Chapter 16
Long-Distance Signaling from Synapse to Nucleus via Protein Messengers

Anna Karpova, Julia Bär, and Michael R. Kreutz

Abstract The communication between synapses and the cell nucleus has attracted considerable interest for many years. This interest is largely fueled by the idea that synapse-to-nucleus signaling might specifically induce the expression of genes that make long-term memory "stick." However, despite many years of research, it is still essentially unclear how synaptic signals are conveyed to the nucleus, and it remains to a large degree enigmatic how activity-induced gene expression feeds back to synaptic function. In this chapter, we will focus on the activity-dependent synapto-nuclear trafficking of protein messengers and discuss the underlying mechanisms of their retrograde transport and their supposed functional role in neuronal plasticity.

Keywords Activity-dependent gene expression • Importins • Jacob/Nelf • Microtubule • NMDA-receptors

16.1 Introduction

Synapse-to-nucleus communication is a classical topic in neuroscience since multiple signaling pathways converge in the nucleus that drive gene expression associated with long-term structural changes of synapto-dendritic input and the formation of long-term memories (Greer and Greenberg 2008; Cohen and Greenberg 2008; Flavell and Greenberg 2008; Alberini 2009). Given that neurons regulate more genes than any other cell type (Deisseroth et al. 2003; Alberini 2009), it is unlikely that nuclear Ca^{2+} rises alone could generate the varied and complex responses to the diverse array of extracellular stimuli involved in neuronal signaling. It has been proposed that the shuttling of synaptic proteins into the nucleus may

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M.R. Kreutz and C. Sala (eds.), *Synaptic Plasticity*,
Advances in Experimental Medicine and Biology 970,
DOI 10.1007/978-3-7091-0932-8_16, © Springer-Verlag/Wien 2012

provide further specificity required for the integration of multiple signaling pathways to the nucleus (Jordan and Kreutz 2009).

A number of arguments speak in favor of the existence of synapto-nuclear protein messenger pathways to the nucleus. Synapses contain components of the nuclear import machinery like importin-α and importin-β (Thompson et al. 2004), and it has been shown that they translocate to the nucleus in an activity-dependent manner (Thompson et al. 2004; Dieterich et al. 2008). In addition, synapses also contain several nuclear localization signal (NLS) containing cargo proteins. Different proteomic studies aimed to elucidate the protein composition of the postsynaptic density (PSD) revealed that at least 166 of more than 1,100 proteins contain *bona fide* NLSs (Jordan et al. 2004; Jordan and Kreutz 2009). Many of these proteins exhibit a dual synaptic and nuclear localization with the latter being frequently overlooked. Together with evidence from proteins like AIDA-1d (Jordan et al. 2007), Jacob (Dieterich et al. 2008), Abi-1 (Proepper et al. 2007), CREB2/ATF4 (Lai et al. 2008), and Lapser1 (Schmeisser et al. 2009), this strongly supports that nucleocytoplasmic shuttling of proteins is an important component of synapse-to-nucleus signaling. Finally, the signaling-dependent nuclear translocation of proteins from cell-cell junctions is an established principle in many cell types, and since synaptic junctions resemble other cell junctions in many aspects, it is as such not a surprise that in recent years many proteins were identified that are able to transit from dendrites to the nucleus in response to various kinds of neuronal stimuli (Jordan and Kreutz 2009; Table 16.1).

At present, however, neither the mechanisms underlying activity-dependent nuclear signaling nor the forms of synaptic plasticity, which are controlled by it, are well understood. There are many remaining concerns, including the lack of demonstrative evidence that nuclear AIDA-1, Jacob, Abi-1, or other nucleocytoplasmic shuttling proteins have a synaptic origin. Moreover, synapses at distal dendrites can be several hundred microns away from the nucleus; it is therefore another principal question how proteins can translocate over long distances. Even though typical textbook illustrations show various signaling molecules traveling from synapses to the nucleus, long-distance travel along axons and/or dendrites can result in the rapid decay of signals. This may result from degradation of signaling molecules or reversal of posttranslational modifications required for nuclear import. Protein modifications like phosphorylation during their way along dendrites or other signaling decay would be more pronounced when transport is based on passive diffusion as it was suggested recently for ERK1/2 (Wiegert et al. 2007). Given the exponentially decaying strength of diffusible molecules, it was therefore concluded that successful nuclear signaling is dependent on the proximity of activated synapses to the nucleus. Accordingly, modeling studies of mechanisms associated with nuclear import have revealed that simple diffusion is inefficient when compared to active transport along microtubules (Howe and Mobley 2005). However, these models describe protein mobility in large and relatively unconfined spaces (unlike dendrites or axons) and did not incorporate directional gradient-dependent motion. Nonetheless, these motions are likely to be low for nuclear messengers and, therefore, might be negligible. Further questions regarding diffusion therefore also include the directionality of signals, such as how are signals directed toward the nucleus as opposed to elsewhere or even into adjacent spines? Active

Table 16.1 Potential synapto-nuclear messengers

Synaptic proteins which can be found in the nucleus	
Name	Putative nuclear function
Cytoskeletal and scaffolding proteins	
GRIP1	Trafficking (Ataman et al. 2006), regulate transcription (Yu et al. 2001; Nakata et al. 2004)
SAP97	?[a] (Kohu et al. 2002)
CASK	Regulate transcription (Tbr-1) (Hsueh et al. 2000)
α-actinin4	Antagonize HDAC7 activity (Chakraborty et al. 2006)
Band 4.1	Splicing (Lallena et al. 1998; Shen et al. 2000)
Ezrin	? (Kaul et al. 1999)
ZO-1	Regulate transcription (ZONAB) (Balda and Matter 2000; Kavanagh et al. 2006)
Catenins	
β-catenin	Regulate LEF-1 transcription (Behrens et al. 1996; Molenaar et al. 1996; Huber et al. 1996)
γ-catenin (plakoglobin)	Regulate LEF-1 transcription (Simcha et al. 1998)
δ-catenin (NPRAP)	Transcriptional regulation? (Rodova et al. 2004)
p120	Regulate KAISO-dependent repression (Kelly et al. 2004)
ARVCF	Regulate ZONAB transcription (?)
JAB-1 (sub 3)	c-Jun, JunD coactivator (Claret et al. 1996)
p0071	Transcriptional regulation?
Proteins that shuttle into the nucleus in response to neuronal activity	
CREB2	Transcriptional regulation (Lai et al. 2008)
AIDA-1	Nucleolar assembly (Jordan et al. 2007)
Jacob	Transcriptional regulation (CREB, Dieterich et al. 2008)
Abi-1	Transcriptional regulation (c-Myc, Proepper et al. 2007)
NF-κB	Transcription factor (Guerrini et al. 1995; Kaltschmidt et al. 1995; Meffert et al. 2003)
CAMAP	Transcriptional coactivator CREB1 (Lee et al. 2007)
NFATc4	Transcription factor (Graef et al. 1999)
HDAC4, HDAC5	Histone deacetylases (Chawla et al. 2003)
LAPSER1	Modulation of gene transcription (Schmeisser et al. 2009)
Transmembrane proteolytic fragments	
APP intracellular domain	Transcriptional regulation (Cao and Südhof 2001)
N-cadherin	Transcriptional regulation (Marambaud et al. 2003)
ErbB4	Transcriptional regulation (STAT5A, N-CoR, Sardi et al. 2006)
Frizzled2-C	? (Mathew et al. 2005; Ataman et al. 2006)
L-type calcium channel	Transcription factor (Gomez-Ospina et al. 2006)
Protocadherin-γ	Transcriptional regulation (Haas et al. 2005; Hambsch et al. 2005)
Neuregulin-1	Transcriptional regulation (Eos, Bao et al. 2004)
Notch	Transcriptional regulation, CBF1 binding (Lu and Lux 1996; Alberi et al. 2011)

[a]Denotes lacking or incomplete evidence

transport along microtubules is also often discussed in the context of nucleocytoplasmic shuttling of nonendosomal proteins, and the retrograde transport via importins attached to dynein motors along microtubules appears to be a plausible mechanism (Thompson et al. 2004; Hanz et al. 2003; Perlson et al. 2005, 2006. However, in a large-scale study to address this issue, Roth et al. (2007) explored the nuclear import of several proteins in the presence or absence of intact microtubules in nonneuronal cells. Surprisingly, seven out of ten proteins showed no significant reduction in nuclear accumulation in the absence of microtubules. Although the relevance of dynein-dependent transport along microtubules for nucleocytoplasmic shuttling of synaptic proteins has not been systemically addressed yet, it was reported that nuclear translocation of AIDA-1d does not require intact microtubules (Jordan et al. 2007). Therefore, questions remain how nuclear messengers arrive at the nuclear pore complex (NPC). The microtubule-depolymerizing drug nocodazole that was used in many studies only depolymerizes tyrosinated α-tubulin. However, microtubules that are rich in detyrosinated and acetylated α-tubulin are resistant to this treatment (Conde and Cáceres 2009). Detyrosinatinon is a reversible posttranslational modification of tubulin subunits. A yet unknown carboxypeptidase removes the C-terminal tyrosine of α-tubulin, and tubulin tyrosine ligase catalyzes tyrosination (Hammond et al. 2008). Therefore, nocodazole would prevent the movement of cargo only along tyrosinated microtubules, and the transport along detyrosinated microtubules will remain intact. Finally, an aspect that has not been stressed at all is the triggering of highly diverse events by the nuclear enrichment of synaptic proteins. Thus, the possible functions for learning and memory that have been attributed to synapse-to-nucleus communication in recent years with particular emphasis on synaptic proteins have not been addressed yet.

16.2 The Many Different Ways to the Nucleus

16.2.1 The Fast Ca^{2+} Track

The fast track from synapse to nucleus is initiated by local membrane depolarization that initiates backpropagating dendritic action potentials (Fig.16.1.I.1), as well as by regenerative calcium waves (Fig.16.1.I.2) that propagate along the endoplasmic reticulum (ER) toward the nucleus. This aspect of synapse-to-nucleus communication is extensively covered in the chapter of Bengtson and Bading in this book and is therefore only briefly summarized here.

The so-called rapid electrochemical model (Adams and Dudek 2005; Saha and Dudek 2008) suggests that synaptic depolarization triggers multiple action potentials which in turn result in an elevation of somatic Ca^{2+} concentration from different sources including influx through voltage-operated calcium channels (VOCC) and release from ER. Alternatively, the “regenerative calcium waves” model suggests that the activation of inositol-1,4,5-triphosphate receptors (IP3Rs) and ryanodine

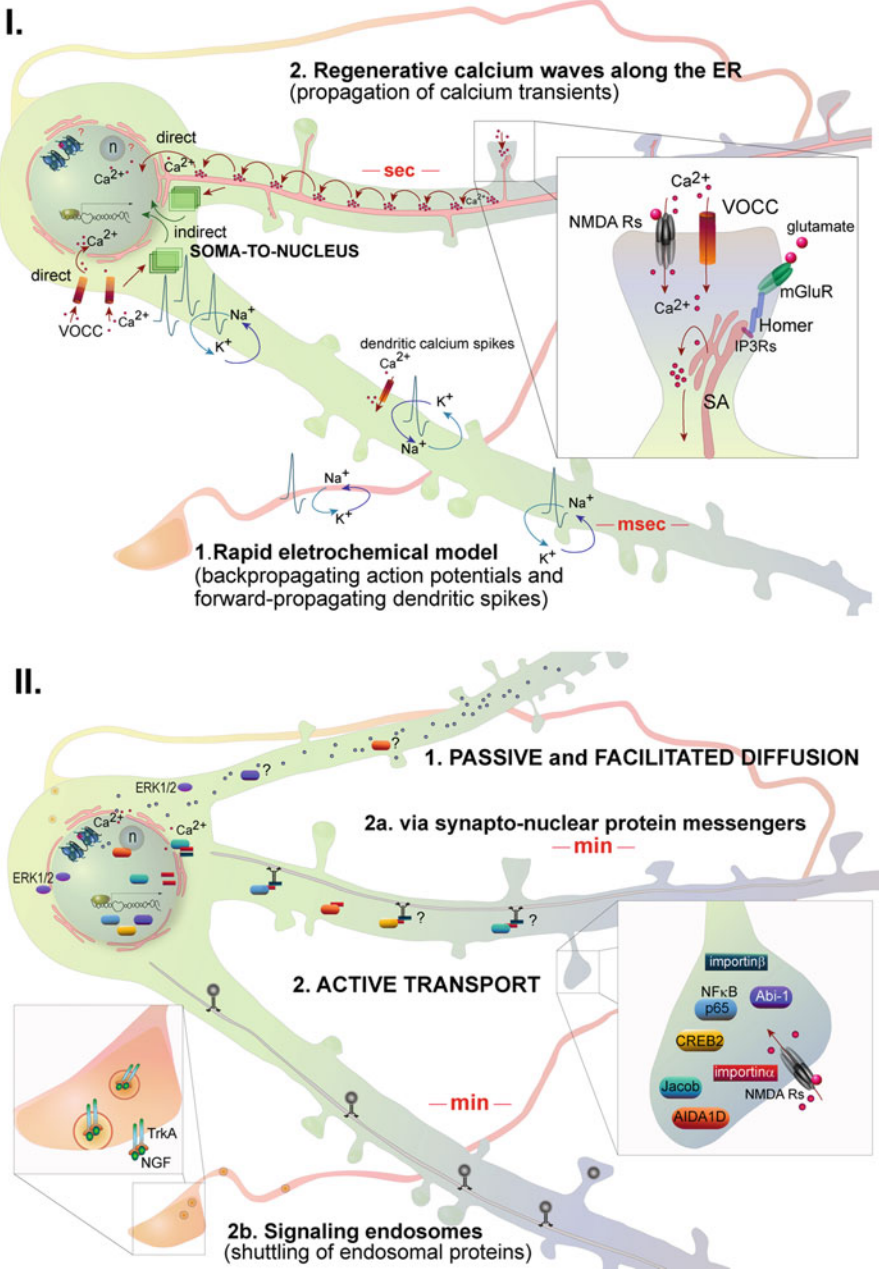

Fig. 16.1 The many ways from synapse to the nucleus. There are many possible ways for the signals to get transduced from a subset of activated synapses into the nucleus where they mediate transcriptional activity and nucleolar (n) assembly and where they might be involved in regulation of epigenetic DNA modification

receptors (RYRs) leads to Ca^{2+}- induced Ca^{2+} release from internal stores, and the resulting Ca^{2+} transients can thereafter rapidly propagate along the ER (Simpson et al. 1995; Berridge 1998; Berridge et al. 2003). A possible starting point for such waves would be the spine apparatus, which represents the specialized ER at the synapse. It continues along the dendrite and fuses with the outer and inner nuclear membrane. Ca^{2+} signals arising from synaptic VOCC and NMDARs can plausibly initiate such regenerative waves along the ER (Kapur et al. 2001; Nakamura et al. 2002; Ross et al. 2005). In addition, metabotropic glutamate receptors (mGluRs) provide a physical link to IP3Rs via Homer proteins and might contribute to the neurotransmitter-induced Ca^{2+} release from internal Ca^{2+} stores. In both scenarios, somatic Ca^{2+} might either directly enter the nucleus to regulate gene expression or initiate soma-to-nucleus signaling via the Ca^{2+}-activated nuclear import of messengers like NFAT (Fig. 16.1.I).

16.2.2 Passive and Facilitated Diffusion Across the Nuclear Pore

Transport of macromolecules across the nuclear border is either realized by passive (energy- and carrier-independent) and facilitating diffusion (Fig. 16.1.II.1) or active importin-α/importin-β-mediated Ran- and GTP-hydrolysis-dependent transport (Fig. 16.1.II.2). The limiting factor for passive diffusion through the pore is the size of the messenger. The diffusion limit for protein passage through the nuclear pore is in the range between 40 and 60 kDa (Paine et al. 1975), but diffusion becomes highly inefficient with increasing molecular weight (Görlich and Kutay 1999).

Facilitated passage (facilitated diffusion) through the nuclear pore is accomplished by direct binding of the substrate to the NPCs and can be mediated by other carriers, distinct from importin-β transport receptors, and therefore does neither require Ran nor its GTP hydrolysis (Görlich and Kutay 1999; Yokoya et al. 1999). It is widely believed that the MAPK-ERK pathway mediates synapse-to-nucleus signaling and is involved in the regulation of activity-dependent gene expression that is required for neuronal plasticity and long-term memory (Impey et al. 1998; Hardingham et al. 2001a, b; Sweatt 2004; Wiegert et al. 2007; Wiegert and Bading 2011). For nonneuronal cells, it has been shown that the nuclear entry of ERK can be accomplished by different mechanisms: direct facilitated diffusion via interaction with nucleoporins or an active importin-7 (importin-β-like transport receptor)-mediated nuclear transport (Chuderland et al. 2008; Jivan et al. 2010). In hippocampal neurons, ERK translocate into the nucleus upon NMDA and TrkB receptor activation, and the passage across the nuclear envelope is largely mediated by passive and facilitated diffusion mechanisms (Wiegert et al. 2007). This, however, is a highly inefficient mechanism for transport from distal dendrites and would limit the activity-dependent translocation of ERK pools into the soma and proximal dendrites. However, the possibility remains that active ERK can be actively transported from distal locations to the nucleus via its interaction with synaptic and dendritic proteins as it has been shown for long-distance transport in axons (Perlson et al. 2005). Such a mechanism would only concern a subfraction of synaptic or dendritic ERK, and the majority of kinase would remain stationary in distal dendrites.

16.2.3 Signaling Endosomes

A pervasive model of signal transmission from axonal synapses to the cell nucleus is the retrograde transport of signaling endosomes (Ginty and Segal 2002; Miaczynska et al. 2004; Howe and Mobley 2005; Cosker et al. 2008; Wu et al. 2009). Especially the transport of activated Trk receptors upon neurotrophin and here especially NGF binding to TrkA has been investigated. The endocytosis of these receptor-ligand complexes into early endosomes (Delcroix et al. 2003) has been shown to be clathrin dependent (Howe et al. 2001). Signaling endosomes are subsequently actively transported to the soma along microtubules (Watson et al. 1999) associated with dynein motors (Heerssen et al. 2004; Yano et al. 2001). Interestingly, endosome isolation (Howe et al. 2001) and studies using compartmentalized chambers with cultured neurons showed that receptor-ligand complexes are transported together with molecules of downstream signaling pathways (e.g., p-ERK of MAP/ERK pathway, Howe et al. 2001) and even the transcription factor CREB is associated with endosomes and can be activated during transport (Cox et al. 2008). Therefore, these self-regenerating organelles (Ye et al. 2003) provide a basis of specifically regulated transport of signals, e.g., supporting neuronal survival, over long distances without decay of signal integrity.

16.2.4 Active Retrograde Transport of Synapto-Nuclear Messenger Proteins

Neuronal processes extend several hundreds of micrometers away from the cell soma. Therefore, signals from activated synapses at distal dendrites and from axonal terminals have to travel a long route to and, eventually, into the nucleus to modulate neuronal function. In pyramidal neurons, the closest dendritic spiny synapses are located at least 40 μm away from the nucleus. This raises a number of important questions on how proteins can translocate from distal synaptic sites to the nucleus. One possible mechanism is the active retrograde transport mediated by the importin-α/importin-β complex. Both importin-α and importin-β are present in synaptic compartment where they are well positioned to mediate direct synapse-to-nucleus signaling. Importin-α family members (importin-α1 and importin-α2) directly associate with the postsynaptic density (Thompson et al. 2004), and particularly, importin-α1 might be docked at synaptic sites by interaction with certain splice isoforms of the NR1 NMDAR subunit (Jeffrey et al. 2009). The fact that importin-α and importin-β1 undergo an NMDA receptor–dependent nuclear translocation (Thompson et al. 2004; Dieterich et al. 2008) suggests that this transport mechanism might be involved in NMDA receptor–activated gene expression. In line with this notion, a number of potential synapto-nuclear protein messengers have been identified in recent years (Jordan and Kreutz 2009). Proteins like Abi-1, AIDA-1d, CREB2/ATF4, Jacob, and p65/RelA (NF-κB) that are localized at postsynaptic sites

and translocate to the nucleus in response to NMDA receptor activity are of particular interest. All abovementioned cargo proteins with the exception of Abi-1 possess NLSs that are recognized by certain members of the importin-α nuclear transport adaptor protein family.

Conventionally, importin-α binds the cargo protein and subsequently forms a heterotrimeric nuclear pore-targeting complex with importin-β1 (Goldfarb et al. 2004). Previous reports have shown that the murine importin-α/karyopherin-α gene family of nuclear transport adaptor proteins comprises at least five members (Otis et al. 2006). Based on sequence homology, importin-α family members are classified into three subfamilies: α-P (Imp-α2/karyopherin-α2/*Gene ID:16647*), α-Q (Imp-α3/Q2/karyopherin-α3/*Gene ID:16648* and Imp-α4/Q1/karyopherin-α4/*Gene ID:16649*), and α-S (Imp-α1/S1/karyopherin-α1/*Gene ID:16646* and Imp-α 6/S2/karyopherin-α6/*Gene ID:16650*). They exhibit differential expression patterns in brain and other tissues (Kamei et al. 1999; Yoneda 2000; Jans et al. 2000; Lai et al. 2008; Hosokawa et al. 2008; Yasuhara et al. 2009). The vast majority of importin-α family members are highly expressed in hippocampal pyramidal neurons (Hosokawa et al. 2008). Recently, a novel member of the murine importin-α/karyopherin-α gene family was identified (Knap7/*Gene ID:381686,* Hu et al. 2010). Knap7 has been shown to interact with the importin-β1 transport receptor, but its expression in brain has not been investigated yet.

The expression of importin-α/karyopherin-α family members is regulated during neural differentiation of mouse embryonic stem cells, and it has been suggested that the switching of importin-α subtype expression might be important for neuronal differentiation (Yasuhara et al. 2007). The multiple family members of importin-α possess both distinct and overlapping cargo specificities (Jans et al. 2000; Yasuhara et al. 2007; Shmidt et al. 2007). It has been reported that a compensatory mechanism for importin-α/karyopherin-α family members might exist which indicates the overlapping cargo specificities. Particularly, importin-α1/karyopherin-α1 (reported as importin-α5) seems to be involved in neuronal differentiation (Yasuhara et al. 2007, 2009). Surprisingly, the homo- and heterozygous karyopherin-α1 knockout mice have no obvious defect in brain development (Shmidt et al. 2007). On the other side, the level of karyopherin-α3 (reported as importin-α4) in brain and other tissues of these animals is dramatically upregulated (Shmidt et al. 2007) suggesting a compensatory mechanism for the depletion of karyopherin-α1. Based on this observation, it has been suggested that some importin-α family members might, at least to a certain degree, functionally substitute each other. Another example of overlapping cargo specificities of importin-α family members in brain tissue has been reported for karyopherin-α1 and karyopherin-α6 regarding CREB2/ATF4 NLS recognition. The primary structure of CREB2/ATF4 harbors defined nuclear targeting sequences: a bipartite NLS (KKLKK motif, Cibelli et al. 1999) and a second putative NLS (RYRQKKR motif). Both are potential recognition sites for transport adaptors. Screening for CREB2/ATF4 interaction with all importin-α family members revealed that it binds exclusively to the importin-αS subclass (importin-α1/karyopherin-α1 and -α6, Lai et al. 2008). Conceivably, the transport of distinct cargos mediated by distinct importins upon particular neuronal stimuli

might provide signal specificity for the nuclear response. It remains elusive whether different transport adaptors compete for the same cargo protein and/or vice versa.

Another synapto-nuclear protein messenger, AIDA-1d, harbors a monopartite NLS. Although its direct interaction with importin-α/karyopherin-α family members has not been reported, mutagenesis of the NLS prevents the accumulation of overexpressed protein in the nucleoli (Jordan et al. 2007) indicating that its translocation is indeed mediated by importins. Abi-1 is transported from synaptic sites into the nucleus upon NMDA application. This process could be abolished by the destruction of the microtubules and microfilaments (Proepper et al. 2007). Since there is no apparent NLS present in Abi-1 and binding to importin family members has not been reported, it remains unclear how Abi-1 is delivered to the nucleus.

Various studies have provided substantial evidences that both p50 and p65/RelA subunits of NF-κB are present at synaptic compartments of hippocampal pyramidal neurons and associate with PSDs (Kaltschmidt et al. 1993; Meberg et al. 1996; Meffert et al. 2003; Marcora and Kennedy 2010). Both p65/RelA and p50 might be targeted to the PSD95 via huntingtin protein (Htt, Takano and Gusella 2002; Marcora and Kennedy 2010). Importin-α1 (Nadler et al. 1997; Cunningham et al. 2003) and importin-α2 (Cunningham et al. 2003; Marcora and Kennedy 2010) recognize the NLS of p65/RelA (KRKR motif) and were proposed to modulate its nuclear transport. In addition, Marcora and Kennedy (2010) could demonstrate that Htt preferentially associates with activated p65/RelA at synapses and facilitates its transport from the PSD toward the nucleus by binding to a dynein/dynactin motor complex. This finding is consistent with previous observations that retrograde transport of p65/RelA along dendrites to the nucleus requires microtubules and is mediated by the dynein/dynactin complex (Mikenberg et al. 2007; Shrum et al. 2009). Jacob's primary structure harbors a bipartite NLS (aa 247–266), and the 247–252 amino acid stretch is necessary for interaction with importin-α1 since the binding was abolished when the RKRRKR motif was deleted (Dieterich et al. 2008). A colocalization study revealed that Jacob and importin-α1 interaction might occur at synaptic sites at distal dendrites. This supports the idea that this transport adaptor protein might interact with Jacob at synaptic sites and therefore mediates direct synapse-to-nucleus signaling (Fig. 16.2)

16.2.5 Control of Nuclear Transport by Regulation of Importin-Cargo Binding

The accessibility of both the NLS on cargo proteins and the NLS recognition site on importins is a prerequisite for the cellular nuclear import machinery. Conventionally, the N-terminal importin-β binding domain of importin-α is autoinhibitory (Kobe 1999; Goldfarb et al. 2004). In the absence of an NLS-containing cargo,

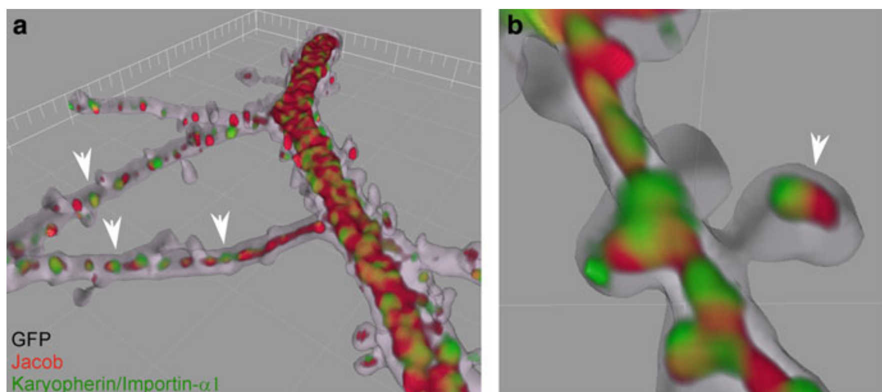

Fig. 16.2 Jacob/importin-α1 clusters are present at the distal dendrites and spines (**a**) and (**b**) 3D reconstructions (Imaris 6.2 software, Bitplane AG, Zürich, Switzerland) of GFP-filled dendrites (gray transparent isosurface) with spines of hippocampal 17DIV neurons immunolabeled with Jacob (red) and karyopherin-α1/importin-α1 (green, BD Biosciences) antibodies. Confocal Z-stacks were acquired using LAS AF (Leica Application Suite Advanced Fluorescence) imaging software and deconvoluted in three dimensions using AutoQuantX2.2, Media Cybernetics. For deconvolution, adaptive PSF (Blind), medium noise suppression, and two iterations were used. The punctated staining of Jacob/importin-α1 within the dendrites and spines was determined by masking these channels with an isosurface generated from GFP fluorescence. Box size is 5 μm. The fact that both proteins are detectable and found partially being colocalized in distal dendrites and spines strongly supports the idea that the transport adaptor importin-α1 might interact with Jacob at synaptic sites and mediate direct synapse-to-nucleus signaling pathway in vivo

the importin-β binding domain can form an intramolecular interaction with the cargo-NLS-binding pocket (Kobe 1999) and therefore masks the NLS recognition sequence (Fig. 16.3.1). However, it remains unclear how this is regulated at the synapse. A mechanism how importin-α might be docked at synapses in an activity-dependent manner was recently provided by Jeffrey et al. (2009). It is plausible to assume that synaptic proteins bearing the NLS sequence might target importins to the synapse. Importin-α1 binds to a bipartite NLS in the NR1-1a subunit of the NMDAR, and this interaction is regulated by phosphorylation of the NLS by PKC (Fig. 16.3.2). Upon activation of NMDAR, importin-α1 is released from the complex and becomes accessible for the interaction with cargo proteins (Jeffrey et al. 2009). Remarkably, the interaction between NR1-1a and importin-α1 is disrupted upon stimuli known to induce late long-term potentiation (late LTP) but not early LTP in CA1 Schaffer collateral synapses.

Synapse-to-nucleus signaling may also be regulated at the level of individual cargos at the synapse. An example for such a regulation is the Ca^{2+}-dependent binding of the IQ domain of caldendrin to the α-helical region of Jacob (Dieterich et al. 2008). Upon synaptic activity, importin-α1 competes with caldendrin for Jacob binding. Therefore, the amount of Jacob that is accessible for the interaction with importin-α1 is regulated by the amount of caldendrin at the synapse

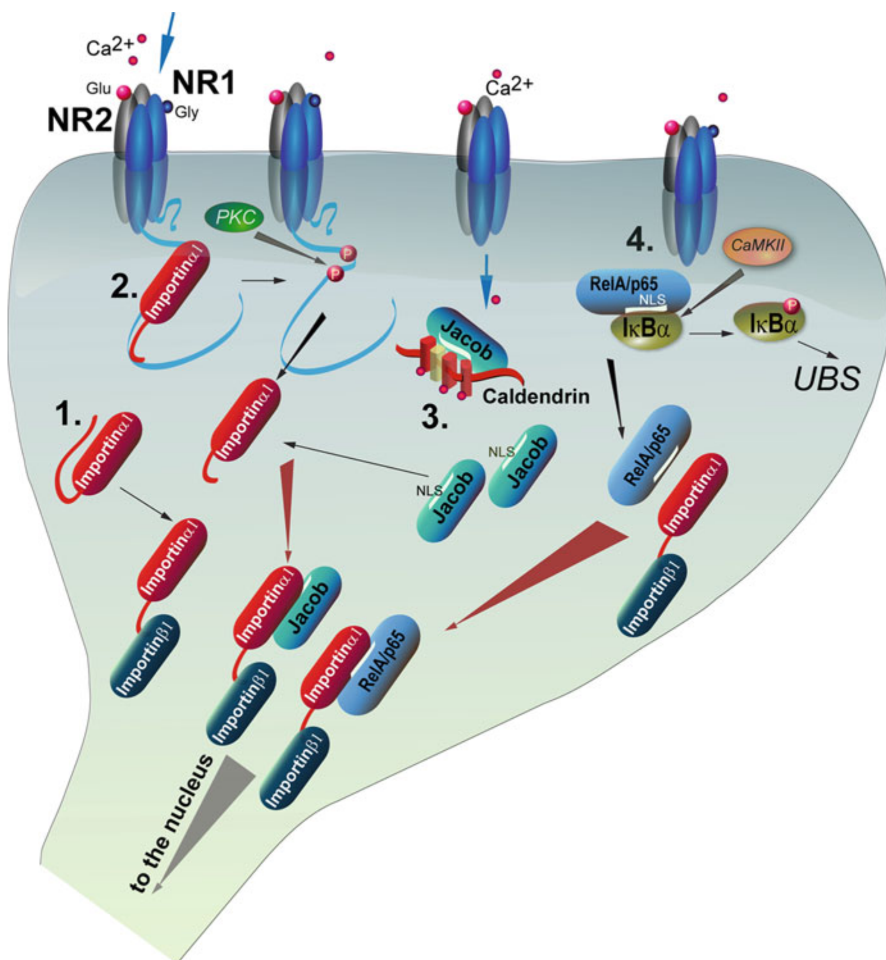

Fig. 16.3 Regulation of synapse-to-nucleus signaling by importin-α/karyopherin-α-cargo binding. *1* – Autoregulation via masking of the NLS recognition sequence in importins; *2* – Anchoring of importin-α at the synapse; *3* – Regulation via the amount of available individual cargoes; *4* – Masking the signal on the cargo by heterologous molecules

(Fig. 16.3.3 see also below). Targeting sequence masking through specific protein binding is best characterized for p65/RelA and IκBα. Phosphorylation of IκBα in an activity-dependent manner, which in neurons can be mediated by CaMKII (Marcora and Kennedy 2010) and subsequent proteolytic degradation, is required for unmasking the NLS of p65/RelA. Thus, unmasking the NLS on the cargo protein and the NLS recognition site of importin-α is conceivably important regulatory mechanisms at synapses to initiate synapto-nuclear trafficking (Fig. 16.3.4).

16.3 The Functional Role of Synapto-Nuclear Protein Messengers

16.3.1 Jacob

Jacob is a putative synapto-nuclear protein messenger that was originally identified as a binding partner of the neuronal calcium-binding protein caldendrin in a yeast two-hybrid screen (Dieterich et al. 2008). It is abundantly expressed in the limbic brain and cortex and prominently present in synapses and neuronal nuclei. The protein is highly conserved between mouse, rat, and human (95% identity) and other mammals. Database searches revealed no known invertebrate orthologue. Subcellular fractionation experiments confirmed that Jacob is enriched in synaptosomes and PSDs of excitatory synapses. Jacob RNA can undergo extensive alternative splicing. Out of 16 exons, at least 5 exons can be alternatively spliced, alone and in various combinations (Kindler et al. 2009). Jacob mRNA is prominently localized in dendrites, as it harbors a cis-acting dendritic targeting element in its 3′-untranslated region (Kindler et al. 2009; see also the chapter of Kindler and Kreienkamp for a more detailed account). The dendritic mRNA of Jacob might replenish local pools after nuclear translocation of Jacob.

Jacob harbors a classical bipartite NLS that is a prerequisite for its nuclear localization as well as an N-myristoylation site, which anchors the protein to membranes and is required for its extranuclear localization. An N-terminal fragment of Jacob can be cleaved by the NMDA receptor– and Ca^{2+}-activated protease calpain (Kindler et al. 2009). Importantly, caldendrin binding to Jacob masks the NLS and competes with importin-α1 binding in a Ca^{2+}-dependent manner. In consequence, the importin-α1-dependent translocation of Jacob can take place only if (a) the myristoylation site is cleaved from Jacob's N-terminus and (b) Jacob is not bound to caldendrin either due to the lack of the latter at the corresponding subsynaptic site or calcium levels that do not allow for both proteins to interact.

In the nucleus, Jacob is associated with zones of active gene transcription (Dieterich et al. 2008). These findings suggest that it can directly or indirectly influence NMDA receptor–regulated gene transcription. Enhancing neuronal activity via bath application of glutamate and NMDA leads to increased Jacob levels in the nucleus (Dieterich et al. 2008). This increase can be blocked by addition of NMDAR antagonists. NMDARs are present at both synaptic and extrasynaptic sites. Differential activation of synaptic vs. extrasynaptic NMDARs showed that the latter is a much more efficient stimulus to drive Jacob into the nucleus. Moreover, the nuclear accumulation of Jacob can be blocked by the NR2B-specific NMDAR antagonist ifenprodil. Thus, Jacob translocates to the nucleus strictly after activation of NR2B containing NMDAR; depolarization alone (e.g., due to KCl) is not sufficient (Dieterich et al. 2008; Rönicke et al. 2011). This suggests that at least an indirect association of Jacob with NMDARs might exist.

Many studies have shown that the stimulation of extrasynaptic NMDARs leads to a long-lasting dephosphorylation of the transcription factor CREB at a serine at position 133, which renders CREB transcriptionally inactive, a phenomenon called CREB shut-

off (Sala et al. 2000; Hardingham et al. 2002; Chandler et al. 2001; Kim et al. 2005; Hardingham and Bading 2002). It is now well established that extrasynaptic NMDA receptors as opposed to their synaptic counterparts trigger the CREB shut-off pathway and cell death. Signaling from extrasynaptic NMDA receptors to the nucleus has been linked to neurodegeneration in a variety of brain disease states including ischemia (Tu et al. 2010) and Huntington's disease (Milnerwood et al. 2010; Hardingham and Bading 2010). We found that nuclear knockdown of Jacob prevents CREB shut-off after extrasynaptic NMDA receptor activation while its nuclear overexpression induces CREB shut-off without NMDA receptor stimulation (Dieterich et al. 2008). Importantly, nuclear knockdown of Jacob attenuates NMDA-induced loss of synaptic contacts and neuronal degeneration (Dieterich et al. 2008). This defines a novel mechanism of synapse-to-nucleus communication via a synaptic Ca^{2+}-sensor protein, which links the activity of NMDA receptors to nuclear signaling events involved in modeling synapto-dendritic input and NMDA receptor–induced cellular degeneration.

However, we also observed a less prominent nuclear accumulation of the protein after triggering the activity of synaptic NMDA receptors (Dieterich et al. 2008). Since this pathway promotes cell survival and induces the expression of plasticity-related genes, we wondered whether Jacob might be also a messenger on this synaptic NMDA receptor pathway to the nucleus in the cellular models of synaptic plasticity. LTP and LTD are activity-dependent forms of synaptic plasticity that, in the cornu ammonis 1 (CA1) region of the hippocampus, require a calcium influx through NMDARs (Bliss and Lomo 1973; Morris and Frey 1997). The induction of LTP and LTD at these synapses correlates with learning processes in vivo and is thought to underlie memory formation (Nguyen et al. 1994; Reymann and Frey 2007). We recently found that LTP-inducing stimuli (strong tetanization consisting of three 1 s trains at 100 Hz; intertrain interval was 10 min) were sufficient to rise the Jacob nuclear level already during tetanization face. This might be a requirement for gene expression that stabilizes LTP type of synaptic plasticity and contributes to the LTP maintenance. Late-LTD-inducing stimuli (900 bursts at 1 Hz; one burst consists of three stimuli with 50 ms interstimulation interval) had no influence on Jacob nuclear import, suggesting that synapto-nuclear protein messengers might provide the input specificity that required for plasticity events (Behnisch et al. 2011). Interestingly, it was shown in one previous study that the transcription factor cyclic AMP-response element-binding protein 2 (CREB2) transits to the nucleus during LTD but not LTP of synaptic transmission in hippocampal primary neurons. Taken together, these findings suggest that the two major forms of NMDA receptor–dependent synaptic plasticity, LTP and LTD, elicit the transition of different synapto-nuclear protein messengers, albeit in both cases importin-mediated retrograde transport and NMDA receptor activation are required.

16.3.2 NF-κB

The transcription factor NF-κB is a homo- or heterodimer of the subunits RelA (also called p65), RelB, c-Rel, p50, and p52. The most common active dimer in

neurons is p65:p50 (Kaltschmidt et al. 1993; Bakalkin et al. 1993; Schmidt-Ullrich et al. 1996; Meffert et al. 2003). Besides the constitutive NF-κB activity in neurons (Kaltschmidt et al. 1994), an inducible, IκB-bound pool also exists (Kaltschmidt and Kaltschmidt 2009). The presence of NF-κB in synaptosomes (Kaltschmidt et al. 1993; Meberg et al. 1996; Meffert et al. 2003; Marcora and Kennedy 2010) and the fact that it can be activated by glutamate stimulation (Guerrini et al. 1995) gave rise to the idea that it plays a role in synapse-to-nucleus communication. It has been shown that p65 translocates to the nucleus upon NMDAR stimulation in a CaMKII- (Meffert et al. 2003) and NLS-dependent manner (Wellmann et al. 2001). Additionally, NF-κB transcriptional activity is enhanced following neuronal depolarization via KCl and kainate stimulation in primary neuronal cultures (Kaltschmidt et al. 1995). Therefore, this transcription factor might directly transmit synapto-nuclear protein messenger.

16.3.3 Abi-1

Abelson interacting protein 1 (Abi-1) is a synaptic and nuclear protein functioning as a regulator of dendritic growth and synaptic contacts (Proepper et al. 2007; Ito et al. 2010). As a direct binding partner of ProSAP2, it is located at PSDs. Upon NMDAR stimulation, Abi-1 immunoreactivity is increased in the nucleus, whereas the staining is diminished in dendritic branches in the presence of protein synthesis inhibitors. This translocation is reversible and microtubule dependent. Inside the nucleus, Abi-1 associates with c-Myc/Max complex and thereby influences gene expression.

16.3.4 CREB2

The CREB repressor and transcription factor, CREB2, is expressed in synapses and distal dendrites, as well as in the nucleus of hippocampal pyramidal neurons (Lai et al. 2008). Its nucleocytoplasmic shuttling upon NMDAR activation is mediated by importins. While the LTD-inducing protocol of NMDA and glycine application leads to an intense nuclear accumulation of CREB2, nuclear levels remain unaffected upon LTP induction with glycine application. This association with plasticity and memory formation has been shown both in rodent models and in *aplysia* (Bartsch et al. 1995; Chen et al. 2003; Lai et al. 2008).

16.3.5 AIDA-1d

Amyloid precursor protein intracellular domain–associated protein-1 (AIDA-1d) is a synaptically localized protein carrying a functional bipartite nuclear localization

signal (NLS) in its N-terminus (Jordan et al. 2004). Its binding to PSD-95 associates AIDA-1d to the NMDAR complex (Jordan et al. 2007). Upon NMDAR stimulation, AIDA-1d is proteolytically cleaved, and the N-terminus translocates to the nucleus (Jordan et al. 2007). The observed AIDA-1d dependent increase in the number of nucleoli, its enrichment in especially Cajal bodies (Jacob et al. 2010; Xu and Hebert 2005), and the increased global protein synthesis suggest a structural function of this synapto-nuclear protein messenger.

16.4 Conclusions and Future Directions

Apart from the lack of demonstrative evidence that synapto-nuclear protein messengers indeed translocate from synapse to nucleus, a number of other open questions have to be addressed in the forthcoming years. It is not clear at all whether synapse-to-nucleus communication via protein messengers is required for long-term memory formation, and if yes, why. It remains to be established which nuclear events are crucial in this respect and how regulation of gene expression feeds back to synaptic integrity and function. In addition, the transport mechanisms have not been analyzed in any detail yet. The association of the messengers to the direction-specific dynein/kinesin motors does not explain their translocation to the nucleus completely, as the microtubules with which these motors in turn associate show a mixed polarity in dendrites. The same ambiguity exists even for those messengers associated with importin-α. Another intriguing question concerns the mechanism how synapto-nuclear protein messengers leave the synapse. In many cases, they are supposedly tightly anchored to the postsynaptic scaffold, and the processes that lead to their release from synaptic sites are not understood at all. Binding to importin-α could be a requisite but does neither explain how the complex leaves the synapse nor how the cargo was set free for nuclear import.

Acknowledgement The work in the lab of M.R.K. is supported by grants from the CBBS/EFRE, the Deutsche Forschungsgemeinschaft (DFG), the German-Israeli (DIP) grant, the DZNE, the Deutsche Akademische Austauschdienst (DAAD), the Bundesministerium für Bildung und Forschung (BMBF), the Leibniz Foundation (Pakt für Forschung), and the Schram Foundation.

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