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Review

Subunit-specific trafficking mechanisms regulating the synaptic expression of Ca^{2+}-permeable AMPA receptors

Jonathan G. Hanley

School of Biochemistry, Medical Sciences Building, University of Bristol, University Walk, Bristol BS8 1TD, United Kingdom

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ABSTRACT

AMPA receptors are the main excitatory neurotransmitter receptor in the brain, and hence regulating the number or properties of synaptic AMPA receptors brings about critical changes in synaptic transmission. Synaptic plasticity is thought to underlie learning and memory, and can be brought about by decreasing or increasing the number of AMPA receptors localised to synaptic sites by precisely regulating AMPA receptor trafficking. AMPA receptors are tetrameric assemblies of subunits GluA1-4, and the vast majority are GluA1/2 and GluA2/3 heteromers. The inclusion of GluA2 subunit is critical because it renders the AMPA receptor channel impermeable to Ca^{2+} ions. The vast majority of synaptic AMPA receptors in the brain contain GluA2, but relatively recent discoveries indicate that an increasing number of specific forms of synaptic plasticity involve not only an alteration of the number of synaptic AMPA receptors, but also changes to their GluA2 content. The resulting change in AMPA receptor Ca^{2+} permeability clearly has profound consequences for synaptic transmission and intracellular signalling events. The subunit-specific trafficking mechanisms that cause such changes represent an emerging field of research with implications for an increasing number of physiological or pathological situations, and are the topic of this review.

Contents

Abbreviations: CP-AMPAR, Ca^{2+} permeable AMPA receptor; CI-AMPAR, Ca^{2+} impermeable AMPA receptor; LTD, long-term depression; LTP, long-term potentiation; VTA, ventral tegmental area; CARP, Ca^{2+}-permeable AMPA receptor plasticity; TARP, transmembrane AMPAR regulatory protein; OGD, oxygen and glucose deprivation; NASPM, 1-naphthyl acetyl spermine; TBOA, threo-β-benzyloxyaspartic acid.

E-mail address: jon.hanley@bristol.ac.uk

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1. Introduction

AMPARs mediate the majority of fast synaptic excitation in the brain. Therefore, the precise regulation of AMPA receptor (AMPAR) trafficking is crucial to excitatory neurotransmission, synaptic plasticity and the consequent formation of appropriate neural circuits during learning and memory. The mechanisms that underlie AMPAR trafficking under basal conditions and during certain forms of synaptic plasticity have been topics of intense research for two decades, and continue to be so [1–4]. In particular, long-term depression (LTD) and long-term potentiation (LTP) at the CA3–CA1 synapse in the hippocampus are the focus of fascinating research programmes from a large number of labs worldwide. LTP and LTD represent an increase or decrease in synaptic strength, respectively and are thought to be the molecular correlates of learning and memory. As well as electrophysiological studies, the quest for molecular cell biological mechanisms for these physiological processes has necessitated the use of dissociated cultures of hippocampal neurons that are amenable to certain imaging techniques that allow the localisation of specific proteins in real time at high resolution. Synaptic phenomena can be modelled in cultured neurons using chemically induced forms of plasticity that trigger receptor trafficking events via relevant signalling pathways. Using the combined approaches of electrophysiology in hippocampal slices and cell biology in dissociated cultures, an impressive amount of mechanistic information has been revealed about these forms of synaptic plasticity. For example, LTD involves dynamin- and clathrin-dependent endocytosis of AMPARs, which are subsequently sorted via specific membrane compartments in the endosomal system through the action of a number of accessory proteins, and may be recycled back to the plasma membrane according to the needs of the synapse in a complex process that we still do not fully understand [5–10]. LTP involves the plasma membrane insertion of additional AMPARs, which originate from the recycling endosomal system [11–13]. Using advanced imaging techniques it is thought that AMPARs are internalised from and inserted into plasma membrane regions away from the synapse, and are transported laterally in the plane of the plasma membrane [14–17]. Hence, as well as vesicle trafficking events, diffusional synaptic trapping represents a further level of regulation of AMPARs at the synapse during plasticity.

Synaptic plasticity has also been studied at a variety of other synapses in the brain, often uncovering striking mechanistic similarities to the hippocampus, but also showing important differences that presumably relate to the specific function of the associated neuronal circuit. General mechanisms of synaptic plasticity will not be described here, although some important examples of CP-AMPAR trafficking, which occur at non-hippocampal synapses will be discussed in some detail in later sections.

AMPARs are tetrameric assemblies of subunits GluA1-4, and the vast majority of AMPARs in the adult brain contain GluA2, which renders AMPARs Ca^{2+}-impermeable [18–21]. This is essential to maintain an appropriately low cytoplasmic Ca^{2+} concentration under basal levels of stimulation. A small population of GluA2-lacking, Ca^{2+}-permeable (CP-)AMPARs exists, which are not expressed at the majority of synapses under resting conditions [19,20]. A precise regulation of their synaptic expression can lead to physiologically important synaptic Ca^{2+} signalling events, usually for a restricted and regulated period of time [22,23]. Such events lead to the activation of Ca^{2+} sensitive signalling pathways that may be important for sustaining synaptic potentiation or for regulating the potential for subsequent plasticity. On the other hand, aberrant regulation of these mechanisms, leading to a prolonged synaptic incorporation of CP-AMPARs in cells that do not normally express synaptic CP-AMPARs, can result in excessive Ca^{2+} influx leading to synaptic dysfunction and cell death (excitotoxicity) in a number of diseases including brain ischaemia [24,25].

The focus of this review is to evaluate the current knowledge about the trafficking mechanisms and associated signalling pathways involved in regulating the synaptic expression of CP-AMPARs. To put these mechanisms in context, I will introduce some examples of physiological and pathological situations that all involve CP-AMPAR trafficking, but may have subtle mechanistic differences. I will then discuss the source of CP-AMPARs, how they are trafficked to the synapse, the upstream signalling pathways and the subunit-specific interacting proteins that regulate these events. Finally, since Ca^{2+} influx must be tightly regulated, the duration of synaptic CP-AMPAR expression and mechanisms that underlie the reversal of this process will also be considered.

2. Physiological paradigms involving the expression of CP-AMPAR at synapses

2.1. Hippocampal LTP

The CA3–CA1 synapse is the most-studied synapse in the mammalian brain, and it is widely accepted that a major component to the mechanism is the incorporation of additional AMPARs into the postsynaptic plasma membrane, which is largely driven by GluA1 subunit [11,26,27]. However, despite many years of extremely active research into LTP mechanisms, a role for CP-AMPARs was overlooked. In 2006, Isaac and colleagues reported the presence of CP-AMPARs at synapses within 3 min after a pairing induction protocol, which lasted for just 20 min [28]. Synaptic CP-AMPARs are needed for the initial expression, but not for the subsequent maintenance of LTP. Studies from other labs have not always reported similar findings [29], but more extensive investigations have revealed that developmental stage [30] and stimulation protocol [31] may be important factors, and another study suggested a shorter period (10 min) for the duration of CP-AMPAR synaptic expression [32].

2.2. Fear conditioning

Potentiation at glutamatergic synapses in the lateral amygdala is central to the formation of fear memory, which is usually induced by pairing an auditory tone (conditioned stimulus) with a foot shock (unconditioned stimulus). Fear, manifested as a “freezing” response, can then be elicited in response to the conditioned stimulus alone [33,34]. As part of this potentiation, synaptic expression of

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