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Review

The mechanistic link between Arc/Arg3.1 expression and AMPA receptor endocytosis

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ABSTRACT

The activity-regulated cytoskeleton associated protein (Arc/Arg3.1) plays a key role in determining synaptic strength through facilitation of AMPA receptor (AMPAR) endocytosis. Although there is considerable data on the mechanism by which Arc induction controls synaptic plasticity and learning behaviours, several key mechanistic questions remain. Here we review data on the link between Arc expression and the clathrin-mediated endocytic pathway which internalises AMPARs and discuss the significance of Arc binding to the clathrin adaptor protein 2 (AP-2) and to endophilin/dynamin. We consider which AMPAR subunits are selected for Arc-mediated internalisation, implications for synaptic function and consider Arc as a therapeutic target.

Contents

1. Introduction

Fast glutamatergic synaptic transmission, through the activation of ionotropic AMPARs, is one of the major mechanisms of neuronal communication in the mammalian brain. AMPARs located within the postsynaptic membrane are tetrameric in structure and consist of a homomeric or heteromeric combination of 4 known subunits (GluA1-4). The mRNA coding for the GluA2 subunit undergoes post-transcriptional editing, with a single amino-acid changed from glutamine (Q) to arginine (R). This is called Q/R editing, with AMPAR containing GluA2(Q) permeable to calcium whilst GluA2(R) containing receptors impermeable. The great majority of the GluA2 subunits expressed in the central nervous system is in the GluA2(R) form and in mature pyramidal neurons of the hippocampus a significant proportion of AMPAR present at the synapses are composed of GluA1 and GluA2 subunit heterodimers. Therefore it is probable that a large number of calcium impermeable AMPARs are present at the cell surface. The subunit composition of AMPAR not only determines Ca^{2+} permeability but also determines kinetics, rectification and receptor trafficking dynamics thus precisely tuning receptor properties to specific synaptic requirements (recently reviewed in [1,2]).

The trafficking of AMPARs in and out of the synaptic membrane is a highly dynamic process which is regulated during development, during synaptic plasticity and can be impaired during disease processes [3,4]. Although there are several mechanisms underlying the trafficking of AMPARs, one of the most studied involves the immediate gene product Arc/Arg3.1 coupling synaptic activity to the endocytosis of AMPARs. Following neural activity (such as high

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frequency stimulation or seizure activity) or exposure to BDNF, Arc/Arg3.1 mRNA is rapidly trafficked to postsynaptic dendritic sites and then translated leading to AMPA receptor endocytosis [5–8]. Arc is involved in specific forms of synaptic plasticity which include homeostatic scaling and LTP (discussed in other reviews in this special issue) and Arc expression is induced by group 1 metabotropic glutamate receptor (mGluR) activation resulting in AMPA receptor endocytosis leading to long term depression (mGluR-LTD) [7]. The effects of inducing mGluR-dependent LTD can be mimicked by overexpression of Arc protein in neurons which reduces the surface expression of specific GluA subunits [7]. Deletion of Arc or inhibition of its synthesis prevents AMPA receptor endocytosis, increases surface AMPARs expression and blocks mGluR-LTD. The importance of Arc in synaptic plasticity has been illustrated by reducing Arc expression in rodents, resulting in disturbances in cognitive function including impaired memory consolidation [9–12].

Although there has been extensive progress in understanding the molecular mechanisms underlying the actions of Arc and its role in synaptic plasticity, many questions still remain unanswered. In this review we will discuss three related questions:

1) How is Arc linked to the endocytic machinery that internalises AMPARs?
2) Does Arc selectively target specific subunits of AMPAR for endocytosis?
3) Arc as a potential target to manipulate AMPAR trafficking defects in disease states?

2. What links Arc expression to the internalisation of AMPARs during synaptic plasticity?

Over the last decade there have been major advances in mapping the mechanism by which activity-dependent activation of Arc expression regulates AMPAR trafficking [10,13]. It is well established that the internalisation of AMPARs from synapses is mediated by the clathrin-mediated endocytic pathway (CME) [14–18]. The first evidence that Arc-mediated internalisation of AMPARs occurs through the CME pathway came from experiments showing that Arc interacts with endophillin and dynamin [19].

Endophilin and dynamin are accessory proteins of the CME machinery that are required for membrane constriction and scission of the clathrin-coated vesicle containing the cargo that is to be internalised (in this case AMPARs). Neither endophilin nor dynamin appear to participate in the cargo selection process as they are only involved in late phases within the sequential events of CME. Dynamin is recruited at late stages of endocytosis and its enrichment coincides with neck fission and release of the vesicle [20,21]. Supporting the idea that endophilin is only recruited at late stages of the endocytosis process is the observation that the assembly and maturation of clathrin-coated pit formation still occurs in cortical neurons obtained from mice where distinct endophilins have been deleted [22]. These findings demonstrate that assembly and early maturation events are independent of endophilin. Therefore an interaction between Arc with either endophillin or dynamin may enhance the processes of vesicle budding and the scission of the vesicle neck but it does not place the Arc-endophillin/dynamin interaction as decisive in the selection and targeting of AMPARs for internalisation.

Recently, da Silva et al. (2016) [23] used specific anti-Arc antibodies to immunoprecipitate endogenous Arc protein from hippocampal homogenised lysate to identify novel Arc binding partners. Using this approach they identified different subunits of the adaptor protein complex-2 (AP-2) as endogenous binding partners of Arc, including the two α adaptin isoforms: α also known as

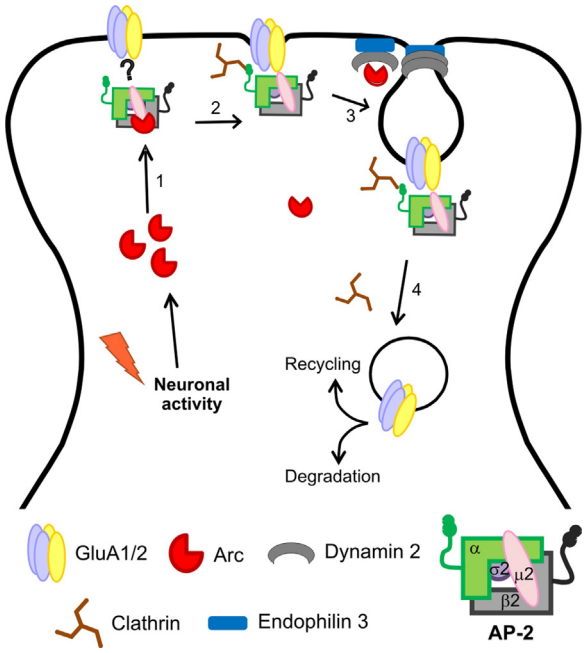

Fig. 1. Arc binds to AP-2 and endophilin/dynamin to facilitate AMPAR endocytosis. A proposed model of the mechanism by which Arc interacts with the clathrin mediated endocytosis (CME) pathway to facilitate AMPAR endocytosis. An increase in neuronal activity (or exposure to BDNF) promotes rapid Arc mRNA translation and protein expression at the dendritic spines. (1) Newly expressed Arc binds to the AP-2 complex, which binds directly or indirectly to AMPAR subunits at the plasma membrane. The identity of these GluA subunits is still open to debate and is discussed in details in the review. To initiate the formation of the clathrin-coated assembly AP-2 also binds and recruits clathrin to the membrane. Once formation of the pit is initiated, the binding affinity between Arc and AP-2 is reduced and Arc dissociates from AP-2. (3) Arc is then available to bind and recruit dynamin and endophilin to promote scission of the endocytic vesicle containing the AMPAR to then be targeted for either recycling or degradation (4). Please note that AP-2 and dynamin bind to Arc at the same motif [19,23], therefore it is likely that Arc first binds to AP-2 and then binds to dynamin. Endophilin binds Arc at a different motif which allows it to bind to Arc at any time during the CME temporal sequence of events. Although this model fits the available data, additional experiments are required to either confirm or refute it.

αA and α2, also known as αC as well as the β2 and μ2 isoforms [23]. In contrast to the late role of dynamin and endophilin in mediating clathrin-mediated endocytosis, the AP-2 complex plays a critical role in initiating this process, as it coordinates cargo recruitment and selection together with clathrin recruitment to the plasma membrane (Fig. 1 [24–27]).

To demonstrate that the Arc/AP-2 interaction is required for the endocytosis of AMPARs, da Silva et al. (2016) [23], expressed in hippocampal neurons an Arc mutant construct, which cannot bind to the AP-2 complex, and showed that this blocks the Arc-dependent reduction in the AMPAR-mediated miniature excitatory postsynaptic current (mEPSC) amplitude [23,28]. This Arc-mediated effect is specific to AMPAR subunits as the internalization of EGF receptors is unaffected by expression of either Arc-WT or Arc mutant that do not bind to AP-2 [23]. Furthermore, da Silva et al. showed that expression of Arc-WT in hippocampal neurons reduces the proportion of synaptic AMPARs that lack the GluA2 subunit, an effect that is impaired in neurons expressing the Arc mutant that cannot bind the AP-2 complex [Fig. 2; [23]]. This finding was unexpected as the AP-2 complex has been shown to directly interact with high affinity to the GluA2 subunit but only weakly with GluA1 subunits [29]. However it is possible that other proteins interact with GluA1 subunits and then interact with the AP2-complex. An example of such a possible candidate protein is Huntingtin interacting protein 1 (HIP1) which is a component of clathrin-coated vesicles and co-localises with AP-2 [30]. In neurons obtained from HIP1$^{-/-}$ mice

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