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REVIEW

MOLECULAR DETERMINANTS OF KAINATE RECEPTOR TRAFFICKING

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Abstract—Glutamate receptors of the kainate subtype are ionotropic receptors that play a key role in the modulation of neuronal network activity. The role of kainate receptors depends on their precise membrane and subcellular localization in presynaptic, extrasynaptic and postsynaptic domains. These receptors are composed of the combination of five subunits, three of them having several splice variants. The subunits and splice variants show great divergence in their C-terminal cytoplasmic tail domains, which have been implicated in intracellular trafficking of homomeric and heteromeric receptors. Differential trafficking of kainate receptors to specific neuronal compartments likely relies on interactions between the different kainate receptor subunits with distinct subsets of protein partners that interact with C-terminal domains. These C-terminal domains have also been implicated in the degradation of kainate receptors. Finally, the phosphorylation of the C-terminal domain regulates receptor trafficking and function. This review summarizes our knowledge on the regulation of membrane delivery and trafficking of kainate receptors implicating C-terminal domains of the different isoforms and focuses on the identification and characterization of the function of interacting partners.

Key words: glutamate receptors, trafficking, cytoplasmic domains, intracellular partners.

Contents

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Abbreviations: AMPAR, AMPA receptor; COPI, coatomer protein complex I; ER, endoplasmic reticulum; Is(AHP), slow Ca^{2+}-activated K^+ current; KAR, kainate receptor; PKA, cAMP-dependent protein kinase; PSD, postsynaptic density; SUMO, small ubiquitin-like modifier protein.

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Kainate receptors (KARs) are a class of glutamate receptors that are widely distributed in the CNS. In the mammalian brain, fast excitatory synaptic transmission is mainly mediated by AMPA receptors (AMPARs) whereas KARs play important roles in regulating synaptic transmission and neuronal excitability (Bettler and Mulle, 1995; Lerma, 2003). These receptors are involved in mechanisms underlying synaptic plasticity and their dysfunction has been implicated in neurodegenerative diseases (Lerma, 2006; Pinheiro and Mulle, 2006). Recently it has been shown that a defect in the *GRIK2* gene (coding for the GluR6 subunit of KARs) is associated with autosomal recessive mental retardation (Motazacker et al., 2007).

KARs form cationic ion channels that can flux Ca^{2+} if the neutral glutamine residue within the channel pore is not converted by RNA editing to a positively charged arginine. At variance with AMPA and NMDA receptors that mainly operate at postsynaptic sites, KARs play different functions depending on their subcellular localization. At postsynaptic sites, they are implicated in synaptic currents of small amplitude and slow decay kinetics that display prominent summation properties in response to repetitive stimulations. Presynaptic KARs can modulate neurotransmitter release such as GABA and glutamate, facilitating presynaptic forms of short and long term synaptic plasticity. Some of their functions involve a metabotropic action through the coupling to a G-protein, that does not require an ionotropic action. For instance, KARs regulate neuronal excitability by inhibition of Ca^{2+}-dependent K^+ channels (for reviews see (Lerma, 2006; Pinheiro and Mulle, 2006)).

Although the physiological function of KARs depends on their highly polarized distribution in the various neuronal compartments, molecular determinants for the localization of KARs are still poorly understood. Assembly, intracellular trafficking and synaptic targeting of KARs are processes controlled, in part, by various determinant domains within the constituent subunits themselves. KARs are tetrameric receptors composed of various combinations of five subunits GluR5, GluR6, GluR7, KA1 and KA2 (Fig. 1a). GluR5, GluR6 and GluR7 can form functional homomeric and heteromeric receptor channels and have multiple iso-

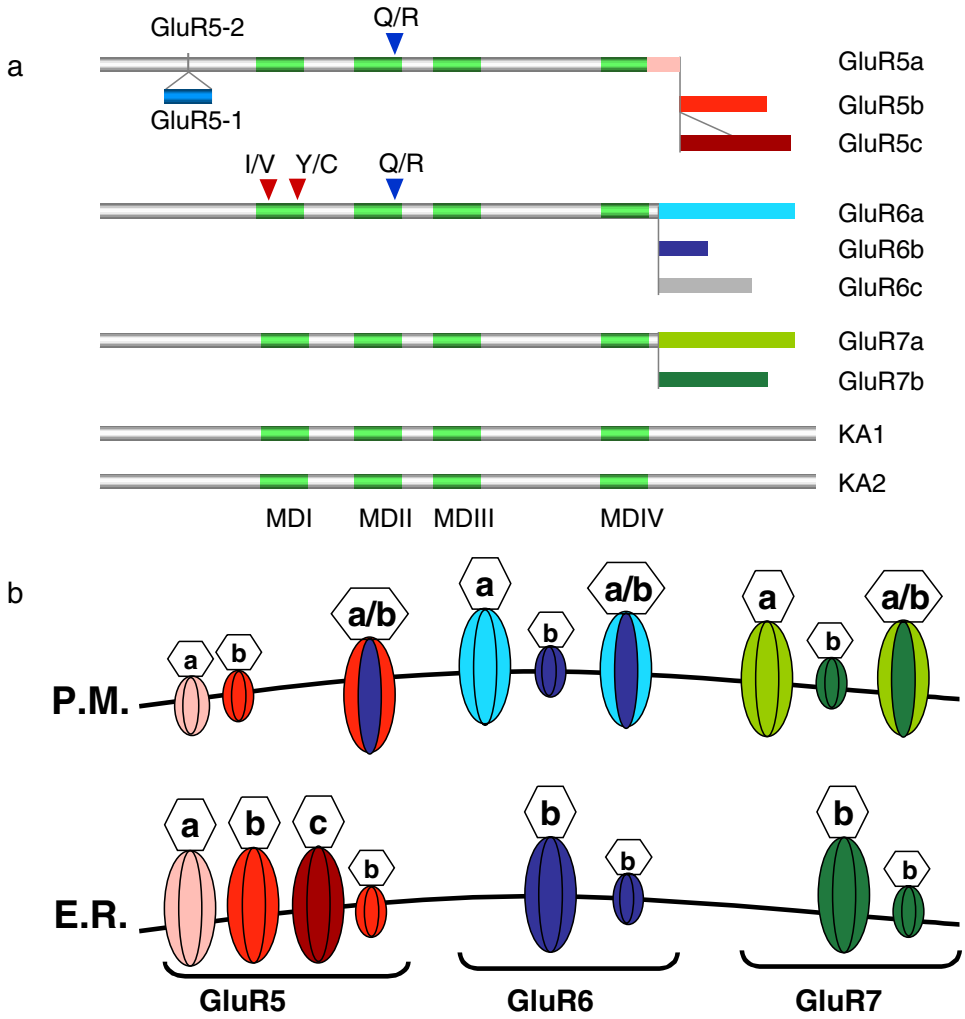

Fig. 1. Subunits, splice variants and trafficking of KARs. (a) Splice variants of KAR subunits. The membrane domains are in green. GluR5 has two N-terminal splice variants, with a 15 amino acid insertion in GluR5-1 compared with GluR5-2, and three C-terminal splice variants in the cytoplasmic domain. GluR6 and GluR7 each have two splice variants (a and b) in their C-terminal cytoplasmic domains. No splice variants for KA1 and KA2 have been found. (b) Trafficking of KARs as homomers and heteromers. Cell surface expression of KAR subunits is regulated by alternative splicing. Low levels of GluR5a and GluR5b are expressed on the cell surface whereas GluR5c is retained in the ER. Small amounts of GluR6b and GluR7b are present at the plasma membrane (P.M.), GluR6a and GluR7a are delivered efficiently at the cell surface and are able to promote surface expression of the others splice variants.

forms derived from alternative splicing and RNA editing. KA1 and KA2 do not form functional homomeric channels but bind glutamate and can co-assemble with GluR5, GluR6 or GluR7 subunits.

The regulated targeting of KARs likely depends on specific interactions with subsets of interacting proteins during their traffic from the endoplasmic reticulum (ER) to the plasma membrane and to the synaptic sites. Elucidating the cellular mechanisms underlying these processes is important to unravel KAR-mediated signaling in the brain. This review will focus on our current understanding of the molecular mechanisms that govern KARs membrane trafficking, and on the identification of proteins that interact with KARs and may regulate their distribution and functional properties in neurons.

SUBCELLULAR LOCALIZATION OF NATIVE KARS

KAR subunits are widely expressed in the nervous system, with distinct overlapping patterns of mRNA expression (Wisden and Seeburg, 1993; Bettler and Mulle, 1995; Jaskolski et al., 2004). Most combinations of the five KAR subunits are possible in heteromeric native KARs. The use of subunit specific antibodies for GluR6, KA1 and KA2 has confirmed that KA1 and KA2 can coassemble with GluR6 in native receptors with undetermined stoichiometry (Wenthold et al., 1994; Darstein et al., 2003; Pinheiro et al., 2005). Molecular composition of native KARs does not relate in a simple manner to their subcellular localization. This distribution could also depend on the neuronal population in which KARs are expressed.