REVIEW ARTICLE   **Open Access**

Synapse development organized by neuronal activity-regulated immediate-early genes

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Abstract

Classical studies have shown that neuronal immediate-early genes (IEGs) play important roles in synaptic processes critical for key brain functions. IEGs are transiently activated and rapidly upregulated in discrete neurons in response to a wide variety of cellular stimuli, and they are uniquely involved in various aspects of synapse development. In this review, we summarize recent studies of a subset of neuronal IEGs in regulating synapse formation, transmission, and plasticity. We also discuss how the dysregulation of neuronal IEGs is associated with the onset of various brain disorders and pinpoint key outstanding questions that should be addressed in this field.

Introduction

Numerous studies have shown that neural activity plays an important role in regulating synaptic strength, neuronal membrane properties, and neural circuit refinement[1–3]. In particular, sensory experiences continually influence brain development at synaptic, circuit, and organismal levels, as Hubel[4] and Wiesel[5] elegantly demonstrated in their work on visual cortex organization during the critical period[5]. The effects of sensory experience are manifested by neurotransmitter release at presynaptic terminals, their reception at postsynaptic membranes, and depolarization of postsynaptic neurons by increased concentration of cytoplasmic calcium. This increase in cytoplasmic calcium activates a program of gene expression in the nucleus[6–9]. Including classic immediately-early genes (IEGs) such as *Fos* and *Jun*, a number of activity-regulated transcription factors have been identified and extensively investigated[3,10,11]. These studies have led to an important hypothesis that transcriptional regulation is a key mechanism by which neuronal activity can trigger

experience-dependent synaptic changes and maturation of neural circuits.

More than dozens of neuronal IEGs were identified by Paul Worley, Elly Nedivi, and colleagues[12], owing to the use of the subtractive hybridization method, in combination with various neural stimulation protocols, most notably seizure paradigms. Among them, cAMP-responsive element-binding protein (CREB) has been the most studied in regulating activity-dependent synapse development and plasticity[13]. Its physiological significance in neuronal development and cognitive behaviors has been consistently shown across a variety of model organisms including mouse, *Drosophila*, and *Aplysia*[13]. In addition to CREB, other IEGs have been extensively investigated[12]. Intriguingly, distinct IEGs are influenced by neuronal stimulation or activity blockade in a pathway-specific and stimulus-specific manner. For example, *Egr1* mRNA levels are N-methyl-D-aspartate-type glutamate receptor-dependent, whereas *c-fos* levels are not[14,15]. Moreover, different IEGs exhibit distinct temporal window with different activation kinetics. Synaptic activity also drives long-term changes in neuronal structure and function, contributing to learning and memory, via mechanisms involving transcriptional activation through

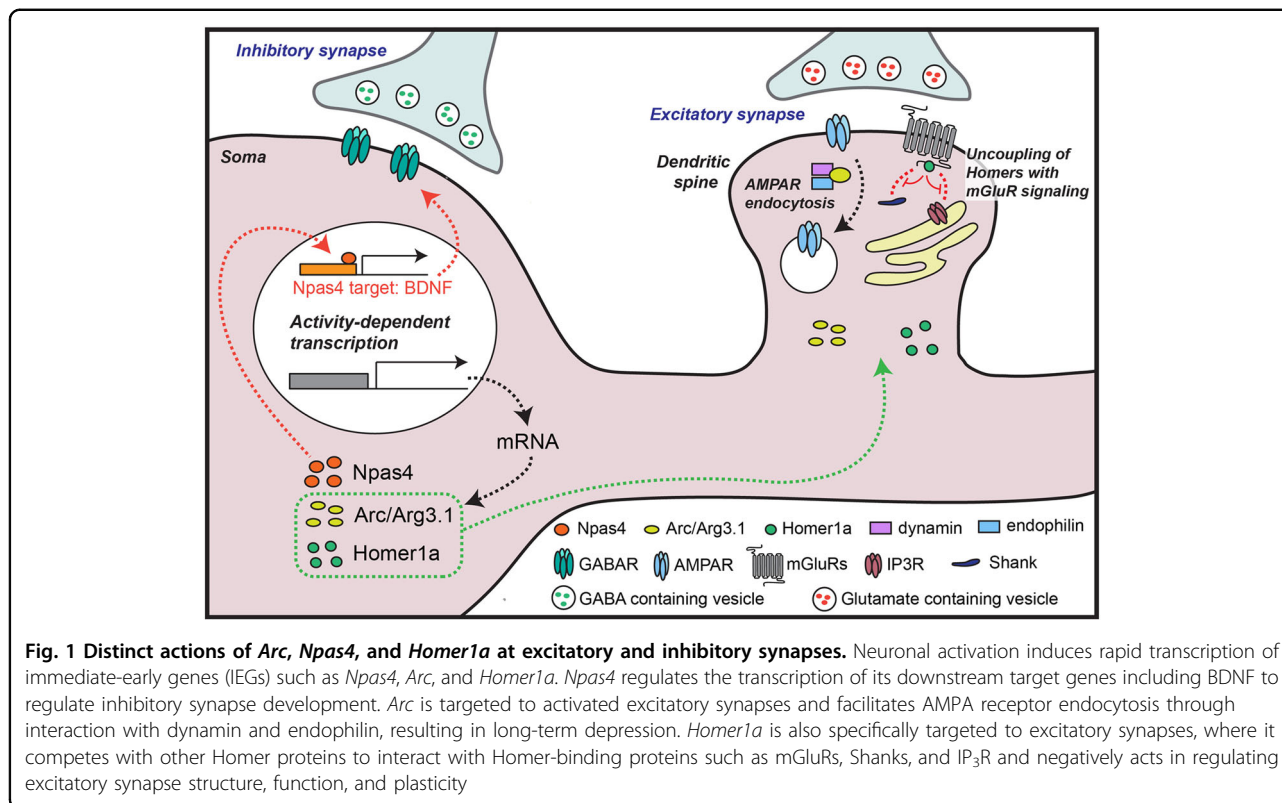Correspondence: Ji Won Um (jiwonum@dgist.ac.kr)
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Fig. 1 Distinct actions of *Arc*, *Npas4*, and *Homer1a* at excitatory and inhibitory synapses. Neuronal activation induces rapid transcription of immediate-early genes (IEGs) such as *Npas4*, *Arc*, and *Homer1a*. *Npas4* regulates the transcription of its downstream target genes including BDNF to regulate inhibitory synapse development. *Arc* is targeted to activated excitatory synapses and facilitates AMPA receptor endocytosis through interaction with dynamin and endophilin, resulting in long-term depression. *Homer1a* is also specifically targeted to excitatory synapses, where it competes with other Homer proteins to interact with Homer-binding proteins such as mGluRs, Shanks, and IP$_3$R and negatively acts in regulating excitatory synapse structure, function, and plasticity

second messenger systems[16]. A mechanistic concept for differential regulation of neuronal IEGs was utilized for mapping specific neural functions onto neuronal activity in different brain regions[17].

In the current review, we discuss three exemplary IEGs (activity-regulated cytoskeleton-associated protein (*Arc/Arg3.1*), neuronal Per/Arnt/Sim (PAS) domain protein 4 (*Npas4*), and Homer protein homolog 1a (*Homer1a*)) that play important roles in distinct facets of synapse and neural circuit development, as excellent reviews for the other neuronal IEGs are available. We describe the involvement of the three IEGs in synapse formation, transmission, plasticity, and cognitive behaviors. We also discuss the possible implications of these proteins in some brain disorders.

Activity-regulated cytoskeleton-associated protein

Arc (also known as *Arg3.1*) is one of the most tightly regulated molecules[18–20]. Neuronal activity regulates its transcription, translation, trafficking, localization, and stability[21,22]. Unlike other IEG products, Arc is not a transcription factor, but acts as an effector involved in various neuronal signaling pathways. Thus, *Arc* mRNA is rapidly transcribed in response to neuronal activity, and precisely targeted to activated synapses in neuronal dendrites[23–25].

Induction of Arc levels in an activity-dependent manner significantly elevates the proportion of thin spines and reduces surface α-amino-3-hydroxy-5-methyl-4-iso-xazolepropionic acid (AMPA) receptor density, which prevents network hyperexcitability, and contributes to maintenance of neuronal circuit homeostasis[26]. Arc induction is also required for late long-term potentiation (LTP) and memory consolidation[27–29], which is regulated by local actin polymerization[28]. *Arc* knockout (KO) mice exhibited a failure to form long-term memories, while their short-term memories were intact[29]. These behavioral defects are associated with the alteration in LTP in vivo. In addition, Arc mediates metabotropic glutamate receptor (mGluR)-dependent long-term depression through facilitation of AMPA receptor endocytosis[30–33] (Fig. 1). One of the proposed mechanisms by which Arc plays a regulatory role in AMPA receptor trafficking is via its interaction with components of the endocytic machinery, dynamin-2 and endophilin-3[30]. Calcium/cal-modulin-dependent protein kinase IIβ plays a role in the targeting of synaptic activity-induced Arc to strong stimulation experienced-inactive synapses where Arc mediates AMPA receptor clearance[34]. Arc is also required for homeostatic plasticity[35–37]. In particular, visual experience-induced Arc controls internalization of AMPA receptors, and as such, regulates homeostatic plasticity of excitatory synaptic transmission in layer 2/3 neurons of

the visual cortex[36]. *Arc* KO mice displayed abnormal ocular dominance plasticity[38], suggesting that Arc is required for the experience-dependent processes that establish synaptic connections in visual cortex.

In addition to regulating synaptic plasticity, Arc is involved in synaptic pruning. Specifically, Arc mediates elimination of redundant climbing axons to Purkinje cell in the developing cerebellum[39]. Neuronal activity-dependent myocyte enhancer factor 2 (MEF2) generates *Arc* transcripts, and subsequently activates local dendritic mGluR5 proteins to promote the translation of MEF2-induced *Arc* mRNAs, which are prerequisite for Arc's mediation of structural and functional synapse elimination in hippocampal neurons[40].

Arc is expressed rapidly and operates in the nucleus. Nuclear Arc level is modulated by synaptic activity[41], and controls the homeostatic response by increasing pro-myelocytic leukemia protein expression and decreasing AMPA receptor GluA1 subunit transcription[41,42]. In addition, nuclear Arc interacts with histone acetyltransferase TIP60 and modifies chromatin structures[43,44], suggesting that nuclear Arc mediates an epigenetic pathway to orchestrate neuronal activity-dependent transcription programs.

Mounting evidence supports the diverse roles of Arc at synapses and within the nucleus, but a precise mechanism for Arc localization is largely elusive. A recent study showed that extracellular signal-regulated kinase-mediated phosphorylation of Arc facilitates its cytosolic localization[45]. In addition to phosphorylation, Arc is rapidly sumoylated during LTP consolidation in the dentate gyrus of the hippocampus, which allows Arc to concentrate at the synapse to modulate actin cytoskeletal dynamics[46]. Moreover, Arc expression is subject to ubiquitination[47,48], and glycogen synthase kinase-3-mediated phosphorylation[49]. In particular, RING domain-containing ubiquitin ligase Triad3A/RNF216 ubiquitylates Arc, which is then rapidly degraded via proteasome[48], suggesting that loss of Triad3A might preclude Arc-dependent forms of synaptic plasticity. A recent study showed that missense mutations in Triad3 identified in patients with Gordon Homes Syndrome (GHS) resulted in defective Arc ubiquitination, thereby leading to impaired spatial learning and memory[50]. Therefore, Arc dysregulation may contribute to cognitive impairment and dementia observed in patients with GHS.

Neuronal PAS domain protein 4

Npas4 is a brain-specific transcription factor, the expression of which is regulated by neuronal activity, similar to Arc[51]. Npas4 plays a role in inhibitory synapse development by regulating the activity-dependent gene programs in cultured neurons[52]. More specifically, an enriched environment-induced Npas4 leads to an increase in the number of inhibitory synapses on the soma, and concurrently, a decrease in the number of inhibitory synapses on the apical dendrites of CA1 hippocampal pyramidal neurons[53]. Mechanistically, the inhibition mode within these subcellular compartments appears to be differentially tuned by distinct sets of Npas4 downstream targets. For instance, brain-derived neurotrophic factor (BDNF) specifically mediates Npas4-mediated somatic inhibition (Fig. 1), while other downstream targets (mostly uncharacterized) are thought to mediate dendritic inhibition. In addition, Npas4 mediates activity-dependent neurite outgrowth through cyclin-dependent kinase 5-dependent phosphorylation of synapsin I proteins in hippocampal cultured neurons[54]. In olfactory bulb interneurons, sensory experience immediately increases Npas4 protein levels, which is pivotal for dendritic spine formation[55].

In addition to regulating inhibitory synapse structure and transmission, Npas4 also controls the homeostatic inhibitory–excitatory balance by regulating adult visual cortical plasticity[56]. For excitatory–inhibitory balance within neural circuits, Npas4 activates distinct programs of late-response genes in a cell-type-specific manner[57]. The late-responsive Npas4 downstream genes differentially regulate the patterns of synaptic inputs onto inhibitory and excitatory neurons, promoting inhibitory actions toward excitatory neurons while inducing excitatory actions toward inhibitory neurons. Moreover, Npas4 shapes the structure and function of prefrontal inhibitory circuits during adolescence in a sex-specific manner[58], suggesting that Npas4 might be involved in the pathophysiological pathways underlying neuropsychiatric disorders that emerge during adolescence.

Npas4 is known as one of the activity-regulated inhibitor of death (AID) genes[59]. AID genes are the core components of a genomic survival program that is induced by nuclear calcium signaling in response to neuronal activity. Intriguingly, synaptotagmin-10 (Syt10) was first identified as the neuroprotective downstream target of Npas4[60], suggesting a role for the Npas4-Syt10 pathway in neuronal survival against excessive synaptic activity leading to excitotoxicity.

Npas4 has been linked to cognitive functions. Specifically, in the lateral nucleus of the amygdala, Npas4 level is elevated in a learning-dependent manner, and is responsible for the fear memory formation without affecting innate fear and expression of fear memory[61]. In CA3 hippocampal neurons, Npas4 level is specifically increased after contextual learning, regulating transcriptional programs required for contextual memory formation[62]. In addition, *Npas4* mRNA levels are decreased in the hippocampus of aged memory-impaired, but not memory-unimpaired, mice, suggesting that Npas4 may contribute to preservation of hippocampus-related cognition[63].

Npas4 deficiency was characterized by impaired spatial recognition memory, decreased anxiety-like behavior, and increased depression-like behavior[64]. These KO phenotypes suggest that Npas4 may be a prominent candidate factor for anxiety, depression, and related cognitive disorders. The role of Npas4 in regulating social behaviors has not been clearly determined; Coutellier et al.[64] showed that *Npas4* KO mice were less social than wild-type littermates, whereas Jaehne et al.[65] reported that the *Npas4* KO mice exhibited normal social behaviors. Intriguingly, *Npas4* KO mice exhibited long-lasting stress-related cognitive defects during adolescence[66]. The cognitive impairments observed in *Npas4* KO mice were accompanied by reduced migration of neuroblast cells in the subventricular zone to cortical regions[66]. Further investigations should determine whether cell biological and behavioral phenotypes reported in *Npas4* KO mice (e.g., cognitive deficits and stress-induced altered neurogenesis) are causally linked, and associated with brain disorders implicated in Npas4 dysfunctions.

Homer protein homolog 1a

The Homer protein family consists of three members (Homer1–3)[67]. Each Homer transcript generates several alternative splicing variants. One of two major splice variants, Homer1a (a shorter variant of Homer1), is induced by neuronal activity and is therefore considered an IEG[68]. Homer proteins typically possess a conserved N-terminal Ena/VASP homology I (EVH1) domain, and a coiled-coil domain at the C terminus. The EVH1 domain of Homer1 binds to a PPXXF motif present in various synaptic molecules, such as SH3 and multiple ankyrin repeat domains proteins (Shanks), group I mGluRs, and inositol-1,4,5-triphosphate (IP_3) receptors[69,70]. The coiled-coil domain of Homer1 mediates its dimerization, which enables Homers to physically and functionally link mGluRs with IP_3 receptors[71]. However, Homer1a lacks the coiled-coil domain and thus acts in a dominant-negative manner to disengage endogenous Homers with other effectors of mGluRs[68] (Fig. 1). Homer1a is expressed both in excitatory and inhibitory neurons across various brain regions, such as amygdala, hippocampus, primary somatosensory cortex, and dorsal striatum[72]. Subcellularly, Homer1a is primarily located at the postsynaptic density where Homer1a competes with other constitutively expressed Homer proteins for interactions with Homer-binding proteins. As such, Homer1a negatively regulates excitatory synapse structure and function[73]. Expression of Homer1a following neuronal activation leads to the dissociation of the mGluRs/IP_3 receptor complex and a reduced mGluR-mediated calcium response[68].

While *Homer1a* KO mice showed normal spine number, morphology, and memory acquisition, and intact short-term memory, they exhibited impaired fear memory consolidation and reconsolidation[74], suggesting a specific role of Homer1a in various stages of long-term, but not short-term, fear memory formation. Homer1a is epigenetically upregulated in the hippocampus and amygdala during the consolidation of cued fear conditioning mediated by BDNF[75]. In addition, Homer1a prevents the development of pain-related synaptic plasticity in the amygdala through disruption of mGluR1 signaling within the basolateral amygdala in an animal model of arthritis pain[76].

Homer1a is crucial for the mGluR-mediated homeostatic scaling process[77,78]. In particular, Homer1a as a molecular integrator of arousal and sleep drives homeostatic downscaling, which is active during sleep for synaptic remodeling[79]. Similarly, Homer1a regulates calcium homeostasis[80], activity-induced presynaptic and postsynaptic structural plasticity[81], and dendritic targeting of mGluR5[82].

Several animal models of epilepsy exhibit a marked increase in *Homer1a* mRNA levels in hippocampal dentate gyrus granule neurons[83,84], and epileptiform stimulus-induced synapse loss involves elevated Homer1a expression[85]. These results suggest that Homer1a may participate in a negative feedback loop to reduce network excitability. In addition to epilepsy, Homer1a could potentially be involved in depression-like behavior[86,87]. Intriguingly, knockdown of Homer1a by RNA interference in medial prefrontal cortex (mPFC) enhanced depressive-like behavior in mice, and overexpression of Homer1a in mPFC showed anti-depressant effects[88]. Given that various anti-depressant treatments increase Homer1a expression in mPFC[88], Homer1a may be a key molecular player in anti-depressant therapy, although the mechanism(s) underlying its anti-depressant action require further elucidation.

Alteration of Homer1a levels was observed in the hippocampus and cingulate gyrus of human patients with various neuropsychiatric disorders, including schizophrenia, bipolar disorder, and major depression[89]. Intriguingly, in *Fmr1* KO mouse model of fragile X syndrome, mGluR5 is more associated with shorter Homer1a rather than the longer Homer isoforms[90,91]. Deletion of Homer1a restores the association of mGluR5 with the longer Homer isoforms, leading to correction of a subset of phenotypes observed in the *Fmr1* KO mice[90]. It remains to be solved how *Fmr1* deficiency induces disrupted mGluR5–Homer interactions, but the altered interactions of mGluR5 with Homer may be an important mechanism underlying cognitive brain disorders involving mGluR5 dysfunction. Furthermore, Homer1a was reported to counteract amyloid-β-induced downregulation of potassium channel activity, hinting its potential as a therapeutic target for Alzheimer's disease[92]. Supporting

this notion, transcranial magnetic stimulation triggers effects on calcium-activated potassium channel facilitating large conductance and leading to enhanced hippocampal LTP and reduced cortical excitability, in Homer1a-dependent manner[93]. Collectively, these studies pinpoint Homer1a as a prominent biomarker and potential therapeutic target for certain brain disorders.

Conclusions and perspectives

It is increasingly apparent that IEGs are critical for the structure, function, and plasticity of both excitatory and inhibitory synapses across various cell types and brain regions. In this review, we highlighted only a subset of IEGs that function in distinct manners to regulate specific aspects of synapse development. Although IEGs have been continually utilized as markers for labeling active population of neurons, their physiological significance remains to be fully clarified. In the future, other neuronal IEGs beyond those discussed in this review should be intensively studied towards a fuller understanding of how IEGs organize synapse development and by extension neural circuit development. Unquestionably, these future directions will aid in clearly defining the role of environment in development of various neurodevelopmental and neuropsychiatric disorders.

Conflict of interest
The authors declare that they have no conflict of interest.

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