Neuroscience Research 69 (2011) 175–186

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Review article

Regulation and function of immediate-early genes in the brain: Beyond neuronal activity markers

Hiroyuki Okuno*

Department of Neurochemistry, University of Tokyo Graduate School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

ARTICLE INFO

Article history:
Received 26 October 2010
Received in revised form 3 December 2010
Accepted 7 December 2010
Available online 14 December 2010

Keywords:
Immediate-early gene
Arc
Synaptic activity
Long-term memory
Synaptic plasticity
CREB
Gene mapping
Hippocampus

ABSTRACT

Long lasting forms of synaptic plasticity and long-term memory formation require new mRNA and protein synthesis. While activity-dependent expression of immediate-early genes has long been thought to account for such critical *de novo* macromolecular synthesis, experimental proof has been scarce until recently. During the past few decades, a growing number of genetic and molecular biological studies have started to elucidate essential roles of immediate-early genes in synaptic plasticity and cognitive functions. I here present an overview of the history and recent work on regulation and function of neuronal immediate-early genes, including *Arc*/*arg*3.1. This review provides a conceptual framework in which various immediate-early genes underlie several distinct processes required for long-term synaptic changes and memory formation.

Contents

1. Introduction

The brain stores information extracted from experiences and utilizes it to modify behaviors throughout the life span of an organism. This large mnemonic capacity is thought to depend on intrinsic neural networks whose synaptic connectivity and strength can be modulated by specific patterns of neuronal activity. Early behavioral studies using protein synthesis inhibitors indicated that newly synthesized protein is required for long-term memory but not for short-term memory (Davis and Squire, 1984). This conceptual framework has been expanded to synaptic plasticity; long-lasting forms of synaptic plasticity, such as long-term potentiation (LTP),

* Tel.: +81 3 5841 3560; fax: +81 3 3814 8154.
E-mail address: okuno@m.u-tokyo.ac.jp

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doi:10.1016/j.neures.2010.12.007

require newly synthesized mRNA and proteins, while short-term plasticity does not (Bliss and Collingridge, 1993; Goelet et al., 1986; Kandel, 2001). This requirement has critical time windows for both memory formation and synaptic plasticity. Administration of protein synthesis inhibitors to animals just after learning effectively blocks long-term memory formation, while administration several hours later has little effect (Freeman et al., 1995; Nader et al., 2000; Rosenblum et al., 1993; Squire and Barondes, 1972; Suzuki et al., 2004). Similarly, LTP is prevented only when mRNA or protein synthesis is blocked immediately after LTP-inducing stimulation (Frey et al., 1988; Nguyen et al., 1994; Otani et al., 1989). Thus, gene expression occurring immediately after the events to be memorized appears to play critical roles for establishment and/or maintenance of long-lasting neuronal changes. Such inducible genes are mostly classified as a subset of genes called immediate-early genes (IEGs) (Lanahan and Worley, 1998; Morgan and Curran, 1991).

The term "immediate-early gene" originated from virology. When viruses infect a host cell, several viral genes are rapidly transcribed. This process requires only pre-existing transcription factors of the host cell and occurs in the absence of *de novo* protein synthesis (Watson and Clements, 1980). Through tremendous work on cellular differentiation and proliferation during the 1980s, it has become evident that various stimuli, such as growth/differentiation factors, hormones or cytokines, induce rapid and transient mRNA synthesis in fibroblasts and other cell lines even in the presence of protein synthesis inhibitors (Almendral et al., 1988; Curran et al., 1985; Greenberg and Ziff, 1984; Kelly et al., 1983; Kruijer et al., 1984; Lau and Nathans, 1985). By analogy to the viral IEGs, these cellular genes that are responsive to extracellular stimuli are called "cellular" IEGs. The cellular IEGs, simply referred to as IEGs, encode many functionally distinct proteins, including structural proteins, signaling molecules, and transcription factors.

In this review, I summarize recent expansion of our understanding of neuronal IEGs regarding their regulation and functions for neuronal plasticity and cognitive functions. In particular, I will focus on the neuron-specific IEG *Arc* (also known as *arg*3.1) (Link et al., 1995; Lyford et al., 1995) because recent studies on this gene have highlighted many characteristic and intriguing regulatory aspects of neuronal IEGs, although the biological function of these remains enigmatic.

2. Neuronal activity-dependent expression of IEGs

2.1. IEG expression in the brain

As in the case of intracellular responses to growth factors in mitotic cells, synaptic transmission and/or action potentials also initiate several intracellular signaling cascades, particularly those related to intracellular Ca^{2+} changes, in postmitotic neuronal cells (Morgan and Curran, 1991; Sheng and Greenberg, 1990). In the late 1980s, it was determined that the IEG encoded transcription factor c-Fos is rapidly induced in specific brain nuclei after pharmacological convulsive stimulation and physiological contexts (Morgan et al., 1987; Saffen et al., 1988; Sagar et al., 1988). As a consequence of these groundbreaking findings, two types of studies have been conducted on neuronal IEGs. One type is aimed at isolating and characterizing novel neuronal IEGs. Because many IEGs are implicated in neuronal plasticity and cognitive functions (discussed in Section 4), much effort has been invested to isolate novel IEGs, probably with the hope of finding "master genes" for learning and memory. The other type of study applies IEG expression as a tool to visualize neuronal activity in the brain. Because IEG expression in a neuron reflects the neuron's recent activity, detection of IEG mRNA or protein products in the brain provides information regarding where and when neurons were activated. A brief overview of both lines of work is described below.

2.2. Isolation of neuronal IEGs

Early following studies revealed that several IEGs that were initially identified in fibroblasts and cell lines are in fact also expressed and activity-regulated in neurons in the brain (Dragunow et al., 1992; Herdegen et al., 1991; Morgan et al., 1987; Saffen et al., 1988; Worley et al., 1991). Thus, it is reasonable to expect that there might be more dynamically regulated and more neuron-specific IEGs that could be relevant to synaptic plasticity and memory formation. In the early 1990s, several laboratories extensively explored new IEGs that could be induced by neuronal activity (Table 1). A group led by Paul Worley at the Johns Hopkins University isolated IEGs from a subtraction cDNA library made from control and electroconvulsive shock-treated hippocampi. Through this strategy, they isolated more than 10 novel IEGs; the clones encode transcription factors (*egr*-3) (Yamagata et al., 1994a), signaling molecules (*rheb*, *rsg*2, *cox*-2) (Ingi et al., 1998; Yamagata et al., 1993, 1994b), and several functionally unknown proteins at that time (*Arc*, *homer*1a, *narp*, etc.) (Brakeman et al., 1997; Lyford et al., 1995; Tsui et al., 1996). Dietmar Kuhl and colleagues at Columbia University and later in Germany isolated several IEGs using a similar differential screening strategy. Their identified clones include *tPA* (Qian et al., 1993), *SNK* (Kauselmann et al., 1999) and *arg*3.1 (Link et al., 1995). Inokuchi's group in Japan independently started to search for activity-induced IEGs through a PCR-based differential cloning strategy and isolated several novel neuronal IEGs, including *vesl*-1s (Kato et al., 1997) and activin-β (Inokuchi et al., 1996). Elly Nedivi and colleagues isolated multiple candidate-plasticity genes (*CPG*s), some of which were shown to be IEGs (Fujino et al., 2003; Nedivi et al., 1993, 1996). These studies used the protein synthesis inhibitor cycloheximide to stabilize or enrich activity-induced mRNAs, which also ensured the definition of IEGs, i.e., *de novo* protein-synthesis independent expression of transcripts. Some of these genes have turned out to be identical. Table 1 presents a list of representative neuronal IEGs with a brief descriptions of structures and function of their products; neuronal IEG products can be classified into several categories including transcription factors, postsynaptic proteins, signaling molecules, secretory factors, and membrane proteins. It is noteworthy that most of the IEGs that were reported by earlier studies encoded transcription factors, while many of those reported more recently encoded non-transcription factor proteins whose function might be directly associated with synaptic properties. The roles and functions of these IEGs *in vitro* and *in vivo* remain central topics in the field (see Section 4).

2.3. Mapping IEG expression in the brain

IEG expression mapping is a powerful method to visualize activated neuronal populations in the brain of animals. Importantly, this technique has been applied to the identification of brain loci related to learning and memory. Historically, c-Fos immunohistochemistry (IHC) and c-*fos* mRNA in situ hybridization (ISH) have been used (Brennan et al., 1992; Rosen et al., 1992, 1998; Vann et al., 2000; Wisden et al., 1990; Zhu et al., 1995). However, because the induction threshold of c-*fos* appears to be rather high compared to those of other IEGs (Waltereit et al., 2001; Wisden et al., 1990; Worley et al., 1993), c-*fos* mapping tends to be applied to behavioral paradigms with a relatively strong cognitive or emotional burden. Expression of *zif*268 is more responsive to synaptic activities at physiological levels (Cole et al., 1990; Worley et al., 1993). Both contextual and cued fear conditioning evoke *zif*268 induction in the amygdala, the center of emotional memory, as well as in the CA1 region of the hippocampus in rodents (Hall

Table 1
Summary of activity-regulated, neuronal immediate-early genes.

Category	Gene	Structure/function of gene product	Reference
Transcription factors	c-*fos*	A bZIP protein; a component of AP-1 complex	Greenberg and Ziff (1984); Morgan et al. (1987)
	fos B	A bZIP protein; a component of AP-1 complex	Hope et al. (1992); Dragunow et al. (1992)
	c-*jun*	A bZIP protein; a component of AP-1 complex	Saffen et al. (1988); Cole et al. (1990)
	junB	A bZIP protein; a component of AP-1 complex	Saffen et al. (1988); Cole et al. (1990)
	*zif*268/egr1/*krox*24/*NGFI-A*	A zinc finger protein	Cole et al. (1989); Worley et al. (1993)
	egr2/*krox*20	A zinc finger protein	Bhat et al. (1992)
	*egr*3/pilot	A zinc finger protein	Yamagata et al. (1994a)
	nur-77/*NGFI-B*	An orphan hormone receptor	Watson and Milbrandt (1989); Wisden et al. (1990)
Postsynaptic proteins	*Arc*/*arg*3.1	A regulator of AMPAR trafficking	Lyford et al. (1995); Link et al. (1995)
	*homer*1a/*vesl*1s	An inducible form of EVH proteins	Brakeman et al. (1997); Kato et al. (1997)
Intracellular signaling	Rheb	A Ras homolog protein: regulating mTOR pathway	Yamagata et al. (1994b)
	RSG2	A regulator of heteromeric G-protein signaling	Ingi et al. (1998)
	SNK/Plk2	A polo-like kinase	Kauselmann et al. (1999)
	Cox-2	An inducible cyclooxygenase	Yamagata et al. (1993)
Secretory factors	BDNF	A member of neurotrophin family	Hughes et al. (1993); Lauterborn et al. (1996)
	Activin β A	A member of the TGF-β superfamily	Andreasson and Worley (1995); Inokuchi et al. (1996)
	Narp	A neuronal pentraxin: presynaptically released	Tsui et al. (1996)
	Tissue-plasminogen activator (tPA)	An extracellular serine protease	Qian et al. (1993)
Membrane proteins	Arcadin	A protocadherin family protein	Yamagata et al. (1999)
	CPG15/neuritin	A GPI-anchored protein: promoting neuritogenesis	Nedivi et al. (1993); Naeve et al. (1997)

Only a subset of immediate-early genes are listed.

et al., 2001; Reijmers et al., 2007). Interestingly, such memory-related expression of *zif*268 is temporal- and region-specific; *zif*268 in the CA1 region is induced more efficiently by a memory test performed at one day post training (recent memory test) compared to by the test done one month later (remote memory test), while *zif*268 expression is more upregulated in several association cortices including the anterior cingulate cortex, the medial prefrontal cortex, and the temporal cortex, during the remote memory test than during the recent memory test (Frankland et al., 2004; Sacco and Sacchetti, 2010). In song birds, associative learning of songs and shocks robustly induces the *zif*268 homolog ZENK in brain regions related to song memories (Jarvis et al., 1995).

Recently, *Arc* ISH and IHC have become more frequently used because *Arc* expression is highly dynamic and correlated with neuronal activity (Guzowski et al., 1999, 2000; Link et al., 1995; Lyford et al., 1995; Ramirez-Amaya et al., 2005). Exploration of new environments strongly induces *Arc* expression in the hippocampus as well as related neocortical areas in rats and mice (Guzowski et al., 1999; Ramirez-Amaya et al., 2005). *Arc* mRNA and protein induction are also observed in specific brain areas during performance of behavioral tasks that test spatial memory (Fletcher et al., 2006; Gusev et al., 2005; Gusev and Gubin, 2010; Guzowski et al., 2001), fear-conditioning memory (Barot et al., 2009; Mamiya et al., 2009; Ploski et al., 2008), olfactory memory (Desgranges et al., 2010; Saddoris et al., 2009), and several types of operant learning (Carpenter-Hyland et al., 2010; Kelly and Deadwyler, 2003; Rapanelli et al., 2010). Furthermore, taking advantage of rapid *Arc* mRNA synthesis, a sensitive fluorescence ISH method called cat-FISH was developed to discriminate neuronal activation history at two different time points (Guzowski et al., 1999).

As alternatives to detect endogenous IEG mRNA and proteins, several transgenic (Tg) mouse approaches have been reported. Genetically encoded markers such as green fluorescent protein (GFP) and β-galactosidase (LacZ) under the control of the c-*fos* promoter were used to effectively visualize neuronal populations activated under both physiological and pathological conditions (Barth et al., 2004; Dai et al., 2009; Robertson et al., 1995; Smeyne et al., 1992). Furthermore, an enduring labeling method specific for neurons activated in a given time window has been developed using c-*fos* promoter Tg mice (Reijmers et al., 2007). Recently, several lines of *Arc*-promoter reporter mice have also been generated (Eguchi and Yamaguchi, 2009; Grinevich et al., 2009; Wang et al., 2006) (Okuno et al., in preparation). With advances in imaging techniques, these Tg mice now open the door for *in vivo* real-time imaging of IEG expression (Eguchi and Yamaguchi, 2009; Wang et al., 2006).

As described above, most IEG mapping studies have been conducted in rodents and other small vertebrates. However, it is noteworthy that there are several studies using larger animals including primates. *zif*268 and c-*fos* mapping effectively visualizes functional architecture in the brain such as the ocular dominance columns in the monkey visual cortex, which could previously only be visualized by radioisotope labeling methods (Chaudhuri and Cynader, 1993; Chaudhuri et al., 1997; Takahata et al., 2009). In an attempt to map memory-related activity, I initiated a series of studies in which declarative memory paradigms were combined with IEG mapping in macaque monkeys, while working with Professor Yasushi Miyashita and colleagues (Fig. 1) (Okuno and Miyashita, 1996; Tokuyama et al., 2000, 2002). In these studies, monkeys were trained to perform a visual long-term memory task, termed the pair-association task, in which a set of two geometrically unrelated pictures had to be memorized for a reward to be given. During the learning period, a couple of IEGs including *zif*268 (Okuno and Miyashita, 1996; Tokuyama et al., 2002) and brain-derived neurotrophic factor (*bdnf*) (Tokuyama et al., 2000) were selectively induced in patch-like patterns in a specific region

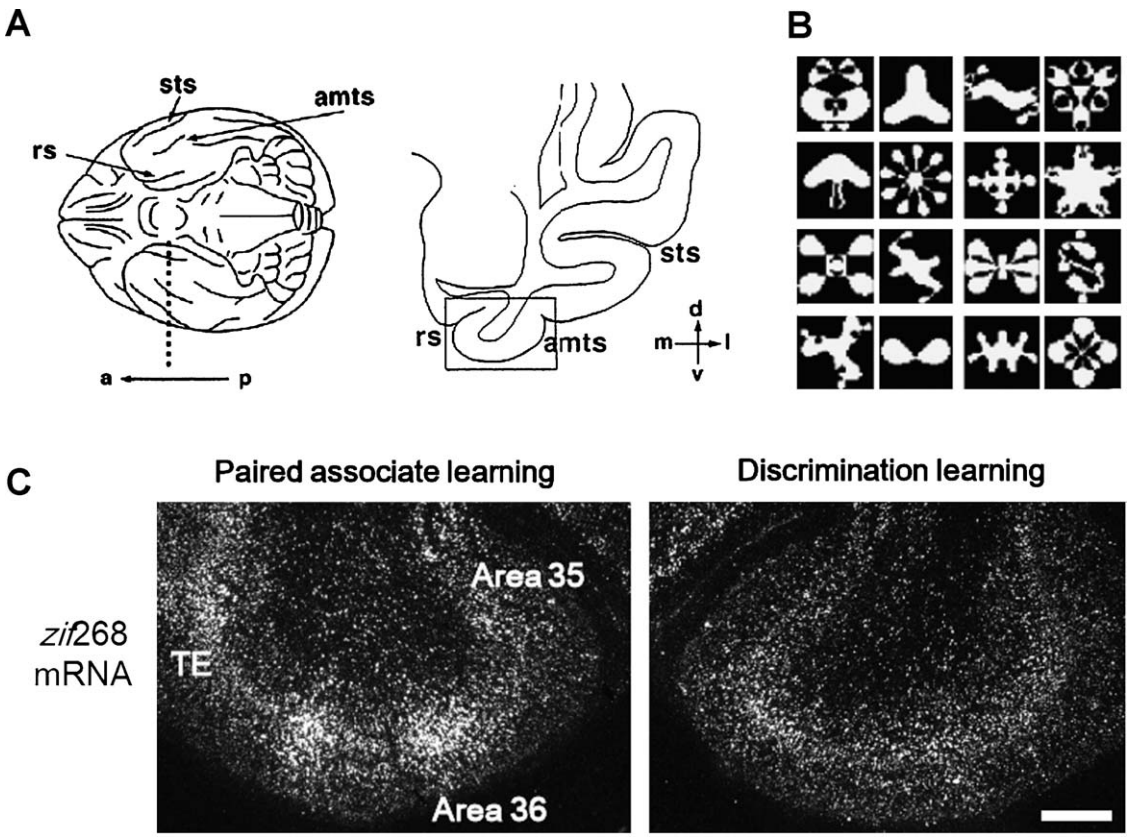

Fig. 1. Induction of *zif*268 in monkey brain during formation of declarative long-term memory. (A) Line drawings of the ventral view of the macaque brain (left) and of a coronal section of the temporal lobe (right). Orientation is indicated by arrows: a, anterior; p. posterior: d, dorsal, v, ventral; m, medial; l, lateral. rs, rhinal sulcus; amts, anterior middle temporal sulcus; sts, superior temporal sulcus. (B) A set of stimulus pictures used in the visual memory tasks. These paired computer-generated pictures were used as paired associates in paired associate learning and also as rewarded and non-rewarded stimuli in discrimination learning. (C) Representative IEG expression in the monkey inferior temporal cortex during visual paired associate learning and control discrimination learning. Transcripts of *zif*268 accumulated in a few patches in Area 36 of the inferior temporal cortex during learning of paired associates (left) but not visual discrimination (right). Scale bars, 1 mm.
Reprinted from Okuno and Miyashita (1996) and Tokuyama et al. (2000, 2002).

(area 36) of the inferior temporal cortex, a presumed storehouse of visual long-term memory (Miyashita, 1993). Parallel electrophysiological studies have demonstrated the existence of clusters of cells that specifically respond to the paired associates within area 36 (Higuchi and Miyashita, 1996; Naya et al., 2001; Sakai and Miyashita, 1991). The size and location of electrophysiologically identified clusters are very much consistent with the IEG patches, suggesting functional relevance of IEG expression in shaping the task-specific responses of neurons (Okuno and Miyashita, 1996; Tokuyama et al., 2000, 2002). Selective induction of *bdnf* mRNA in the parietal association cortex related to tool-use learning in monkeys has also been reported by another group (Ishibashi et al., 2002).

3. Molecular basis of dynamic IEG regulation

3.1. Transcriptional regulation of IEGs

Accumulating evidence from mapping studies indicates a strong correlation between IEG expression and neuronal activity in the brain. As such, questions about the molecular regulation of activity-dependent expression of IEGs have arisen. Traditional and straightforward approaches include evaluation of genomic sequences in the promoter regions of IEGs and identification of the transcription factors involved in their regulation. In this section, I briefly describe molecular aspects of activity-dependent regulation of the c-*fos* and *bdnf* genes, followed by a more detailed description of the molecular regulation of the *Arc* gene.

The first IEG whose regulatory mechanisms were studied in detail in neurons is c-*fos* (Schilling et al., 1991; Sheng et al., 1990). The activity-dependent regulation of the c-*fos* gene can be recapitulated with a relatively simple regulatory structure; most of the essential *cis*-acting regulatory elements seem to be located within a 600-bp proximal promoter sequence (Robertson et al., 1995; Smeyne et al., 1992). In neurons, c-*fos* expression is induced by both cAMP and Ca^{2+} signaling. One of the genomic elements responsible for this regulation is the Ca^{2+}/cAMP responsive element (Ca/CRE), which is located close to the transcription start site (TSS) of the c-*fos* gene (Sheng and Greenberg, 1990). The activity-dependent transcriptional regulator CREB (c-AMP responsive element binding protein) mediates the Ca/CRE-dependent transcriptional activation. Another essential regulatory element within the c-*fos* promoter is the serum response element (SRE), which resides 250 bp upstream from the Ca/CRE (Schilling et al., 1991). Serum response factor (SRF), which is also a major activity-dependent transcriptional regulator, binds to SRE and mediates transcription (Johnson et al., 1997). Tg mice with point mutations in either SRE or Ca/CRE of the c-*fos* promoter showed greatly reduced transgene expression in the brain (Robertson et al., 1995).

The *bdnf* gene is another well-studied activity-dependent gene. The *bdnf* gene has at least 8 distinct promoters, and each has different activity dependencies (Aid et al., 2007; Pruunsild et al., 2007). Transcripts from some of the promoters fulfill the criteria for IEGs (Hughes et al., 1993; Lauterborn et al., 1996). Promoter IV, which exhibits the most dynamic activity dependency, has three distinct calcium response elements, CaRE-1 (calcium response element-1),

CaRE-2 and CaRE-3, which bind CaRF (calcium-response factor), USF (upstream stimulatory factor) and CREB, respectively [for comprehensive reviews, see (Greer and Greenberg, 2008; West et al., 2001)]. Promoter I of *bdnf* also contains a CRE and a USF-binding site (Tabuchi et al., 2002).

These pieces of evidence indicate that several well known transcription factors play essential roles in neuronal activity-dependent IEG transcription. In particular, CREs exist in the promoter regions of almost all neuronal IEGs examined, including c-*fos*, *bdnf*, *zif*268 (Changelian et al., 1989), *homer*1a/*vesl*1s (Bottai et al., 2002), *cpg*15 (Fujino et al., 2003), and *Arc* (see below). Therefore, CREB is believed to be one of the key players in the control of IEG expression. Additionally, its critical roles in cognitive functions and neuronal plasticity have been repeatedly reported (Bito and Takemoto-Kimura, 2003; Carlezon et al., 2005; Lonze and Ginty, 2002; Silva et al., 1998). For such reasons, understanding of the molecular mechanisms that regulate transcriptional activity of CREB and other transcription factors is of particular importance. A comprehensive description of the activity-driven regulation of these transcription factors is beyond the scope of this review, but it should be noted that phosphorylation/dephosphorylation is a major regulatory switch for CREB and other transcription factors (Bito et al., 1996, 1997; Deisseroth et al., 1996; Mayr and Montminy, 2001; Shaywitz and Greenberg, 1999; Takemoto-Kimura et al., 2010) (see also below).

3.2. Regulation of Arc expression through the synaptic-activity responsive element (SARE)

As described above, *Arc* expression is highly dynamic and correlates with neuronal activity related to cognitive processes in the brain. Thus, many efforts have been invested to dissect signaling cascades and molecular determinants that control the expression of *Arc* transcripts. Similar to many other IEGs, *Arc* expression depends on NMDA receptor activation in the brain (Link et al., 1995; Lyford et al., 1995). However, until recently, it remained unclear as to what intracellular signaling was involved and what types of transcription factors were crucial for *Arc* induction.

Waltereit et al. analyzed an approximately 2-kb sequence upstream from the *Arc* TSS (Waltereit et al., 2001). The 2-kb *Arc* promoter sequence has little ability to respond to cAMP elevation by forskolin treatment, while endogenous *Arc* mRNA is effectively induced with the same treatment, suggesting that upstream sequences are critical for *Arc* regulation. Within the 2-kb sequence, they identified a couple of SREs and AP-1 (the binding motif for Fos/Jun complex) sites, but no CRE sites (Waltereit et al., 2001). They also showed involvement of the MAPK pathway in endogenous *Arc* induction. Minimal progress had been made on understanding the molecular basis of *Arc* transcriptional regulation; however, due to recent advances in available genomic information and molecular biological techniques, a genomic locus that dominantly controls synaptic activity-dependent expression of *Arc* has been identified. Kawashima et al. extended the analysis of *Arc* promoter sequences up to 10 kb upstream of TSS (Kawashima et al., 2009). They initially found that the 7-kb upstream sequence of *Arc* replicated the dynamic expression of the endogenous *Arc* gene. Further extensive analyses revealed that an approximately 100-bp sequence, located at the most distal region of the 7-kb *Arc* promoter, is the critical element for dynamic *Arc* expression. This element is highly responsive to synaptic activity and is thus named the synaptic activity-responsive element (SARE) (Inoue et al., 2010; Kawashima et al., 2009). SARE has a unique structure consisting of a CREB-binding site (half CRE) and an SRF-binding site that flank a MEF2-binding site (MRE) (Fig. 2). MEF2 is another major player in activity-dependent transcription (Flavell et al., 2006). Cooperativity of CREB, MEF2 and SRF appears to be critical for SARE activation because the integrity of all 3 transcription factor binding sites is required for full activity dependency (Kawashima et al., 2009). Interestingly, these 3 transcription binding sites are evolutionally well conserved across placental mammals, while the CRE site is missing in some non-placental mammals such as the platypus, perhaps suggesting that evolutionary selection might be achieved through SARE-dependent gene regulation of *Arc* (Kawashima et al., 2009). Both CaMK- and MAPK-dependent pathways are involved in SARE activation (Kawashima et al., 2009). The importance of the SRF-binding site in SARE was also reported independently by two groups (Pintchovski et al., 2009; Smith-Hicks et al., 2010).

In addition to the pre-existing transcription factors mentioned above, lines of evidence from recent studies indicate that several transcriptional coactivators that interact with specific transcription factors may also impact activity-dependent gene expression. CBP (CREB binding protein) and its paralogue p300 are well-known coactivators that regulate gene expression in a manner dependent on Ser133-phosphorylation of CREB (Chrivia et al., 1993). CRTCs (CREB-regulated transcription coactivators, also known as TORCs) may also regulate CREB-dependent gene expression (Conkright et al., 2003). CRTC1, a brain-enriched isoform of CRTC, regulates dendritic morphology in developing cortical neurons (Li et al., 2009) and IEG expression in mature hippocampal neurons (Espana et al., 2010; Nonaka et al., personal communication). Two different families of coactivators, TCF (ternary complex factor) (Treisman, 1994) and MKL (megakaryoblastic leukemia or megakaryocytic acute leukemia, MAL) (Miralles et al., 2003; Selvaraj and Prywes, 2003), are known as SRF cofactors. Phosphorylation of TCF is correlated with c-*fos* expression in the brain (Vanhoutte et al., 1999) and MKL cofactors have been shown to be involved in actin-regulated dendritic morphology and IEG-mediated synaptic plasticity (Ishikawa et al., 2010; Smith-Hicks et al., 2010; Tabuchi et al., personal communication). These findings indicate the critical importance of coactivators in transcriptional regulation of IEGs. Fig. 2 illustrates a model of *Arc* regulation via SARE, although identity of the constituents in the SARE–protein complex must be confirmed through further experiments.

4. Function of IEG products

In this section, I first review molecular functions of representative IEG products and then summarize recent knock-out (KO) mouse studies investigating physiological roles of IEGs in synaptic plasticity and memory formation.

4.1. Biological and cellular functions

4.1.1. IEG transcription factors

As shown in Table 1, one category of products encoded by IEGs is transcription factors. *In vitro* experiments have revealed that most of these inducible transcription factors can work as activators, and their DNA binding sequences have been characterized. However, genes that are regulated by the IEG-encoded transcription factors (i.e., target genes) under physiological conditions or *in vivo* have not been well characterized yet. For example, c-Fos and other Fos-related proteins heterodimerize with Jun family proteins and bind to the AP-1 site during transcriptional regulation (Curran and Franza, 1988; Karin et al., 1997). The AP-1 sites are frequently found in the promoter regions of many genes, but only a few have been actually shown to be regulated by the Fos/Jun family in the brain (Zhang et al., 2002, 2006). Similarly, several putative target genes of Zif268 have been proposed, but their dependency *in vivo* still needs to be confirmed (James et al., 2005). Recent "deep sequencing" technologies (e.g., ChIP-seq and RNA-seq) combined with genetically modified animal resources (see below) may greatly facilitate the identification of genuine targets of IEG transcription factors.

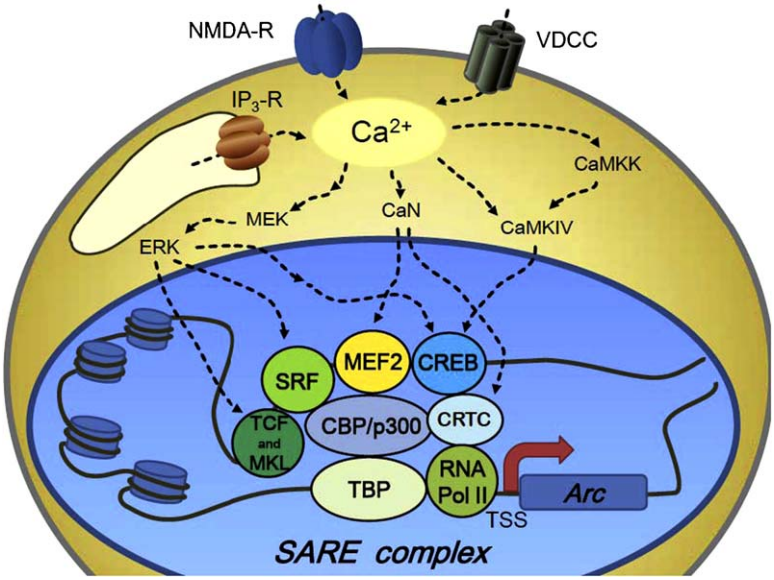

Fig. 2. Putative molecular mechanisms of synaptic activity-dependent expression of *Arc*. Upon strong synaptic activation, a transient increase in intracellular Ca^{2+} concentrations by Ca^{2+} influx through NMDA-type glutamate receptors (NMDA-R) initiates several intracellular kinase and phosphatase pathways. Voltage-dependent calcium channels (VDCC) and IP_3 receptors (IP_3-R) may also contribute to the intracellular Ca^{2+} rise. The synaptic signaling converges on the distally located key regulatory element SARE by forming a complex consisting of the critical activity-dependent transcription factors, CREB, MEF2 and SRF as well as their coactivators such as TCF, MKL, CBP, p300 and CRTC. The putative SARE complex recruits the preinitiation complex close to transcription start site (TSS) and initiates transcription of *Arc*. Only direct phosphorylation/dephosphorylation events or transcription factors/coactivators are illustrated for simplicity, but more complex cross-talks are very likely to occur. CaMKIV, calcium/calmodulin kinase IV; CaMKK, calcium/calmodulin kinase kinase; CaN, calcineurin/PP2B; CREB, cAMP-responsive element binding protein; CBP, CREB-binding protein; CRTC, CREB-regulated transcription co-activator; ERK, extracellular signal-regulated kinase; MEF2, myocyte enhancer factor-2; MEK, mitogen-activated protein kinase; MKL, megakaryoblastic leukemia; SARE, synaptic-activity responsive element; SRF, serum-response element; TCF, ternary complex factor.

4.1.2. *Effector IEG proteins*

Functions of other categories of IEG-encoded products such as cytosolic and synaptic proteins have been extensively investigated in this decade, and some of these IEGs have attracted a great amount of attention because of their direct involvement in synaptic functions (Table 1). For example, molecular and biological functions of *Arc*, *homer*1a/*vesl*-1s and *narp* have been uncovered during the past several years. Arc protein is enriched in the postsynaptic density. Chowdhury et al. reported the first critical clue of the biological and cellular function of *Arc* in neurons (Chowdhury et al., 2006). They demonstrated that Arc interacted with specific isoforms of endophlins and dynamins to enhance membrane receptor endocytosis (Chowdhury et al., 2006). Consistent with this finding, forced expression of Arc reduces surface expression of AMPA receptors in wild-type neurons, while surface expression of AMPA receptors is enhanced in cultured neurons prepared from *Arc*-KO mice (Chowdhury et al., 2006). Consistently, electrophysiological analyses revealed reduced AMPA currents under the condition in which *Arc* was virally over-expressed in hippocampal slice cultures (Rial Verde et al., 2006). Because *Arc* expression is activity-regulated, it is proposed that *Arc* is involved in synaptic scaling, a form of homeostatic synaptic plasticity (Gao et al., 2010b; Shepherd et al., 2006). In addition to rapid induction, *Arc* mRNA is known to have an interesting property involving dendritic mRNA targeting (Steward et al., 1998; Wallace et al., 1998) and local translation of Arc in the dendrites is implicated in synaptic long-term depression (Park et al., 2008; Waung et al., 2008). Although these studies demonstrate roles of Arc protein in regulating AMPA-Rs at synapses, it is still currently unknown how synaptic delivery of Arc is achieved and what regulates Arc-mediated AMPA-receptor endocytosis.

*Homer*1a/*vesl*-1s is the IEG isoform of the *homer* gene family. The activity-dependent alternative splicing mechanism results in Homer1a/Vesl-1s protein having the N-terminal EVH domain but lacking the C-terminal coiled-coil domain (thus called the short-form Homer). In contrast, the long-form Homer proteins, which are encoded by the non-IEG-isoforms, have both the EVH domain and the coiled-coil domain, both of which are critical for orchestrating a large Homer-mediated protein–protein network consisting of mGluRs, IP_3 receptors and Shank in the postsynapse (Hayashi et al., 2006, 2009; Sala et al., 2003, 2005; Tu et al., 1999; Xiao et al., 1998; Yuan et al., 2003). Therefore, it is assumed that the activity-dependent expression of Homer1a/Vesl-1s triggers disruption and reorganization of the Homer-mediated network (Sala et al., 2003, 2005; Tu et al., 1999; Xiao et al., 1998; Yuan et al., 2003). Furthermore, Homer1a/Vesl-1s protein is the first experimentally qualified candidate for putative plasticity-related proteins in the synaptic tagging and capture hypothesis (see below) (Okada et al., 2009).

Narp (neuronal activity-regulated pentraxin) is a secreted lectin protein (Tsui et al., 1996). Together with other pentraxin proteins, Narp makes a complex that has the ability to induce clustering of AMPA-Rs on the cell surface (O'Brien et al., 1999; Xu et al., 2003). Recently, a cell-type specific effect of Narp on AMPA-R clustering was found in paravalbumin-positive interneurons (Chang et al., 2010). This function of Narp supposedly contributes to homeostatic maintenance of the excitatory/inhibitory balance at the network level (Chang et al., 2010).

4.2. *KO mouse model: memory and synaptic plasticity*

Physiological roles of IEG expression on synaptic and cognitive functions have been mainly evaluated using genetically modified mice. To this date, various behavioral phenotypes in individual IEG-disrupted mice have been reported (Table 2). Below, I review several representative animal studies.

Arc-KO mice show augmentation of early-phase LTP with loss of late-phase LTP and a wide range of deficits in long-term spatial memory, fear memory, taste aversion, and object recognition (Plath et al., 2006). Short-term memories are not impaired. Also, *Arc*-KO mice showed reduced orientation tuning in the visual cortex (Wang et al., 2006) and impaired experience-dependent cortical plasticity such as ocular-dominance shifts following monocular deprivation

Table 2
A limited list of IEG mutant mice that exhibit abnormality in neuronal plasticity and cognitive functions.

Gene	Type of knockout	Phenotypes (impairments otherwise mentioned)	Reference
Arc/*arg*3.1	Conventional full knock-out (KO)	Hippocampal late-LTP/LTD; spatial and fear memory; taste aversion	Plath et al. (2006)
	GFP knock-in (KI) full KO	Orientation selectivity in visual cortex	Wang et al. (2006)
	GFP-KI full KO	Ocular-dominance plasticity in visual cortex	McCurry et al. (2010)
	Conventional full KO	Experience-dependent synaptic scaling in visual cortex	Gao et al. (2010b)
bdnf	Promoter IV-specific mutation KI	Inhibitory circuit development in neocortex	Hong et al. (2008)
	GFP-STOP KI in Exon IV	Aberrant spike-timing-dependent plasticity in prefrontal cortex	Sakata et al. (2009)
c-*fos*	CNS-specific KO	Hippocampal LTP; spatial and contextual fear memory	Fleischmann et al. (2003)
	D1R-expressing cell-specific KO	Cocaine-induced dendritic morphological and behavioral changes	Zhang et al. (2006)
*fos*B	Conventional full KO	Enhanced cocaine sensitivity	Hiroi et al. (1997)
*homer*1a/*Vesl*1s	IEG-subtype specific KO	Long-term fear memory formation; remote memory transition	Inoue et al. (2009)
Tissue plasminogen activator (t-PA)	Conventional full KO	Hippocampal late-LTP with GABA-transmission inhibition	Frey et al. (1996)
	Conventional full KO	Striatal LTD; hippocampal late-LTP; active avoidance task	Huang et al. (1996)
*zif*268 (*egr*1, *krox*24, *NGFI-A*)	LacZ-KI full KO	*In vivo* dentate gyrus late-LTP; spatial memory; taste aversion	Jones et al. (2001)
	LacZ-KI full KO	Reconsolidation of object recognition memory	Bozon et al. (2003)

(Gao et al., 2010b; McCurry et al., 2010). Consistently, infusion of *Arc*-specific antisense oligonucleotides into the brain resulted in impaired late-phase LTP and memory formation in rats (Guzowski et al., 2000; Messaoudi et al., 2007; Ploski et al., 2008).

Similarly, *zif*268-KO mice showed impaired *in vivo* late-phase LTP and wide-spectrum deficits in long-term memory formation in water maze, taste aversion, and object recognition tasks (Jones et al., 2001). Furthermore, *zif*268-KO mice exhibited specific impairment of recognition memory in a reactivation paradigm (Bozon et al., 2003). These deficits were reproduced in rats infused with *zif*268 antisense oligonucleotides into the brain (Lee et al., 2004, 2005).

Conventional KO of c-*fos* resulted in severe developmental abnormality (Johnson et al., 1992); thus the roles of c-*fos* in behavioral and synaptic functions have been examined using CNS-specific KO mice (Fleischmann et al., 2003; Zhang et al., 2006). These mice exhibited normal emotional behaviors, but had specific impairments in hippocampal-dependent spatial and fear memory (Fleischmann et al., 2003). Electrophysiology using hippocampal slices from c-*fos* CNS-KO mice showed reduced LTP (Fleischmann et al., 2003).

Tissue plasminogen activator (tPA) is a serine protease that may contribute to the reconstruction of the extracellular matrix (Table 1). This protease also plays a role in the cleavage of precursor forms of growth factors (Pang et al., 2004). Hippocampal slices from tPA-KO mice showed deficits in late-phase LTP (Huang et al., 1996) and exhibited atypical GABA-transmission dependent LTP (Frey et al., 1996). The tPA-KO mice also showed deficits in learning active avoidance and contextual fear memory (Calabresi et al., 2000; Huang et al., 1996).

Establishment of splicing-specific KO mice is a challenging task. However, Inoue et al. successfully generated *homer*1a/*vesl*-1s-specific KO mice in which the expression of the IEG isoform of *homer*/*vesl* was specifically disrupted (Inoue et al., 2009). These mice exhibited impairment in formation of long-term and remote memory of fear (Inoue et al., 2009).

BDNF has pleiotropic effects on neuronal differentiation, survival, dendritic growth, and synaptic plasticity (Bramham and Messaoudi, 2005; Lu, 2003; McAllister, 2002; Stoop and Poo, 1996). Because conventional KO mice show severe developmental abnormalities, mnemonic functions in these animals have not been successfully evaluated (Conover et al., 1995; Liu et al., 1995). In addition, existence of multiple promoters has prevented the dissection of activity-dependent and activity-independent components of BDNF expression. Recently, promoter IV-specific disrupted mice have been developed (Hong et al., 2008; Sakata et al., 2009); reports of behavioral analyses are awaited.

In addition to the above IEG KO mice studies, it is worth noting that many genetically modified mice with mutations in transcription factors that regulate IEG expression exhibit abnormal synaptic plasticity and memory formation that are similar to IEG KO mice. For examples, CREB-KO mice and dominant-negative CREB Tg mice exhibit impaired long-term memory formation and hippocampal LTP (Bourtchuladze et al., 1994; Kida et al., 2002). Similarly, hippocampus-specific deletion of SRF showed abolishment of SRE-dependent IEG expression and attenuated LTP (Ramanan et al., 2005). Furthermore, impairment of hippocampus-dependent learning in mice with brain-specific deletion of MEF2C has been reported (Barbosa et al., 2008).

4.3. Functional significance of IEG expression

The above-mentioned studies demonstrate that many IEG KO mice share similar behavioral and synaptic abnormalities. This may indicate that individual IEGs are necessary, but not sufficient, for neural processes to consolidate long-term synaptic plasticity and memory formation. Questions then arise about when and in what processes individual IEG expression is required, i.e., whether the timing of IEG expression is critical for memory formation or whether IEG expression before or after memory tasks has any impacts. Although the answers are not yet known, some clues can be garnered from brain slice electrophysiology and behavioral studies.

The synaptic tagging and capture of long-term synaptic plasticity may explain how short-lasting synaptic potentiation induced by weak stimuli can be converted into a long-lasting form when plasticity-related proteins (PRPs) are induced via application of strong stimuli to different sets of synapses (Frey and Morris, 1997). This hypothesis adopts a conceptual framework in which activity-triggered local changes at synaptic sites, i.e., synaptic tagging, permit the use of activity-induced PRPs at the cell body and den-

drites, i.e., PRP capture, to stabilize changes in synaptic efficacy (Frey and Morris, 1997; Martin et al., 2000; Redondo et al., 2010). Several expanded versions of this hypothesis have been proposed and are experimentally supported (Fonseca et al., 2004; Sajikumar et al., 2005, 2007). Provided that most PRPs are encoded by IEGs, it is reasonable to postulate that insufficient IEG expression would result in instability of long-lasting forms of synaptic plasticity, which might be the case in many IEG KO mice.

The *in vivo* relevance of this synaptic tagging and capture could be embodied in "behavioral tagging", in which a weak training protocol that normally only produces short-term memory can elicit long-term memory if the training is combined with a novel experience during a critical time window around the training (Ballarini et al., 2009; Moncada and Viola, 2007; Wang et al., 2010). Because the enhancement of memory by this paradigm depends on *de novo* protein synthesis, the novel experience-induced gene expression may serve to replenish molecules that are needed to strengthen memories, as in the synaptic tagging and capture in brain slices. Indeed, novel experiences such as exploration of a new environment are known to strongly induce several IEGs including *zif*268, *Arc*, and *homer*1a/*vesl*-1s in the hippocampus and related areas (Guzowski et al., 1999; Ramirez-Amaya et al., 2005; Vazdarjanova et al., 2002). It would be intriguing to test whether or not artificially manipulated IEG expression, i.e., without any experiences, can affect on memory formation.

As described above, IEG expression reflects recent neuronal activity. Some IEGs, especially *Arc* or *zif*268, appear to be highly correlated with sensory and behaviorally evoked neuronal activities. However, some studies suggest that, in certain circumstances, neuronal activity is not always sufficient for IEG expression. Rats with fornix legions maintained place-field activity in the hippocampus (Shapiro et al., 1989) while the lesions disrupted novelty-induced *Arc* expression (Fletcher et al., 2006). Repeated exposure to the same environment within a single day reduced novelty-induced *Arc* expression in the rat hippocampus while electrophysiological activity was unaffected (Guzowski et al., 2006). Furthermore, a dissociation between neuronal activity and *Arc* expression was found in the auditory cortex during the learning of a tone-detection task in rats (Carpenter-Hyland et al., 2010). Then, the question remains as to what actually regulates IEG expression *in vivo*. Related questions arise about "basal" IEG expression in the brain; does it reflect spontaneous activity or is it related to on-going plasticity? These open questions should be addressed in future studies.

5. Concluding remarks and perspectives

As described in this review, many IEGs are crucial for long-lasting changes in synaptic function, as well as consolidation and/or retention of memory. Our current knowledge of IEGs, however, needs to be expanded further for a more comprehensive understanding of IEG function in the brain. Future research directions, for example, should include the following topics. (1) *Where and When*: recent rapid increases in the availability of conditional IEG KO mice will greatly help dissection of the roles of IEG expression in specific brain areas and cell types for memory formation. (2) *Isolation of new IEG members*: many neuronal IEGs have been characterized so far, but most of them were initially isolated from brain tissues that received pathological levels of stimuli. It would be intriguing to search for additional IEGs that are induced only under physiological conditions and/or only in a specific population of neurons. (3) *Target genes*: characterization and identification of target genes of IEG transcription factors such as c-Fos or Zif268 in physiological contexts are of importance because many "delayed-response" genes are also likely involved in synaptic plasticity and memory formation. (4) *Non-coding RNAs*: recent studies have revealed many non-coding RNAs, such as microRNA (miRNA), to be activity-dependent molecules; some have been shown to possess the ability to modify neuronal morphology and function (Gao et al., 2010a; Schratt et al., 2006). Of particular interest may be the newly identified non-coding RNA species, enhancer RNA (eRNA), which is transcribed from IEG enhancers such as SARE (Kim et al., 2010). Although the biological functions of this new non-coding RNA are not yet known, eRNA and miRNA, together with activity-regulated mRNAs, may orchestrate activity-dependent mechanisms for IEG expression.

In summary, current lines of evidence now clearly establish fundamental roles of IEGs in synaptic plasticity and cognitive processes, notably learning and memory. Future studies on the regulation and function of IEGs should help our further understanding of the multi-layer, activity-dependent processes distributed throughout the brain, i.e., the synapses, neurons, and circuits, which underlie the flexible adaptive behaviors of animals in response to environmental changes.

Acknowledgements

I apologize to the many authors whom I could not mention due to space limitations. I thank Drs. Haruhiko Bito (Univ. of Tokyo, Japan), Yasushi Miyashita (Univ. of Tokyo) and Paul Worley (Johns Hopkins Univ., USA) for their continuous encouragement, support, discussion and mentorship. I also thank Drs. Mio Nonaka (Univ. of Tokyo), Takashi Kawashima (Univ. of Tokyo), and Akiko Tabuchi (Toyama Univ, Japan) for sharing unpublished data and for comments on drafts. This work was supported in part by grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan and in part by an award from the Astellas Foundation for Research on Metabolic Disorders.

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