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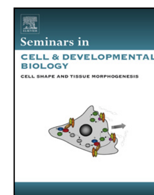

Review

Roles for Arc in metabotropic glutamate receptor-dependent LTD and synapse elimination: Implications in health and disease

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ABSTRACT

The *Arc* gene is robustly transcribed in specific neural ensembles in response to experience-driven activity. Upon induction, *Arc* mRNA is transported to dendrites, where it can be rapidly and locally translated by activation of metabotropic glutamate receptors (mGluR1/5). mGluR-induced dendritic synthesis of Arc is implicated in weakening or elimination of excitatory synapses by triggering endocytosis of postsynaptic AMPARs in both hippocampal CA1 and cerebellar Purkinje neurons. Importantly, CA1 neurons with experience-induced *Arc* mRNA are susceptible, or primed for mGluR-induced long-term synaptic depression (mGluR-LTD). Here we review mechanisms and function of Arc in mGluR-LTD and synapse elimination and propose roles for these forms of plasticity in Arc-dependent formation of sparse neural representations of learned experience. We also discuss accumulating evidence linking dysregulation of Arc and mGluR-LTD in human cognitive disorders such as intellectual disability, autism and Alzheimer's disease.

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1. Introduction

Arc/Arg3.1 is one of the most strongly induced immediate early genes in response to experience and neural activity and evidence indicates that *Arc*-induction marks neuronal ensembles that encode learned behaviors [1–7]. Deletion of *Arc* in mice leads to deficits in many forms of learning and memory, as well as experience-dependent plasticity of circuits [5,8–11]. Thus, it is hypothesized that experience-dependent induction of *Arc* in a neuron, or network of neurons, leads to plasticity circuits that mediate memory of that experience [3–5,11]. *Arc* has unique qualities among the immediate early genes that make it well suited to cause plasticity of circuits; its mRNA is rapidly transported to dendrites [12] where it is locally translated in response to glutamate [13–16] and it encodes a protein that affects synapse function directly [17–19]. An accumulating body of work implicates dendritic Arc translation in synaptic weakening, or long-term depression (LTD) [13,14,20], and synapse elimination in response to activation of

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Group 1 metabotropic glutamate receptors (mGluR1/5) [21,22]. Here we will review the roles of Arc in these related forms of synaptic depression and evidence for their dysfunction in human cognitive disease. We also attempt to integrate roles for mGluR-LTD and/or synapse elimination with recent results revealing roles for Arc in formation of sparse neural representations of learned experience [5].

2. *Arc* mRNA is rapidly translated in dendrites in response to Group 1 metabotropic glutamate receptors

The robust transcriptional and translational regulation of the *Arc* gene and mRNA make it an ideal candidate to couple experience-dependent activation of neuronal circuits to synaptic plasticity within these circuits. For example, in hippocampal CA1 neurons, which encode a memory for place or a spatial environment, *Arc* is induced rapidly, within 30 s, in response to a novel environment [23]. Once *Arc* is induced in neurons, its mRNA is promptly transported to dendrites [12,24,25] where it can be rapidly translated, within seconds to minutes, in response to activation of glutamatergic synapses [13–16]. A specific agonist for Group 1 metabotropic glutamate receptors (mGluR1/5), DHPG, is sufficient to induce Arc translation [13–15], but glutamate-induced dendritic *Arc* translation relies on both NMDA receptors and mGluR1/5 [16], which may be more relevant *in vivo*. Glutamate or DHPG induces remarkably fast (~15s) translation of Arc in dendrites as observed by imaging newly synthesized Arc tagged with a bright, rapidly decaying *Gaussia*-Luciferase (Gluc) [16] or Venus [15]. Interestingly, Arc translation did not occur primarily at synapses, but appeared to be coordinated within a dendritic segment. Although the Arc 3′UTR enhances dendritic trafficking of *Arc* mRNA [26], the coding region of Arc mRNA is sufficient for glutamate-stimulated local translation [16]. This result, combined with the fact that glutamate stimulates Arc translation in seconds, and occurs in the presence of translation initiation inhibitors, suggested that glutamate stimulates ribosomal movement, or elongation, onto *Arc* mRNA that is already initiated and ribosomes may be stalled on *Arc* mRNA in dendrites [16]. In support of this idea, mGluRs potently activate elongation factor 2 kinase and phosphorylation of elongation factor 2 which regulates translational elongation and is necessary for mGluR-induced Arc translation [13]. Furthermore, *Arc* mRNA interacts with Fragile X Mental Retardation Protein (FMRP), an RNA binding protein implicated in ribosomal stalling and processivity [27,28] that is necessary for mGluR-induced translation of Arc [15,29–31].

3. Dendritic translation of Arc is necessary for an mGluR1/5-induced long-term synaptic depression

A major function of Arc is to weaken synapses by stimulating endocytosis of postsynaptic ionotropic AMPA subtype receptors (AMPARs) and reducing their surface and synaptic expression [16–18]. Arc contributes to multiple forms of activity-induced synaptic weakening; including homeostatic downscaling of synapses [19], mGluR-LTD [13,14,20] and synapse elimination [21,22]. If and how these different forms of Arc-dependent synaptic weakening interact, if they affect the same synapses or utilize the same molecular mechanisms (e.g. endocytosis of AMPARs), but are induced in diverse ways is unclear at present and discussed below. For this review, we focus on forms of Arc-dependent synaptic weakening and elimination that require mGluR1/5.

Brief activation of mGluR1/5 (minutes) leads to a LTD of excitatory and inhibitory synaptic transmission in multiple brain regions, which are expressed through different pre-or postsynaptic loci [32,33]. A well characterized form of mGluR-LTD is mediated postsynaptically at excitatory synapses, and occurs through removal of postsynaptic AMPARs in cerebellar Purkinje (Pkj) neurons and hippocampal CA1 neurons and requires Arc [33–35]. Arc is also necessary for an activity-dependent elimination of inputs onto both Pkj and CA1 neurons, which are mGluR1 or mGluR5 dependent, respectively, suggesting that LTD mechanisms contribute to synapse elimination [36] and these are conserved roles for Arc across distinct brain regions.

In CA1 neurons, brief activation of mGluR1/5 with either the selective agonist, DHPG, or synaptic stimulation (paired-pulse low-frequency (1 Hz) stimulation) induces LTD that requires new protein synthesis from pre-existing mRNA and is mediated by postsynaptic endocytosis and decreases in surface AMPAR subunits GluA1 and GluA2 (reviewed [33,34]). While *de novo* protein synthesis is not required to trigger endocytosis, and decreases in surface of AMPARs, it is required to maintain decreases in surface AMPARs and the persistent increases in endocytosis rates that accompany LTD [14,37]. mGluR-LTD is deficient in area CA1 of acute hippocampal slices from *Arc* KO mice and postsynaptic inhibition of new Arc translation with antisense oligonucleotides blocks LTD, as well as DHPG-induced decreases in surface AMPARs and persistent increases in AMPAR endocytosis rates [13,14]. These results suggest that Arc levels are rate limiting for AMPAR endocytosis and mGluR-induced increases in local Arc concentration enhance endocytosis rates which maintain decreased surface AMPARs and synaptic depression [14]. In contrast to this view, recent data demonstrated that DHPG induced a rapid synthesis of Arc, which is then followed by ubiquitination and degradation of Arc by the proteasome, resulting in a long-term decrease in Arc protein levels (>1h) [38]. This result suggested that increases in Arc levels trigger LTD, but do not maintain it. Of note, in cultured forebrain or hippocampal neurons, *Arc* levels are induced and remain elevated for an hour after DHPG suggesting that there is little Arc degradation in cultured neurons after DHPG [13,31] where persistent increases in AMPAR endocytosis rates accompany LTD. Remarkably, if proteasomal degradation is blocked with proteasome inhibitor, mGluR-LTD no longer requires new protein synthesis [38]. Although these manipulations are not specific for Arc, it supports the view that new Arc synthesis is not absolutely required for mGluR-LTD and mGluRs trigger posttranslational modifications of Arc, or proteins in complex with Arc to cause LTD. Such mechanisms may include tyrosine dephosphorylation of GluA2, which is implicated in mGluR-LTD [39] and phosphorylation of Arc by ERK [40], a protein kinase required for mGluR-LTD [41].

In cultured cerebellar Purkinje (Pkj) neurons, Arc is necessary for mGluR-LTD of granule cell inputs but is specifically required for a transcription-dependent "late-phase" of mGluR-LTD, occurring >1h after induction [35]. The late-phase of mGluR-LTD also requires the transcription factor, Serum Response Factor (SRF), and its binding to the *Arc* promoter [35]. mGluR-LTD inducing stimulation (e.g. DHPG) can induce both transcription and translation of *Arc* in cultured hippocampal or cortical neurons [13,42], the former of which likely occurs through regulation of SRF [43]. In contrast to Pkj neurons, mGluR-LTD in area CA1 of acute hippocampal slices is independent of transcription and relies on rapid translation of Arc, within 20–30 min, from preexisting mRNA [14,44]. New *Arc* transcription may be required for mGluR-LTD in cultured Pkj cells because *Arc* levels are very low in this culture preparation, whereas, as discussed below, CA1 neurons in acute hippocampal slices express *Arc* transcripts induced *in vivo* [20]. An interesting possibility is that mGluR-LTD in acutely prepared cerebellar slices may depend on rapid Arc translation from preexisting mRNA, as observed in CA1. In support of this idea, protein synthesis inhibitors rapidly block mGluR-LTD in Pkj neurons in acute slices [45].

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