Acta Pharmacol Sin 2007 Jul; 28 (7): 928–936

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Invited review

Synaptic plasticity, AMPA-R trafficking, and Ras-MAPK signaling[1]

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Key words

AMPA receptors; MAPK; neuromodulator; NMDA receptors; plasticity; Ras; Rap1; Rap2; synaptic transmission; trafficking

[1] Work from the Julius ZHU Laboratory is supported in part by the US Department of Defense and National Institutes of Health USA.

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[5] Dr Yun GU is a visiting postdoctoral fellow supported by a scholarship from the Chinese Ministry of Health.

Received 2007-01-03
Accepted 2007-02-05

doi: 10.1111/j.1745-7254.2007.00609.x

Abstract

Synaptic modification of transmission is a general phenomenon expressed at almost every excitatory synapse in the mammalian brain. Over the last three decades, much has been discovered about the cellular, synaptic, molecular, and signaling mechanisms responsible for controlling synaptic transmission and plasticity. Here, we present a brief review of these mechanisms with emphasis on the current understanding of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA-R) trafficking and Ras-mitogen-activated protein kinase (MAPK) signaling events involved in controlling synaptic transmission.

Introduction

Long-term synaptic plasticity, the sustained synaptic modification after brief periods of repetitive synaptic activity, was first discovered in the hippocampus[1]. This phenomenon has since been the subject of intense investigation because it was immediately recognized as an experimental model for understanding human cognitive behavior, learning, and memory[2,3]. Although many types of synaptic plasticity have been described, *N*-methyl-*D*-aspartate (NMDA)-sensitive glutamate (Glu) receptor (R)-dependent forms of synaptic plasticity in the hippocampal CA1 region remain the most extensively studied. Over the past three decades, significant progress has been made in understanding the cellular and molecular mechanisms underlying these forms of synaptic plasticity[4–9]. Here, we attempt to highlight the progress with emphasis on the last ten years.

Cellular and synaptic mechanisms

The initial studies on synaptic plasticity focused on its cellular mechanisms[2]. These studies revealed that the activation of NMDA-Rs and an influx of calcium ions through the receptor channels are two key processes that trigger synaptic plasticity[2,3]. The activation of NMDA-Rs requires both depolarization and glutamate binding, which explains the two basic properties of synaptic plasticity: input-specificity and input-associativity. Input-specificity means that only synapses activated by repetitive activation can be modified, whereas other synapses on the same cell are normally not modified. This is due to the requirement of glutamate binding for the activation of NMDA-Rs. Input-associativity means that neighboring even weakly-activated synapses can be modified if co-activated with other synapses because the summated depolarization meets the threshold for opening NMDA-Rs.

After resolving the basic cellular mechanisms for synaptic plasticity, much work has been directed to understanding whether the modification occurs on the pre- or postsynaptic sites of synapses, generating a vigorous, highly visible debate for over a decade[3]. The most convincing evidence lands on the postsynaptic side of synapses[10]. However, the discovery of silent synapses and the activation of silent

synapses by long term potentiation (LTP) by Malinow and colleagues[11], and later confirmed by many other laboratories[12–17], largely ends the debate. These studies indicate that synaptic plasticity can change the amount of silent synapses, suggesting a simple postsynaptic model that unifies many of the previously conflicting observations.

Synaptic AMPA-R trafficking

The silent synapse theory suggests synaptic trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-sensitive GluRs as a promising mechanism for synaptic modification of transmission efficacy. AMPA-Rs are tetrameric proteins[18,19], which are composed of GluR1, GluR2, GluR2L, GluR3, GluR4, or GluR4c, 6 subunits that are coded by 4 genes, GluR1–4[20–22]. The imaging of green fluorescent protein (GFP)-tagged recombinant GluR1 receptors with 2-photon microscopy has provided the first evidence that AMPA-Rs move into dendritic spines, synaptic sites, during synaptic potentiation[23]. Subsequent studies have revealed that the cytoplasmic carboxyl termini of the constituent subunits, which can be either long or short, govern the synaptic trafficking characteristics of AMPA-Rs[7,24]. So

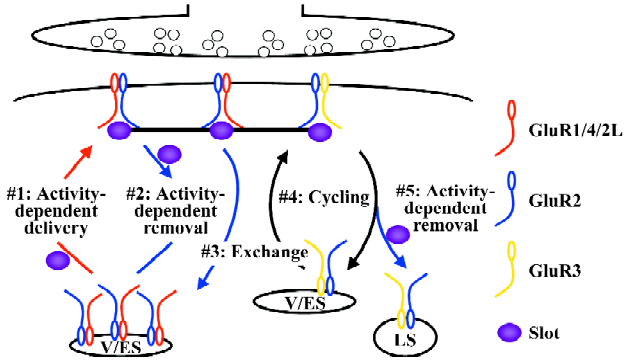

Figure 1. Model for synaptic AMPA-R trafficking. LS, lysosome; V/ES, vesicles/endosomes.

far, multiple distinct synaptic AMPA-R trafficking events have been characterized (Figure 1).

AMPA-Rs with long cytoplasmic termini (ie GluR1-, GluR2L- or GluR4-containing AMPA-Rs) are normally restricted from synapses (Figure 1). During synaptic potentiation (eg long-term potentiation or LTP), synaptic activity activates NMDA-Rs and drives GluR1-, GluR2L-, or GluR4-containing AMPA-Rs into synapses[25–27]. The synaptic delivery of GluR1- and GluR2L-containing AMPA-Rs can be a rapid process, taking approximately 15–25 min during LTP[27,28]. During LTP, GluR1-containing AMPA-Rs are transported to the plasma membrane via exocytosis from recycling endosomes[29]. In hippocampal CA1 neurons, GluR4 is expressed only in the first postnatal week[25]. Spontaneous activity delivers GluR4-containing AMPA-Rs into synapses, which mediates synaptic potentiation during early development[25,30]. The expression of GluR2L peaks at the end of the second postnatal week and declines by half in adults[27]. The synaptic delivery of GluR2L-containing AMPA-Rs requires spontaneous activity[27]. GluR1 expression increases with increasing age and reaches a maximal expression level after the third postnatal week[25]. Strong synaptic activity, such as LTP-inducing stimuli, is required to drive GluR1-containing AMPA-Rs into synapses[26,31]. In the intact brain, experience-independent, spontaneous activity is sufficient to drive GluR2L- and GluR4-containing AMPA-Rs into synapses, whereas experience-dependent activity and/or the presence of other neuromodulatory physiological factors (eg neuromodulators, hormones, and neurotrophic factors) are required for the synaptic delivery of GluR1-containing AMPA-Rs[32–34]. An intriguing hypothesis for how transmission efficacy is maintained despite continuous AMPA-R trafficking and protein turnover involves the simultaneous delivery of slot proteins or slot protein complexes containing AMPA-Rs with long cytoplasmic termini during synaptic potentiation[35]. A recent study has provided evidence supporting the existence of slot proteins and the idea that the hypothesized slot proteins code synaptic transmission strength[36].

Within a short window (approximately 0.5–2 h) after synaptic potentiation, some of the newly-delivered AMPA-Rs with long cytoplasmic termini can be removed from synapses (Figure 1). This process requires synaptic activity and the activation of NMDA-Rs, and mediates depotentiation[37]. The synaptic removal of GluR2L- and GluR1-containing AMPA-Rs occurs rapidly and the process takes approximately 15–25 min[37]. Most likely, the slot proteins are removed together with AMPA-Rs with long cytoplasmic termini in order to reduce transmission efficacy[36].

Other synaptic AMPA-Rs with long cytoplasmic termini (ie those not removed by depotentiation) are eventually exchanged with AMPA-Rs with only short cytoplasmic termini (Figure 1). The synaptic exchange of GluR1-, GluR2L-, and GluR4-containing AMPA-Rs with GluR2-containing AMPA-Rs (ie GluR2/3 AMPA-Rs) requires no synaptic activity[25,27,36]. This process has a slow rate time constant of approximately 16 h and is essential for maintaining the capacity for bidirectional plasticity[36]. The slot proteins play a key role in maintaining transmission strength during this slow exchange[36].

AMPA-Rs with only short cytoplasmic termini, constitutively cycle between synaptic and non-synaptic sites (Figure 1). The synaptic cycling of GluR2-containing AMPA-Rs (ie GluR2/3 AMPA-Rs) has a rapid time rate(time constant of approximately 15–20 min) and the process requires no synaptic activity[38–42]. Recent studies suggest that most of the cycling GluR2-containing AMPA-Rs may bind to slot proteins at the synaptic site, and the pool of cycling GluR2-containing AMPA-Rs at the non-synaptic site is most likely very small[36,43]. Together, synaptic AMPA-R exchange and cycling serve to maintain synaptic strength despite continuous protein turnover.

AMPA-Rs with only short cytoplasmic termini can be removed from synapses (Figure 1). During synaptic depression [eg long-term depression (LTD)], synaptic activity activates NMDA-Rs and removes GluR2-containing AMPA-Rs (ie GluR2/3 AMPA-Rs)[28,44–46]. The synaptic removal of GluR2-containing AMPA-Rs can be a rapid process, taking approximately 15–25 min during LTD[28], and the receptors are diverted to the late endosomes/lysosomes via clathrin-dependent endocytosis[47–50]. The slot proteins are most likely removed together with GluR2-containing AMPA-Rs, which accounts for the reduced transmission efficacy after LTD[36].

GluR2-lacking AMPA-Rs may also traffic into synapses in physiological and pathological conditions[51]. Although the endoplasmic reticulum (ER) normally only allows properly assembled AMPA-Rs to exit, and the majority of AMPA-Rs that exit from the ER contain GluR2 subunits[19], some endogenous GluR2-lacking AMPA-Rs do egress from the ER and travel into synapses[25,52,53]. For example, during early postnatal development, the expression of GluR2 is relatively low[25,27], and GluR2-lacking AMPA-Rs may mediate a significant portion of synaptic transmission[25,54]. In juvenile and adult neurons, the synaptic presence of GluR2-lacking AMPA-Rs is regulated by the synaptic trafficking of GluR2-containing AMPA-Rs, which are controlled by an interaction with protein kinase C (PKC)-interacting protein 1 (PICK1) or glutamate receptor-interacting protein (GRIP1, also called AMPA-binding protein)[55,56]. In the normal condition, the number of GluR2-lacking AMPA-Rs at synapses is limited due to synaptic exchange and replacement by GluR2-containing AMPA-Rs[36,53,57,58]. Because GluR2-lacking AMPA-Rs are permeable to calcium, their synaptic presence is often associated with pathological conditions, such as brain ischemia and amyotrophic lateral sclerosis[59–61].

Synaptic Ras/MAPK signaling

The heavy, regulated trafficking of AMPA-Rs at synapses implicates the existence of a trafficking control system. Ras family small GTPase–mitogen-activated protein kinase (MAPK) signaling pathways are ideal candidates for signaling synaptic AMPA-R trafficking events for several reasons. First, these signaling pathways are known to control a variety of intracellular processes[62–64]. In addition, Ras family small GTPases Ras, Rap1, and Rap2, as well as their upstream regulators and downstream effectors, including p42/44 MAPK, phosphoinositide 3 kinase (PI3K), c-Jun amino-terminal kinase (JNK), and p38 MAPK, are expressed at synapses[6,9,65]. Finally, diseases causing cognitive impairment are associated with genetic defects of molecules involved in Ras-MAPK signaling (eg calcineurin with schizophrenia[66], H-Ras with autism[67], p38 MAPK, and JNK with Alzheimer's disease[68,69], B-Raf with cardio-facio-cutaneous (CFC) syndrome[70], RasGap neurofibromin with neurofibromatosis type 1 (NF1)[71,72], tuberin with tuberous sclerosis[73], and Rsk with Coffin-Lowry syndrome and X-linked mental retardation[74,75]. In support of this notion, recent findings have shown that different Ras-MAPK signaling pathways differentially control synaptic trafficking of AMPA-Rs during distinct forms of synaptic plasticity.

During LTP, the activation of NMDA-Rs stimulates small GTPase Ras-extracellular signal-regulated kinase kinase (MEK), extracellular signal-regulated kinase (ERK, also named p42/44 MAPK), PI3K, and protein kinase B (PKB, also called Akt) signaling pathways (Figure 2)[28,34,76]. Different signaling molecules relay the activation of NMDA-Rs to Ras at different developmental stages, whereas neonatal neurons require cyclic AMP-dependent protein kinase A (PKA) and Ras activator son of sevenless and juvenile and adult neurons need calcium/calmodulin-dependent protein kinase II and Ras activator Ras-guanyl-nucleotide releasing factor (GRF)[25,77,78]. The activation of the Ras-MEK-ERK pathway stimulates phosphorylation of S841 of GluR2L and S845 of GluR1, whereas the activation of the Ras-PI3K-PKB pathway stimulates phosphorylation of S831 of GluR1[34]. S841 phosphorylation of GluR2L is sufficient to drive GluR2L-containing AMPA-Rs into synapses, while phosphorylation of both S845 and S831 of GluR1 is required for the synaptic delivery of GluR1-containing AMPA-Rs[34]. Because ERK and PKB are unlikely to directly phosphorylate GluR1 and GluR2L, other molecules must exist at synapses to relay the signaling[63,64]. The likely candidates include PKA[79], PKC[80,81], ribosomal S6 kinase[74,75,82], and the mammalian target of rapamycin[83,84]. Determining the precise functional relationships (ie sequential or parallel, and downstream or upstream) of the signaling molecules involved in Ras pathways during LTP will be central to future studies[6].

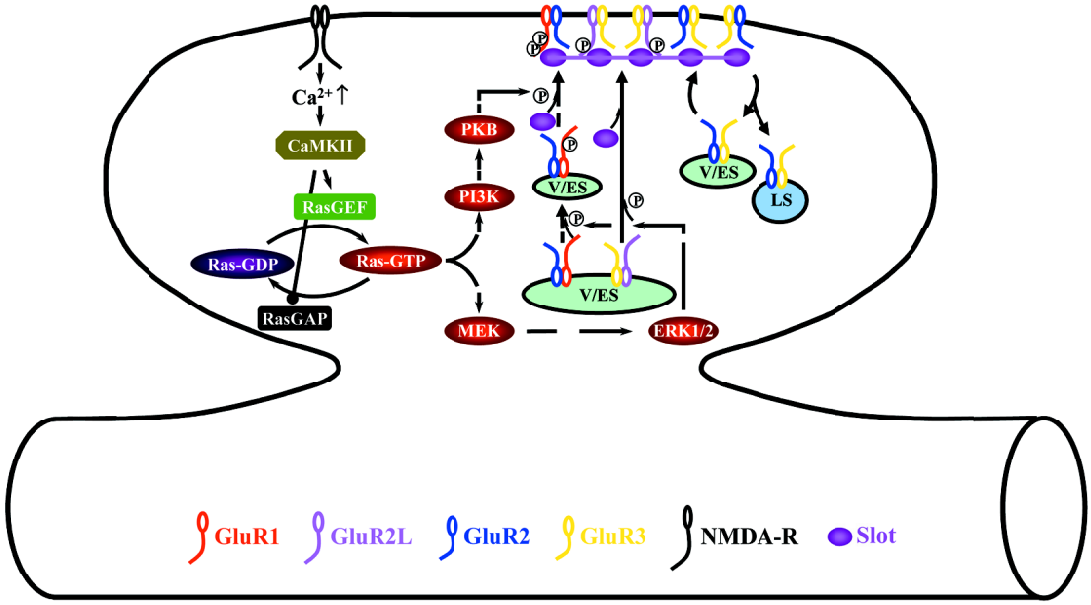

Figure 2. Model for Ras signaling-regulated synaptic delivery of AMPA-Rs during LTP. LS, lysosome; V/ES, vesicles/endosomes.

During depotentiation, the activation of NMDA-Rs stimulates the small GTPase Rap2-Traf2 and NCK-interacting kinase (TNIK)-JNK signaling pathway (Figure 3)[37]. The activation of the Rap2-TNIK-JNK pathway dephosphorylates S841 of GluR2L, and S845 and S831 of GluR1, which removes GluR2L- and GluR1-containing AMPA-Rs from synapses during depotentiation[37]. Dephosphorylation seems to be mediated by protein phosphatase 2B (also named calcineurin) downstream of Rap2-TNIK-JNK[37], which is consistent with the finding that calcineurin mediates depotentiation[85–87].

During LTD, the activation of NMDA-R stimulates the small GTPase Rap1-p38 MAPK signaling pathway (Figure 4)[28]. Phosphorylation of S880 of GluR2 modulates the interaction of GluR2 with GRIP1 and PICK1[46,88,89], which

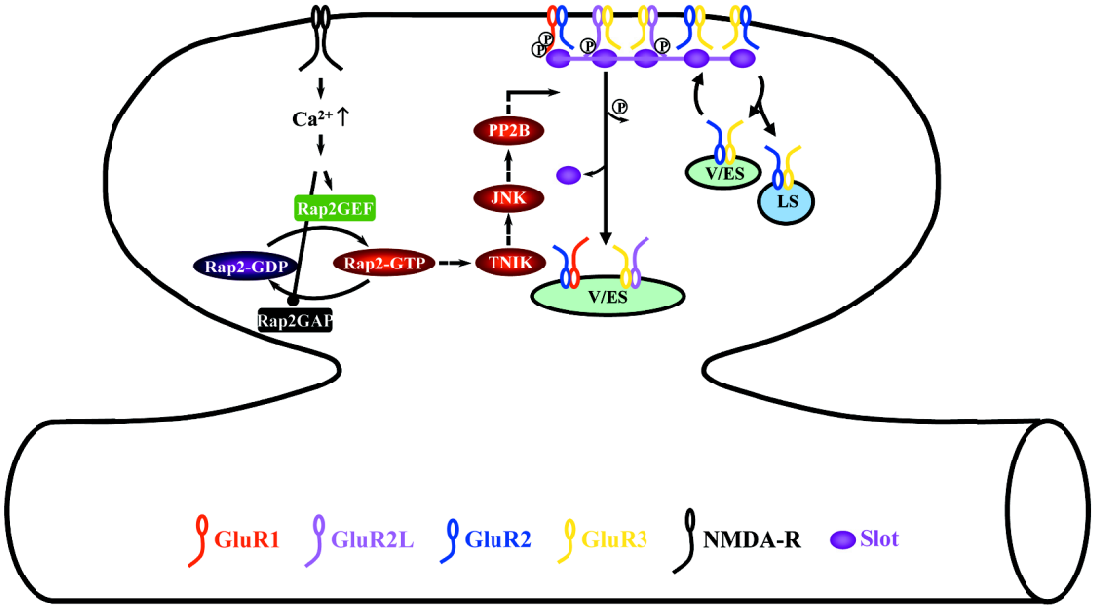

Figure 3. Model for Rap2 signaling-regulated synaptic removal of AMPA-Rs during depotentiation. LS, lysosome; V/ES, vesicles/endosomes.

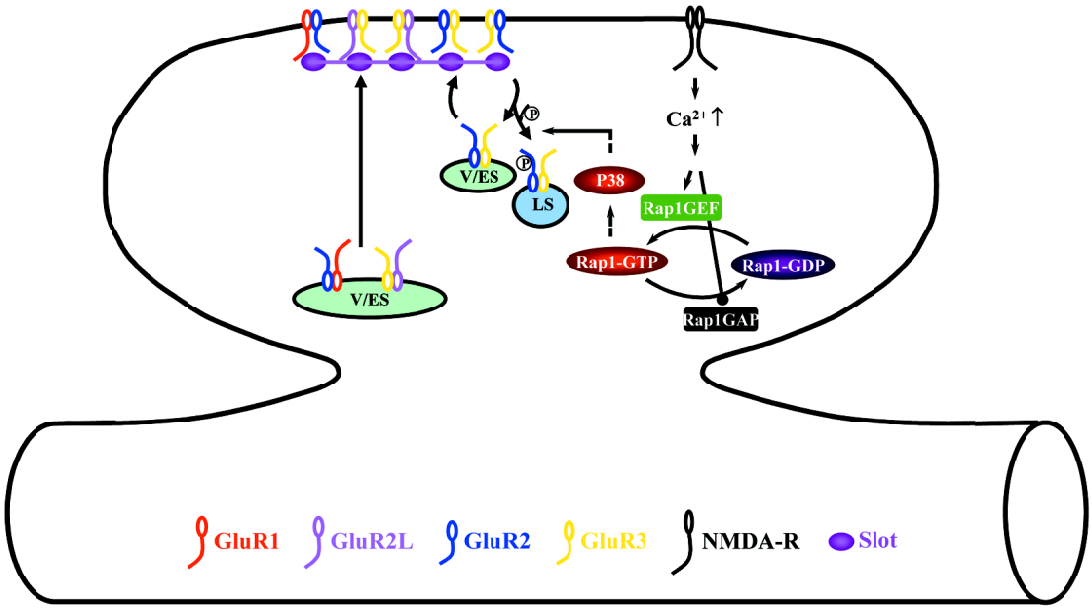

Figure 4. Model for Rap1 signaling-regulated synaptic removal of AMPA-Rs during LTD. LS, lysosome; V/ES, vesicles/endosomes.

controls the synaptic anchoring of GluR2-containing AMPA-Rs[90–96]. Thus, the activation of the Rap1-p38 MAPK pathway most likely controls the synaptic removal of GluR2-containing AMPA-Rs during LTD via regulating phosphorylation of S880 of GluR2[28,44,46]. Because p38 MAPK does not phosphorylate AMPA-Rs directly[63,97], other synaptic signaling molecule(s), such as PKC[88,89,92] and/or MAPK-interacting kinase[98], may relay the signaling and phosphorylate GluR2.

Conclusion

In the last decade, accumulating evidence indicates that postsynaptic trafficking of AMPA-Rs plays a key role in regulating synaptic transmission and plasticity. Multiple Ras-MAPK signaling pathways control the regulated synaptic trafficking of AMPA-Rs during different forms of synaptic plasticity. However, a few fundamental issues remain unsolved, for example, different populations of synapses in individual neurons having distinct AMPA-R compositions. How AMPA-Rs recognize and traffic into different types of synapses remains puzzling. Also, many of the regulators in Ras-MAPK signaling pathways have poor selectivity in interacting with their effectors. How different Ras-MAPK pathways differentially signal trafficking of distinct pools of AMPA-Rs at single synapses is still elusive. More importantly, how synaptic AMPA-R trafficking and Ras-MAPK signaling are regulated in different behavioral states in the intact brain remains largely unknown. One speculation is that AMPA-R trafficking and Ras-MAPK signaling are compartmentalized between and within synapses, and compartmentalized trafficking and signaling are differentially regulated in different behavioral states. Resolving the subcellular compartmental protein trafficking and signaling in these physiological conditions demands high-resolution experimental techniques. Several recently-refined techniques, including multiple whole-cell *in vivo* recordings[99–103], real time single spine Ras/kinase activity monitoring[104,105], living cell imaging and immunogold electron microscopy[106–110], when combined with a recombinant DNA *in vivo* delivery technique[32–34,36,111], provide powerful high-resolution approaches that may resolve these pivotal issues.

Acknowledgements

We thank the members of the Zhu Laboratory for helpful comments and discussions. In addition, we apologize to those whose work we did not cite because of space limitations.

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International Symposium on Drug Discovery and Development for Gastrointestinal Tract and Liver Diseases

Nanjing, China

2007 October 12–14

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