INTRACELLULAR TRAFFICKING OF AMPA-TYPE GLUTAMATE RECEPTORS

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1. SUMMARY

AMPA receptors are one of the most dynamic components of excitatory synapses. They are responsible for most excitatory transmission in the brain, and therefore, their presence at synapses is tightly controlled. We now know that AMPA receptors reach their synaptic targets after a complicated intracellular trafficking pathway, in which almost every step is subject to precise regulation. In particular, neuronal activity is able to trigger the addition or removal of AMPA receptors at synapses, leading to long-lasting forms of synaptic plasticity known as long-term potentiation (LTP) and long-term depression (LTD). This chapter summarizes our current knowledge of the intracellular trafficking of AMPA receptors, and its relation to synaptic function and plasticity.

2. INTRODUCTION

Most excitatory transmission in the brain is mediated by two types of glutamate receptors, namely, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and N-methyl-d-aspartate (NMDA) receptors. These two types of receptors play very different roles in synaptic function. AMPA receptors (AMPARs) are responsible for most excitatory responses in conditions of basal synaptic transmission. In contrast, NMDA receptors (NMDARs) remain silent at resting membrane potential, but they are crucial for the induction of specific forms of synaptic plasticity, such as LTP and LTD2.

Although AMPARs and NMDARs reside in the same synapses in most brain regions, they reach their final synaptic targets following very different programs. In early postnatal development, most excitatory synapses contain only NMDARs, whereas the prevalence of AMPARs gradually increases as the brain develops3.

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Interestingly, the delivery of AMPARs into synapses is a regulated process that depends on NMDAR activation and underlies some forms of synaptic plasticity in early postnatal development and in mature neurons\(^4\).

Although dendritic synthesis of AMPARs has been recently reported\(^5\), most receptors are likely to be synthesized in the neuronal cell body, far away from their synaptic targets. Therefore, newly synthesized receptors have to engage in a long journey that starts at their points of biosynthesis, continues with their transport along dendrites, and ends with their translocation into dendritid spines and insertion into the postsynaptic membrane. This review summarizes our current knowledge of the intracellular trafficking pathways that lead to the synaptic delivery of AMPA receptors, with special emphasis on the late stages that contribute to synaptic plasticity. Mobile NMDA receptor clusters have also been observed, as described in Chapter 14 of this series. The intracellular transport of these mobile NMDARs is covered in other recent reviews\(^6\).

3. AMPA RECEPTOR SYNTHESIS AND REGULATED EXIT FROM THE ENDOPLASMIC RETICULUM

AMPARs are hetero-tetrameric molecules\(^7\) composed of different combinations of GluR1, GluR2, GluR3, and GluR4 subunits\(^8\). In the mature hippocampus, most AMPARs are composed of GluR1–GluR2 or GluR2–GluR3 combinations\(^9\), whereas GluR4-containing AMPARs are expressed mainly in early postnatal development\(^10\). These oligomeric combinations are formed in the endoplasmic reticulum (ER) through mechanisms that are not well understood but that seem to depend on interactions between the luminal, N-terminal domains of the subunits\(^11\) and the presence of an edited arginine residue (R\(^607\)) at the channel pore of the GluR2 subunit\(^12\). GluR1–GluR2 hetero-oligomers exit the ER rapidly, and traffic to the Golgi compartment where they become fully glycosylated\(^13\). In contrast, GluR2–GluR3 hetero-tetramers have a much longer residence time at the ER. In fact, a significant fraction of the GluR2 subunit is retained within the ER as an immature protein, in an active manner that depends on the presence of the positively charged R\(^607\) at the channel pore\(^13\). GluR1, GluR3, and GluR4 mRNAs are not edited at this position, and therefore, these subunits contain a noncharged glutamine residue at the channel pore and do not undergo retention at the ER. The retention protein that prevents immature GluR2 from exiting the ER is not known; however, a fraction of AMPARs associates with the ER chaperones BiP and calnexin\(^14\), and GluR2 colocalizes extensively with BiP in the ER\(^13\). Therefore, it is plausible that chaperons residing at the ER are related with the retention mechanism.

Additionally, export of AMPARs from the ER may require the interaction of the cytoplasmic, C-terminal domain of the AMPAR subunits with other proteins. The GluR2 C-terminus has a PDZ motif (-SVKI) that interacts with several PDZ domain-containing proteins, including PICK\(^15\), which is thought to be necessary for GluR2’s exit from the ER\(^13\). The GluR1 C-terminus also contains a PDZ motif (-ATGL), which interacts with SAP97\(^16\). This interaction is known to occur early in the secretory pathway, probably while the receptor is still in the ER\(^17\). However, it is not known whether the SAP97–GluR1 interaction is necessary for this subunit to exit the ER.

Finally, AMPAR exit from the ER and acquisition of mature glycosylation at the Golgi complex is assisted by a family of transmembrane AMPA receptor