeneity arising from these modifications are addressed. In most cases, details on localization and physiological properties of individual receptor isoforms can be found in Chapter 3.

2. Alternative Splicing

Alternative splicing of ionotropic GluR subunits was first described for the AMPA receptor subfamily (Sommer et al., 1990). Molecular cloning of additional GluR genes revealed further examples of alternative splicing in subunits of each ionotropic GluR subfamily in both N- and C-terminal domains. Figure 1 summarizes the molecular structure of the splice variations found in the different GluR subfamilies.

2.1. Events of Alternative Splicing

2.1.1. NMDA Receptors

Alternative splicing has been described for NMDAR1 (or NR1), the "master" subunit of the NMDA receptor complex. A total of eight splice