Calcium Signaling in Synapse-to-Nucleus Communication

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Changes in the intracellular concentration of calcium ions in neurons are involved in neurite growth, development, and remodeling, regulation of neuronal excitability, increases and decreases in the strength of synaptic connections, and the activation of survival and programmed cell death pathways. An important aspect of the signals that trigger these processes is that they are frequently initiated in the form of glutamatergic neurotransmission within dendritic trees, while their completion involves specific changes in the patterns of genes expressed within neuronal nuclei. Accordingly, two prominent aims of research concerned with calcium signaling in neurons are determination of the mechanisms governing information conveyance between synapse and nucleus, and discovery of the rules dictating translation of specific patterns of inputs into appropriate and specific transcriptional responses. In this article, we present an overview of the avenues by which glutamatergic excitation of dendrites may be communicated to the neuronal nucleus and the primary calcium-dependent signaling pathways by which synaptic activity can invoke changes in neuronal gene expression programs.

The significance of intracellular calcium (Ca^{2+}) increases for the regulation of gene expression in neurons is well established (Bading et al. 1997; Chawla 2002; Greer and Greenberg 2008; Redmond 2008; Hardingham and Bading 2010). Activity-dependent changes in gene expression in neurons participate in a broad range of processes and behaviors, including synaptic activity-induced acquired neuroprotection (Hardingham et al. 2002; Papadia et al. 2005; Zhang et al. 2007b, 2009; Lau and Bading 2009), activity-dependent regulation of synapse number, size, and function (Flavell et al. 2006; Shalizi et al. 2006; Saneyoshi et al. 2010;

Mauceri et al. 2011), modulation of dendritic complexity (Redmond et al. 2002; Mauceri et al. 2011), growth factor signaling (Gall and Lauterborn 1992; Castren et al. 1998; Greenberg et al. 2009), regulation of long-term changes in synaptic strength (Korzus et al. 2004; Limback-Stokin et al. 2004; Raymond and Redman 2006), and memory consolidation (Bailey et al. 1996; Pittenger et al. 2002; Limback-Stokin et al. 2004; Wood et al. 2005; Etkin et al. 2006; Mauceri et al. 2011). Increases in the intracellular concentration of Ca^{2+} ($[\text{Ca}^{2+}]_i$) that might trigger gene transcription as a consequence of neuronal activity are mediated by

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Ca^{2+} entry through L-type voltage-dependent Ca^{2+} channels (VDCCs) and ligand-gated channels such as *N*-methyl-D-aspartate receptors (NMDARs) (Bading et al. 1993, 1995) and α -amino-3-hydroxyl-5-methyl-4-isoxazolepropionate receptors (AMPA receptors) (Jonas and Burnashev 1995; Cohen and Greenberg 2008), and by release of Ca^{2+} from the endoplasmic reticulum (ER) (Fig. 1) (Hardingham and Bading 1998; Power and Sah 2002, 2007; Stutzmann et al. 2003; Watanabe et al. 2006; Hagenston et al. 2008). Ca^{2+} transients that invade the cell nucleus appear to play a particularly important role in activity-dependent transcription (Hardingham et al. 1997, 2001b; Zhang et al. 2007b, 2009) and are critical for several long-lasting adaptive responses, including acquired neuroprotection and memory formation (Bading 2000; Limback-Stokin et al. 2004; Papadia et al. 2005; Zhang et al. 2009, 2011; Mauceri et al. 2011).

Molecular studies of Ca^{2+} -regulated genomic responses have largely focused on the interactions between synaptic excitation, the particular sources of cytoplasmic $[\text{Ca}^{2+}]_i$ increases, the stimulation of downstream identified signaling cascades, and the activation or repression of specific transcription factor targets. Prominent among the Ca^{2+} sources, Ca^{2+} -dependent second messenger cascades, and transcription factors are NMDARs and L-type VDCCs, Ca^{2+} /calmodulin-dependent protein kinase (CaMK) and Ras/mitogen activated protein kinase (Ras/MAPK) signaling cascades, and the transcription factor cyclic AMP response element binding protein (CREB) as well as the ternary complex factor (TCF)/serum response factor (SRF) transcription factor complex (Fig. 2) (Bading et al. 1993; Xia et al. 1996; Cruzalegui and Bading 2000; Greer and Greenberg 2008). Briefly summarized, synaptically released glutamate binds to and activates NMDARs and AMPARs, leading to a depolarization of the postsynaptic membrane and the activation of L-type VDCCs. Ca^{2+} influx through synapse-associated dendritic NMDARs and L-type VDCCs is sensed by calmodulin (CaM), which initiates a chain of signaling events including stimulation of CaMK and

Ras/MAPK cascades. The culmination of these and other kinase cascades is the phosphorylation and activation of a variety of transcription factors, most notably CREB, but also TCF, nuclear factor κB (NF- κB), myocyte enhancer factor 2 (MEF2), and others (Cruzalegui and Bading 2000; Greer and Greenberg 2008). Several important genomic responses following neuronal activity are controlled by Ca^{2+} signals in the nucleus (Bading 2000; Zhang et al. 2009). For example, increases in nuclear $[\text{Ca}^{2+}]_i$ stimulate gene transcription indirectly through the nuclear resident Ca^{2+} /calmodulin-dependent protein kinase IV (CaMKIV) (Hardingham et al. 2001b) or directly by interaction with regulators of gene transcription such as transcription factor downstream regulatory element antagonistic modulator (DREAM) (Carrion et al. 1999; Ledo et al. 2002).

Cumulating evidence suggests that, in addition to regulating transcription via its influence on specific transcription factors, Ca^{2+} -dependent modulation of genomic responses also operates at a global level by influencing chromatin structure. Nuclear Ca^{2+} signals acting via CaMKIV, for instance, stimulate the histone acetyltransferase CREB binding protein (CBP). Activated CBP, which interacts physically with numerous transcription factors (e.g., CREB) to promote transcription, influences gene transcription by catalyzing histone acetylation and subsequent chromatin decondensation (Chawla et al. 1998; Cruzalegui and Bading 2000; Alarcon et al. 2004; Korzus et al. 2004; Bedford et al. 2010). In a similar vein, nuclear Ca^{2+} signals induce the subcellular redistribution of class II histone deacetylases (HDACs), enzymes whose activity leads to chromatin compression and diminished accessibility by several transcription factors to their target binding sequences (Chawla et al. 2003; Tian et al. 2009, 2010b). Recent results indicate that also de novo DNA methylation, a mechanism stimulating global chromatin remodeling and gene transcription, is controlled by a neuronal activity and Ca^{2+} -dependent mechanism (Chen et al. 2003; Martinowich et al. 2003; Zhou et al. 2006; Skene et al. 2010). Ca^{2+} -dependent synapse-to-nucleus communication

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Figure 1. Sources of synaptic activity induced calcium signals. Here we consider five distinct routes by which Ca^{2+} may enter the neuronal cytoplasm. (1) Ca^{2+} may enter the cell from the extracellular space via ionotropic glutamate receptors, particularly NMDARs. (2) Ca^{2+} may also pass from the extracellular space into the cytoplasm by way of VDCCs, most notably the dihydropyridine-sensitive class of high voltage-activated, or L-type, VDCCs. (3) Stimulation of mGluRs can trigger release of Ca^{2+} into the cytoplasm from intracellular Ca^{2+} stores like ER: synaptically released glutamate activates mGluRs, which are coupled via $G_{q/11}$ GTP-binding proteins to PLC. Activated PLC cleaves membrane-bound PIP_2 to yield DAG and soluble IP_3 , which may then diffuse to and activate IP_3Rs on the ER membrane. (4) Cytosolic Ca^{2+} signals originating from any of the ligand-gated glutamate receptors, VDCCs, or from IP_3Rs can be amplified via the Ca^{2+} -dependent activation of RyRs and subsequent internal release of Ca^{2+} from intracellular stores. (5) Synaptically released glutamate may activate mGluRs on the inner nuclear envelope subsequent to being taken up by EAATs on the plasma membrane first into the cytosol, and then by EAATs on the nuclear envelope into the nuclear lumen. Stimulation of intranuclear mGluRs may consequently lead to the release of Ca^{2+} directly into the nucleus from IP_3Rs localized on the inner nuclear envelope.

therefore involves changes both in the activity of specific transcription factor targets as well as chromatin structure-dependent changes in the accessibility of transcription factors to their respective genomic binding sites.

One of the basic functions subserved by synaptic activity and Ca^{2+} -dependent transcriptional regulation is the experience-dependent induction of persistent changes in synaptic efficacy. Long-term potentiation (LTP), an activity

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Figure 2. Activity-dependent gene expression in neurons is regulated by distinct calcium signaling pathways. Distinct activity-dependent genomic responses may be explained by the differential activation of regulatory signaling cascades and transcription factors. (1) Ca^{2+} influx through L-type VDCCs and synaptically activated NMDARs binds to and activates CaM, leading to activation of the GTP-binding protein Ras and subsequent induction of the Ras/MAPK signaling pathway. Ras binds and activates the mitogen activated protein kinase kinase Raf. Raf in turn phosphorylates and activates MEK, which phosphorylates and activates ERK 1 and 2. Following its translocation into the nucleus, ERK can phosphorylate intermediate kinases like RSK2, which in turn phosphorylate CREB. ERK may also phosphorylate and activate the TCF-family transcription factors, which upon forming a complex with SRF may initiate gene transcription downstream from SRF binding sites. (2) CaM activation by Ca^{2+} entering through NMDARs and VDCCs, but especially through L-type VDCCs, also stimulates the CaMK signal transduction cascade. Ca^{2+} /CaM binds to and activates CaMKK. Next, CaMKK phosphorylates and activates cytoplasmic CaMKI, which can in turn translocate into the nucleus (Sakagami et al. 2005; Wayman et al. 2008). CaMKK also phosphorylates Ca^{2+} /CaM-bound CaMKIV. CaMKIV and perhaps also CaMKI can phosphorylate the transcription factor CREB (Wayman et al. 2008). Stimulation of CREB-mediated transcription, however, requires the additional activation by CaMKIV of the CREB coactivator CBP. It follows that VDCC and NMDAR-mediated $[\text{Ca}^{2+}]_i$ increases and subsequent activation of Ras/MAPK pathways are sufficient to induce TCF/SRF-dependent transcription. However, activation of CREB-dependent transcription necessitates the additional Ca^{2+} -dependent stimulation of CaMKIV and CBP by nuclear Ca^{2+} .

induced persistent increase in synaptic efficacy, is thought to underlie certain forms of learning and memory in the mammalian brain. A critical event leading to the induction of LTP is the postsynaptic influx of Ca^{2+} (Raymond 2007). The persistence of LTP and that of other simple forms of synaptic plasticity is dependent on gene transcription taking place within approximately two hours of the instigating event (Nguyen et al. 1994; Arnold et al. 2005). Although it is unclear exactly which genes are critical for LTP, it is well established that genomic responses following synaptic activity and Ca^{2+} entry vary according to the selection of transcription factors these signals target (Greer and Greenberg 2008). Which transcription factors are activated depends, in turn, on the source and characteristics of stimulatory [Ca^{2+}]_i; increases and on the selection of intracellular signals they induce (Bading et al. 1993, 1997; Dudek and Fields 2001; Hardingham et al. 2002; Greer and Greenberg 2008). Ca^{2+} influx originating at L-type VDCCs and synaptic NMDARs, for example, couples to both CaMK and Ras/MAPK signaling pathways and can thus lead to the phosphorylation of both CREB and the SRF-associated factor, TCF (Cruzalegui and Bading 2000). However, while MAPK signaling is sufficient to stimulate TCF/SRF-dependent transcription, CREB-dependent transcription requires the additional nuclear Ca^{2+} -dependent activation of CaMKIV (Fig. 2) (Hardingham et al. 1997, 2001a,b; Chawla et al. 1998).

A second role for synaptic activity-dependent transcriptional regulation is in activating survival-promoting genes that enable neurons to build up a neuroprotective shield. Activity-dependent neuronal survival is induced by Ca^{2+} entry through synaptic NMDARs and requires—for neuroprotection to be long-lasting—that Ca^{2+} transients invade the cell nucleus, suggesting a mechanism involving CREB-mediated transcription (Wang et al. 1995; Hardingham et al. 2001b; Arnold et al. 2005; Zhang et al. 2007b; Hardingham 2009; Dick and Bading 2010). Procedures that interfere with electrical activity and compromise NMDAR function or nuclear Ca^{2+} signaling

can have deleterious effects on neuron health. For example, the selective blockade of nuclear Ca^{2+} signaling prevents cultured hippocampal neurons from building up antiapoptotic activity upon synaptic NMDAR stimulation (Hardingham et al. 2002; Arnold et al. 2005; Papadia et al. 2005; Hardingham 2009; Lau and Bading 2009; Dick and Bading 2010). Conversely, enhancing neuronal firing and synaptic NMDAR activity is neuroprotective: networks of cultured hippocampal neurons that have experienced periods of action potential bursting causing Ca^{2+} entry through synaptic NMDARs show enhanced resistance to cell death-inducing stimuli (Hardingham et al. 2001b; Hardingham 2009; Lau and Bading 2009; Dick and Bading 2010). On the other hand, stimulation of extrasynaptic NMDARs (ES-NMDARs) counters these effects and activates proapoptotic signaling cascades (Hardingham et al. 2002, 2009; Vanhoutte and Bading 2003; Papadia et al. 2005; Zhang et al. 2007b, 2009, 2011; Leveille et al. 2008; Stanika et al. 2009; Wahl et al. 2009). In vitro studies using cultured neurons have revealed that two mechanistically distinct processes mediate the activity-dependent survival afforded by Ca^{2+} entry through synaptic NMDARs. One involves the PI3K-AKT pathway (reviewed in Hardingham 2009). The second requires Ca^{2+} signaling to the nucleus and the activation or inhibition of a variety of different target genes (Hardingham et al. 2001b, 2009; Francis et al. 2004; Lau and Bading 2009; Dick and Bading 2010). Within the pool of nuclear Ca^{2+} -stimulated survival genes are a set of ten induced genes shown to provide neurons with a neuroprotective shield both in cell culture and in animal models of neurodegeneration (Zhang et al. 2009). Some of these genes, which were termed “Activity-Regulated Inhibitors of Death,” or AID genes, may be induced by activation of the transcription factor CREB, and appear to protect neurons via a common process that yields mitochondria more resistant to cellular stressors and toxins (Zhang et al. 2007b, 2009, 2011; Lau and Bading 2009; Leveille et al. 2010). Another synaptic NMDAR-, nuclear Ca^{2+} -, and CREB-dependent prosurvival gene is brain-derived neurotrophic factor

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(BDNF), a synaptic plasticity associated neurotrophic factor whose expression can both protect neurons from future insult and rescue neurons from cell death induced by synaptic activity blockade (Favaron et al. 1993; Hardingham et al. 2002; Hansen et al. 2004; Jiang et al. 2005; Zhang et al. 2009).

LOCAL Ca^{2+} SIGNALING HAS GLOBAL FUNCTIONAL CONSEQUENCES

The predominance of excitatory synaptic transmission in the central nervous system occurs at dendritic protuberances called synaptic spines. These spines are distributed throughout the dendritic arbors of hippocampal and cortical pyramidal neurons. However, the soma, the first $\sim 100\ \mu\text{m}$ of the primary apical dendrite, and the first $30\text{--}50\ \mu\text{m}$ of the basal dendrites of these neurons are nearly devoid of spines (Spruston and McBain 2007). Indeed, the mean distance between the soma and the first synaptic spine is estimated to be $40\ \mu\text{m}$ (Bannister and Larkman 1995). Moreover, the most distal spines are situated on terminal branches many 100s of μm away from the soma (Spruston and McBain 2007). In view of the tight control placed on cytoplasmic Ca^{2+} transients by the numerous Ca^{2+} buffers, pumps, exchangers, and other Ca^{2+} -binding proteins in neurons, these morphological features pose an interesting problem for Ca^{2+} -dependent synapse-to-nucleus communication. At least three Ca^{2+} -dependent routes have been proposed by which neurons may surmount this problem and successfully communicate synaptic excitation from spine to nucleus. Briefly, these are the diffusion and/or active transport and subsequent translocation of Ca^{2+} -regulated proteins from their synaptic sites of activation into the nucleus (Fig. 3A) (Deisseroth et al. 1998; Mermelstein et al. 2001; Otis et al. 2006; Wiegert et al. 2007; Lai et al. 2008; Jordan and Kreutz 2009; Zehorai et al. 2010); the influx of Ca^{2+} through somatic and perisomatic VDCCs during excitatory postsynaptic potential (EPSP)- and action potential-associated depolarizations (Fig. 3B) (Westenbroek et al. 1990; Murphy et al. 1991;

Bading et al. 1993, 1995; Dudek and Fields 2002; Saha and Dudek 2008); and propagating inositol trisphosphate (IP_3) receptor (IP_3R)-dependent waves of internal Ca^{2+} release that invade the somatonuclear compartment (Fig. 3C) (Hardingham et al. 2001b; Power and Sah 2002, 2007; Watanabe et al. 2006; Hagenston et al. 2008). An additional means by which synaptic activity could be conveyed to the nucleus involves the passive propagation of electrical potentials along ER membranes to the nuclear envelope (Fig. 3D) (Shemer et al. 2008).

The first step in excitatory neurotransmission is the release of glutamate into the cleft between a presynaptic terminal and the electron-dense region of its apposing synaptic spine known as the postsynaptic density. This rich structure is composed of scaffolding molecules, cell adhesion proteins, glutamate receptors, VDCCs, and a wide array of signal transducers involved in the regulation of synaptic function, gene transcription, and memory (Okabe 2007). Therefore, in addition to generating EPSPs, the postsynaptic reception of glutamate by AMPARs and NMDARs may set into motion a wealth of intracellular signaling cascades through local interactions with second messengers. A central player in this relay is Ca^{2+} , and its most prominent source in the postsynaptic density is the NMDAR (Cole et al. 1989; Xia et al. 1996; Pinato et al. 2009). NMDAR-mediated $[\text{Ca}^{2+}]_i$ increases in dendritic spines may be amplified by ryanodine receptor (RyR)-dependent Ca^{2+} -induced Ca^{2+} release from spine ER (Emptage et al. 1999; Raymond and Redman 2006). Imaging studies suggest nonetheless that synaptic NMDAR-dependent Ca^{2+} transients are essentially confined within spine heads, with little to no invasion of dendritic shafts (Yuste et al. 2000; Nakamura et al. 2002; Sabatini et al. 2002; Noguchi et al. 2005). If not via the generation of global Ca^{2+} signals, synaptic NMDARs must communicate with the nucleus via locally activated Ca^{2+} -regulated proteins and processes in the postsynaptic density. This idea is supported by studies employing exogenously applied EGTA. EGTA is a Ca^{2+} buffer that allows

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Figure 3. Possible routes of communication between synapse and nucleus. Schematic illustration of four pathways by which information impinging onto synapses may be conveyed to the nucleus. (A) Glutamatergic activation of synaptic AMPARs and NMDARs trigger increases in Ca^{2+} within synaptic spines. These Ca^{2+} increases may be amplified locally by Ca^{2+} -induced Ca^{2+} release via RyRs on spinous ER. $[\text{Ca}^{2+}]_i$ increases within spines trigger the activation of numerous NLS-harboring second messengers (cargo-NLS) and the mobilization of importin. Importin/cargo complexes then diffuse or are actively transported through the dendritic cytosol to invade the soma and nucleus. (B) Synaptic activity evokes synaptic EPSPs, which travel along the plasma membrane to the soma. When the summation of inputs exceeds firing threshold, an action potential is triggered. Membrane depolarizations accompanying EPSPs and action potentials activate somatic and perisomatic L-type VDCCs, which allow Ca^{2+} to flow down its concentration gradient from the extracellular space into the soma, from where it crosses the nuclear envelope to invade the nucleus. (C) Robust stimulation of glutamatergic afferents can result in the activation of perisynaptic $\text{G}_{q/11}$ -protein-coupled glutamate receptors, or mGluRs, which in turn trigger a signaling cascade that results in the production of the second messenger IP_3 . IP_3 subsequently binds to and activates IP_3Rs on the ER membrane, causing their Ca^{2+} -permeable channels to open and allowing Ca^{2+} to flow down its concentration gradient from the ER lumen into the cytosol. Ca^{2+} , an IP_3R coagonist, may then stimulate neighboring IP_3Rs , thus triggering a propagating wave of regenerative internal Ca^{2+} release. Robust Ca^{2+} waves that invade the soma are able to freely cross the nuclear envelope and generate robust nuclear Ca^{2+} transients. (D) Stimulation of ligand-operated and voltage-dependent ion channels in the plasma membrane of spines evokes local currents across the plasma membrane, I_{pm} . (Legend continued on next page.)

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the generation of submembranous $[Ca^{2+}]_i$ increases near the mouth of Ca^{2+} influx channels, but prevents the spread of free Ca^{2+} from synaptic spines into the dendritic shaft and soma (Stern 1992; Deisseroth et al. 1996; Hardingham et al. 2001a). Introduction of EGTA into cultured hippocampal neurons thus effectively blocks global Ca^{2+} signaling, but permits the generation of cytoplasmic Ca^{2+} transients in the immediate vicinity of NMDARs. Under these conditions, synaptic activity has been observed to both induce Ras/MAPK signaling and trigger the phosphorylation of CREB (Deisseroth et al. 1996; Hardingham et al. 2001a).

MOBILE SECOND MESSENGERS IN SYNAPSE-TO-NUCLEUS COMMUNICATION

The diffusion and/or active transport of calcium-regulated proteins between synaptic NMDAR-associated Ca^{2+} signaling microdomains in the postsynaptic density and their targets in the nucleus represent attractive mechanisms for synapse-to-nucleus communication (Fig. 3A) (Deisseroth et al. 1998; Mermelstein et al. 2001; Thompson et al. 2004; Otis et al. 2006; Dieterich et al. 2008; Lai et al. 2008; Jordan and Kreutz 2009). The hypothesis that synaptic activity is relayed to the nucleus via mobile second messengers is supported by studies showing that NMDARs interact directly or indirectly with several different signaling molecules implicated in neuronal activity-dependent gene transcription, including CaM, CaMKs, protein phosphatase 1 (PP1), calcineurin, and members of the Ras/MAPK signaling cascade (Seidenbecher et al. 1998; Graef et al. 1999; Westphal et al. 1999; Zuhlke et al.

1999; Husi et al. 2000; Dolmetsch et al. 2001; Tolias et al. 2005; Wheeler et al. 2008), as well as by studies showing that synaptic activation of NMDARs and VDCCs induces the active transport and nuclear import of a broad range of synaptically localized proteins involved in transcriptional regulation, including the transcription factors NF- κ B, nuclear factor of activated T-cells (NFAT), and CREB2 (Graef et al. 1999; Wellmann et al. 2001; Meffert et al. 2003; Tomida et al. 2003; Fagerlund et al. 2008; Lai et al. 2008; Jordan and Kreutz 2009). In this regard, it is particularly interesting that NMDARs have been observed to interact also in an activity-dependent fashion with importin α (Thompson et al. 2004; Jeffrey et al. 2009), a soluble transport receptor that mediates the transport and/or nuclear import of a variety of nuclear localization signal (NLS)-containing cargoes from distal dendritic locations to the nucleus (Otis et al. 2006; Jordan et al. 2007; Dieterich et al. 2008; Lai et al. 2008). More specifically, the NR1-1a NMDAR subunit and importin α were recently reported to colocalize within synaptic spines and to coimmunoprecipitate in extracts derived from hippocampal neuronal cultures and acute slices (Jeffrey et al. 2009). These interactions were found to depend on the binding of importin α to an NLS sequence in the cytoplasmic tail of NR1-1a, and to be negatively regulated by phosphorylation of nearby residues via the Ca^{2+} -dependent kinase protein kinase C. Accordingly, treatments that stimulate synaptic NMDARs and up-regulate protein kinase C activity—glutamate stimulation of neuronal cultures or high-frequency, LTP-inducing stimulation of presynaptic afferents in acute brain slices—were observed to disrupt the coimmunoprecipitation

Figure 3. (Continued) Either as a result of capacitative conduction of plasma membrane potential fluctuations combined with Ca^{2+} uptake into the ER via sarcoendoplasmic reticulum Ca^{2+} ATPases, or as a consequence of the release of Ca^{2+} via RyRs and IP₃Rs localized to spines and dendrites, synaptic currents are predicted to evoke an electrotonic signal across and along the ER membrane, such that synaptic currents flow simultaneously through the cytosol (I_i) and within the ER (I_{ER}) toward the soma. Summation of many such excitatory electrotonic signals can give rise to an EPSP-like depolarization across the nuclear envelope. Importantly, action potentials initiating at the soma would also result in propagating electrotonic signals along the ER. In this case, however, the resultant changes in potential across the nuclear envelope would be hyperpolarizing, thereby distinguishing these signals from others that originate distally in synaptic spines.

and colocalization of NR1-1a with importin α (Jeffrey et al. 2009). These findings suggest a mechanism by which importin α may be made available in a Ca^{2+} - and activity-dependent fashion to facilitate the transport and translocation of synaptically localized NLS-harboring proteins such as NFAT to the nucleus.

Might such a mechanism underlie synaptic activity regulated genomic responses through the Ras/MAPK signaling cascade? Until recently, there were no indications either that the MAPKs harbor an NLS enabling binding to importins or that they might interact with another NLS-containing protein (Lange et al. 2007; Zehorai et al. 2010). These findings made it difficult to clarify evidence suggesting that the nuclear translocation of extracellular signal-regulated kinase (ERK), a key player in Ras/MAPK signaling within the nucleus, was mediated by both facilitated diffusion and active transport mechanisms (Adachi et al. 1999; Xu and Massague 2004; Zehorai et al. 2010). A recent study introduced the possibility, however, that nuclear import of ERK may be controlled by its interaction with a member of the importin β family of nuclear import proteins (Chuderland et al. 2008). In this study, the authors identified a novel nuclear transport sequence in ERK's kinase insert domain that enabled ERK to bind importin β and diffuse across the nuclear envelope. ERK's interaction with importin β necessitated its prior phosphorylation by MAPK/ERK kinase (MEK) and consequent release from anchoring proteins into the cytoplasm (Chuderland et al. 2008). These findings suggest that importin-dependent transport is likely to contribute to the somatonuclear translocation of active, diffusible ERK. They do not, however, resolve the question of whether ERK translocation from distal dendritic processes into the soma is likewise facilitated by an active transport mechanism involving importins (Thompson et al. 2004; Otis et al. 2006; Lai et al. 2008). We would suggest that this is an unlikely scenario. NMDAR-dependent $[\text{Ca}^{2+}]_i$ increases activate the Ras/MAPK pathway through a Ca^{2+} pool in their immediate vicinity (Hardingham et al. 2001a), and synaptically activated Ras spreads

along dendrites by diffusion, reaching distances of only $\sim 10 \mu\text{m}$ from its spine of origin before inactivating (Harvey et al. 2008). In an investigation employing exogenously expressed ERK fused to a photoactivable and photobleachable probe, it was found that synaptic activity similarly mobilizes the Ras effectors ERK 1 and 2, and that their trafficking in dendrites likewise proceeds by passive diffusion (Wiegert et al. 2007). Significantly, ERK was observed in this study to have a very limited reach within dendrites, and showed a length constant of only $\sim 30 \mu\text{m}$ (Wiegert et al. 2007). These findings indicate that successful signal propagation to the nucleus by the Ras/MAPK pathway most probably depends on the distance between the nucleus and the site of activated synapses. Thus, while perisomatic synaptic NMDAR activation and subsequent ERK mobilization may suffice to trigger new ERK-dependent nuclear responses, distal synaptic NMDARs are unlikely to stimulate transcription through the Ras/MAPK signaling cascade (Wiegert et al. 2007).

Phosphorylation and activation of CREB following synaptic NMDAR activity is achieved by the convergence of at least two Ca^{2+} -dependent kinase pathways: CaMKIV in the nucleus mediates rapid CREB phosphorylation whereas the Ras/MAPK pathway acting through ERK promotes CREB phosphorylation in a slower, but more long-lasting manner (Hardingham et al. 2001a; Wu et al. 2001). For its part, CaMKIV activation requires that it bind Ca^{2+} -activated calmodulin ($\text{Ca}^{2+}/\text{CaM}$) and be phosphorylated by cytosolic Ca^{2+} /calmodulin-dependent protein kinase kinase (CaMKK) to achieve an enzymatically active state (Anderson et al. 1998; Means 2000; Sakagami et al. 2000). The reported constitutive localization of CaMKIV within the nucleus (Jensen et al. 1991; Nakamura et al. 1995; Bito et al. 1996) combined with its requisite involvement in the activation of CREB-mediated transcription (Chawla et al. 1998) raised the possibility that CREB induction via CaMKIV involves the translocation of a synaptically activated Ca^{2+} effector such as CaM or CaMKK. Stimulus-triggered $[\text{Ca}^{2+}]_i$ increases have been reported to induce the rapid translocation of both

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endogenous $\text{Ca}^{2+}/\text{CaM}$ and fluorescently labeled $\text{Ca}^{2+}/\text{CaM}$ from the cytoplasm to the nucleus of cultured hippocampal neurons, possibly in a complex with CaMKK (Deisseroth et al. 1998; Mermelstein et al. 2001). However, these findings are inconsistent both with the observed prominent nuclear localization of CaM in cortical and hippocampal neurons in vivo and in vitro (Caceres et al. 1983; Hoskins et al. 1986; Hardingham et al. 2001b), and with the lack of evidence supporting CaMKK nuclear localization or translocation (Deisseroth et al. 1998; Sakagami et al. 2000). Moreover, in a similar series of experiments, no evidence was found for signal-regulated translocation either of endogenous CaM or of microinjected fluorescently labeled CaM (Hardingham et al. 2001b). Instead, it was observed that rapid CaMK-dependent CREB phosphorylation can be evoked even when nuclear transport is blocked, and that an increase in nuclear $[\text{Ca}^{2+}]_i$ suffices to induce this response (Hardingham et al. 2001b).

Following these studies, a model has emerged for the activation of CaMKIV, which involves not the nuclear translocation of CaM, but rather the generation of nuclear calcium transients. Accordingly, the initial stimulation of CaMKIV begins with an increase in nuclear $[\text{Ca}^{2+}]_i$ and a physical association between CaMKIV and nuclearly localized $\text{Ca}^{2+}/\text{CaM}$ (Hardingham et al. 2001b; Anderson et al. 2004). Binding of $\text{Ca}^{2+}/\text{CaM}$ by CaMKIV is accompanied by its disengagement from the negative regulator protein phosphatase 2a (Park and Soderling 1995; Westphal et al. 1998; Kasahara et al. 1999; Anderson et al. 2004) and is followed by its phosphorylation and activation through CaMKK (Anderson et al. 1998, 2004; Chow et al. 2005). Interestingly, although CaMKK is triggered by $[\text{Ca}^{2+}]_i$ increases, it also shows a substantial level of activity at basal $[\text{Ca}^{2+}]_i$ (Anderson et al. 1998). It follows that synaptic activity-associated nuclear $[\text{Ca}^{2+}]_i$ increases may be sufficient for stimulating CaMKIV-dependent CREB phosphorylation (Chawla et al. 1998; Hardingham et al. 2001b). Yet where does the phosphorylation of CaMKIV occur? Although

CaMKIV is localized to the nucleus, it has been observed to dynamically redistribute between cytoplasmic and nuclear compartments (Matthews et al. 1994; Lalonde et al. 2004; Lemrow et al. 2004; Kotera et al. 2005). CaMKK, on the other hand, shows a strictly cytoplasmic distribution (Anderson et al. 1998; Sakagami et al. 2000). Thus, CaMKIV appears to be phosphorylated by CaMKK in the cytoplasm (Lemrow et al. 2004), after which it is transported into the nucleus, perhaps via a mechanism involving importin α -mediated facilitated diffusion (Matthews et al. 1994; Lemrow et al. 2004; Kotera et al. 2005).

VDCCs are important for the neuronal activity-dependent regulation of gene expression. Neurons express a variety of VDCCs having varying pharmacological sensitivity, activation thresholds, conductances, and localizations (Catterall et al. 2005; Vacher et al. 2008). Of these, the L-type family of high voltage-activated VDCCs plays the most prominent role in postsynaptic signal transduction to the nucleus. These Ca^{2+} channels are expressed in the soma and proximal dendrites at both synaptic and extrasynaptic locations (Westenbroek et al. 1990; Hell et al. 1993; Obermair et al. 2004; Leitch et al. 2009), and are strongly implicated in the somatodendritic $[\text{Ca}^{2+}]_i$ increases that are generated in response to action potentials (Westenbroek et al. 1990; Liu et al. 2003; Vacher et al. 2008). In view of their somatodendritic localization, it may be tempting to conclude that the involvement of L-type channels in transcriptional regulation can be accounted for solely through the global Ca^{2+} transients associated with their activation. Numerous studies have shown, however, as is the case for NMDARs, that Ca^{2+} can act locally near the mouth of the channel to trigger transcription-relevant events (Deisseroth et al. 1996; Dolmetsch et al. 2001; Hardingham et al. 2001a; Weick et al. 2003; Wheeler et al. 2008). This reliance of VDCC-mediated genomic responses on local Ca^{2+} signaling suggests that L-type channels reside within Ca^{2+} signaling microdomains in close physical proximity to Ca^{2+} -dependent molecular machinery. Indeed, not only are L-type VDCCs localized to postsynaptic

densities in synaptic spines, where they interact with CaM, CaMKs, the Ca^{2+} -dependent protein phosphatase calcineurin, and other Ca^{2+} -dependent second messengers (Graef et al. 1999; Weick et al. 2003; Greer and Greenberg 2008; Vacher et al. 2008; Wheeler et al. 2008; Dai et al. 2009), the L-type channel also harbors a CaM-binding motif on its carboxy-terminus enabling the tethering of CaM within several nanometers of its Ca^{2+} -conductive pore (Zuhlke and Reuter 1998; Dolmetsch et al. 2001). Consistent with these findings, L-type VDCC-dependent phosphorylation of transcriptional activators has been reported to depend—at least in part—on the activation of synaptically localized Ca^{2+} /CaM-dependent kinases (Deisseroth et al. 1998; Dolmetsch et al. 2001; Weick et al. 2003; Wheeler et al. 2008). An additional means by which synaptic L-type channels can control genomic responses is via local interactions with the protein kinase A anchoring protein (AKAP79/150) and the protein phosphatase calcineurin (Gray et al. 1998; Oliveria et al. 2007). In particular, anchoring of calcineurin to L-type VDCCs by AKAP79/150 is thought to facilitate its activation by L-type VDCC-mediated Ca^{2+} influx. Ca^{2+} -activated calcineurin, in turn, can dephosphorylate the transcription factor NFAT, unmasking its NLS and leading to nuclear import (Beals et al. 1997; Graef et al. 1999; Greer and Greenberg 2008; Vashishta et al. 2009).

EXTRASYNAPTIC NMDA RECEPTORS ANTAGONIZE SYNAPSE-TO-NUCLEUS COMMUNICATION

Up to this point, we have concentrated on delineating the routes by which glutamatergic synaptic input may be conveyed to the nucleus. Just as significant, however, are the extrasynaptic routes by which glutamatergic excitation-transcription coupling is controlled. In the brain, signal reception by extrasynaptic glutamate receptors, particularly ES-NMDARs, has been suggested to play a pivotal role in the neurodegenerative processes associated with cerebral ischemia, seizure, and traumatic brain injury. ES-NMDARs are also implicated in the etiology of several neurodegenerative disorders,

including Huntington's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (Hardingham and Bading 2003, 2010; Vanhoutte and Bading 2003; Arundine and Tymianski 2004; Bossy-Wetzel et al. 2004; Bezprozvanny 2007; Kalia et al. 2008; Hardingham 2009; Milnerwood et al. 2010). The functional importance of ES-NMDARs in these disorders has been proposed to follow from their influence on cell survival and cell death pathways.

Although Ca^{2+} entry through synaptic NMDARs promotes neuronal survival via the activation of a neuroprotective gene program and suppression of apoptotic cascades, Ca^{2+} influx through ES-NMDARs both opposes cell survival pathways and triggers cell death signals leading to neuron loss (Hardingham et al. 2002, 2009; Vanhoutte and Bading 2003; Papadia et al. 2005; Zhang et al. 2007b, 2009; Leveille et al. 2008; Stanika et al. 2009; Wahl et al. 2009). For example, synaptic NMDAR activation both inhibits transcription of the proapoptotic gene *Puma* and triggers the nuclear Ca^{2+} - and CREB-dependent expression of AID genes and the prosurvival immediate early gene, *BDNF* (Favaron et al. 1993; Hardingham et al. 2002; Hansen et al. 2004; Jiang et al. 2005; Zhang et al. 2007b, 2009; Lau and Bading 2009; Leveille et al. 2010). Conversely, stimulation of extrasynaptic receptors is linked to up-regulated expression of the proapoptotic putative Ca^{2+} -activated chloride channel *Clca1* (Zhang et al. 2007b; Wahl et al. 2009). Moreover, ES-NMDARs activate a dephosphorylating CREB shut-off pathway and antagonize synaptic activity induced BDNF expression and cell survival (Hardingham and Bading 2002; Hardingham et al. 2002; Vanhoutte and Bading 2003; Papadia et al. 2005; Ivanov et al. 2006; Zhang et al. 2007b).

One important messenger in synaptic NMDAR- and Ca^{2+} -dependent coupling to CREB is ERK. Although Ca^{2+} influx through synaptic NMDARs induces the phosphorylation and mobilization of ERK, Ca^{2+} entry via ES-NMDARs instead leads to ERK inactivation and retention at the plasma membrane, thus preventing its interaction with and activation of nuclear transcription factor targets (Cruzalegui and Bading 2000; Krapivinsky et al. 2003;

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Ivanov et al. 2006; Leveille et al. 2008; Zehorai et al. 2010). Consequently, stimulation of the total (synaptic and extrasynaptic) NMDAR pool triggers a reduced level of ERK activity and associated transcription factor activation (Bading and Greenberg 1991; Chandler et al. 2001; Hardingham et al. 2001a, 2002; Krapivinsky et al. 2003; Ivanov et al. 2006; Leveille et al. 2008; Gao et al. 2010). Such antagonism by ES-NMDARs of synaptic NMDAR-dependent signaling to the nucleus extends to a number of additional signaling pathways. For example, ES-NMDAR signaling has been observed to disrupt the nucleocytoplasmic shuttling of class II HDACs, thereby preventing disinhibition of pro-survival transcription factors MEF2 and CREB in response to synaptic NMDAR stimulation (Chawla et al. 2003; Vanhoutte and Bading 2003; Bolger and Yao 2005). Furthermore, synaptic NMDARs signals promote the phosphorylation and subsequent nuclear export of the forkhead box O (FOXO) family of proapoptotic transcription factors, and also inhibit subsequent FOXO nuclear import. Stimulation of ES-NMDARs, on the other hand, induces rapid translocation of FOXO from the cytoplasm into the nucleus (Brunet et al. 1999; Gilley et al. 2003; Al-Mubarak et al. 2009; Hardingham 2009; Dick and Bading 2010). A picture is thus emerging in which neurons' genomic responses to Ca^{2+} entry through NMDARs depends on the subcellular localization of these receptors (Fig. 4). The particular means by which ES-NMDARs antagonize intracellular signals induced by synaptic NMDARs remains to be clearly delineated. One intriguing possibility is that the two receptor populations experience distinct biochemical environments harboring different sets of Ca^{2+} -dependent effector molecules (Hardingham and Bading 2010).

NUCLEAR Ca^{2+} SIGNALING IN SYNAPSE-TO-NUCLEUS COMMUNICATION

An increasing number of studies suggest that $[\text{Ca}^{2+}]_i$ increases within the nucleus represent an essential component of synapse-to-nucleus communication: nuclear Ca^{2+} signals have been implicated in the regulation of neuronal

gene expression programs (Chawla et al. 1998; Carrion et al. 1999; Ledo et al. 2000; Hardingham et al. 2001b; Ledo et al. 2002; Zhang et al. 2009) and are a critical component in the molecular machinery that translates different sets of stimuli into distinct transcriptional responses (Hardingham et al. 1997; Mellstrom et al. 2004). Nuclear Ca^{2+} signaling is linked also to a number of neuronal functions that have been shown to depend on regulated gene expression (Limback-Stokin et al. 2004; Papadia et al. 2005; Raymond and Redman 2006; Schneider et al. 2007; Alexander et al. 2009; Fontan-Lozano et al. 2009). For instance, 100 Hz and θ -burst synaptic stimulation of afferent fibers—both of which are known to induce transcription-dependent LTP—evoke robust nuclear Ca^{2+} transients (Raymond and Redman 2002, 2006; Johnsen and Holthoff 2007; Power and Sah 2007). Conversely, blockade of somatonic $[\text{Ca}^{2+}]_i$ increases during stimulation prevents the development of transcription-dependent, but not transcription-independent LTP (Raymond and Redman 2002, 2006), whereas antagonism of nuclear Ca^{2+} /CaM signaling inhibits both neuronal activity-induced gene transcription and transcription-dependent LTP, and selectively prevents the formation of transcription-dependent long-term memory (Limback-Stokin et al. 2004). The means by which nuclear Ca^{2+} signaling controls memory processes include the transcriptional regulation of vascular endothelial growth factor D (VEGFD), a mitogen for endothelial cells whose expression modulates dendritic length and complexity (Mauceri et al. 2011). Nuclear Ca^{2+} /CaM signaling is also critically important for the activation of a neuroprotective gene program, and its inhibition has been linked to an increased susceptibility to cellular stressors (Papadia et al. 2005; Zhang et al. 2007b, 2009; Lau and Bading 2009; Dick and Bading 2010).

The first indication that nuclear Ca^{2+} might play a part distinct from cytoplasmic Ca^{2+} in the neuronal activity-dependent regulation of gene expression was gained by an investigation employing a dextran-conjugated Ca^{2+} chelator (Hardingham et al. 1997). AtT20 cells, into whose nuclei this chelator had been injected,

Figure 4. Extrasynaptic NMDARs antagonize synaptic NMDAR-dependent synapse-to-nucleus signaling. NMDAR-dependent Ca^{2+} signaling promotes neuronal survival, but can also cause cell degeneration and apoptotic death. The location of the activated NMDAR pool specifies the transcriptional response. In particular, Ca^{2+} influx through synaptic NMDARs leads to the activation and nuclear translocation of ERK followed by phosphorylation of the neuroprotection-associated transcription factor, CREB, and transcription of prosurvival gene products including the prosurvival neurotrophic factor BDNF. Synaptic NMDAR activity also induces the nuclear export of HDACs and of the proapoptotic transcription factor FOXO. Export of HDACs allows for the acetylation and disinhibition of transcription mediated by prosurvival transcription factors such as MEF2 and CREB. Conversely, ES-NMDAR-mediated Ca^{2+} entry triggers the rapid dephosphorylation and inactivation of ERK, thus preventing its nuclear translocation, interferes with the nuclear export of HDACs, and triggers the rapid nuclear import of FOXO proteins. Thus, whereas activation of synaptic NMDARs promotes the transcription of neuroprotective target genes via CREB and MEF2, ES-NMDAR activation actively represses CREB- and MEF2-dependent gene transcription, and leads to the transcription of genes associated with neuronal degeneration and apoptotic cell death.

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showed intact cytoplasmic Ca^{2+} transients, but significantly reduced nuclear Ca^{2+} signals in response to stimulation of plasma membrane Ca^{2+} channels. Analysis of transcriptional responses subsequently revealed that the reduction in nuclear Ca^{2+} signaling could be specifically linked to an inhibition of CREB-dependent gene transcription. In contrast, TCF/SRF-dependent gene transcription was shown to be contingent only on the generation of $[\text{Ca}^{2+}]_i$ increases in the cytoplasm (Hardingham et al. 1997). A follow-up study subsequently unveiled a critical role for nuclear Ca^{2+} in CREB-dependent gene transcription stimulated by the activity of synaptic NMDARs in neurons (Hardingham et al. 2001b).

How does nuclear Ca^{2+} support synaptic NMDAR-mediated signaling to CREB? Synaptic activity-dependent signaling to CREB is achieved primarily via two different Ca^{2+} -dependent kinase cascades: the CaMK and the Ras/MAPK pathways (Chawla et al. 1998; Hardingham et al. 1999). Although both pathways cause phosphorylation of CREB on its activator site serine 133, additional stimulation of CBP, a transcriptional coactivator that interacts with phosphorylated CREB, is also crucial for the induction of CREB-mediated transcription (Chawla et al. 1998; Hu et al. 1999; Impey et al. 2002). The induction of CBP, in turn, critically depends on CaMKIV, the activation of which can be achieved by an increase in nuclear $[\text{Ca}^{2+}]_i$ (Chawla et al. 1998; Hardingham et al. 1999; Impey et al. 2002). CREB-mediated transcription triggered by synaptic NMDARs thus necessitates convergence of the Ras/MAPK signaling cascade with a nuclear Ca^{2+} - and CaMKIV-dependent signal to CBP. It follows that the presence or absence of nuclear $[\text{Ca}^{2+}]_i$ increases during up-regulated NMDAR-dependent Ras/MAPK signaling has the capacity to determine whether these may induce CREB-mediated gene transcription. Nuclear Ca^{2+} signaling is thus a critical determinant of whether the activation of synaptic NMDARs leads to solely TCF/SRF-, or both TCF/SRF- and CREB-dependent transcription (see Fig. 2) (Hardingham et al. 1997, 2001a,b; Chawla et al. 1998).

It has been proposed that $[\text{Ca}^{2+}]_i$ increases must originate at synapses to trigger neuronal activity-dependent CREB-mediated transcriptional responses (Murphy et al. 1991; Deisseroth et al. 1996). An important point therefore is that CaMKIV, which resides in the nucleus, not only is necessary for the activation of CBP, but can also phosphorylate CREB. Consequently, nuclear Ca^{2+} signaling to CaMKIV is sufficient to induce gene transcription via CREB (Hardingham et al. 2001b). The duration of nuclear $[\text{Ca}^{2+}]_i$ increases, a feature which correlates with the duration of CBP activation and CREB phosphorylation, is an important factor for determining the magnitude of genomic responses (Bito et al. 1996; Chawla and Bading 2001; Hardingham et al. 2001b). It would therefore seem that—whether arising from synaptic NMDARs, L-type VDCCs, or intracellular Ca^{2+} stores—any Ca^{2+} signal that invades the nucleus and is of sufficient duration and magnitude to stimulate CaMKIV, may likewise be sufficient to trigger CREB-mediated gene transcription.

An additional means by which nuclear Ca^{2+} can regulate genomic responses is via a direct interaction with the transcriptional repressor DREAM. DREAM is a Ca^{2+} - and DNA-binding protein that inhibits gene transcription by restricting the access of stimulatory transcription factors like CREB to their DNA-binding domains (Carrion et al. 1999; Ledo et al. 2002). Binding of Ca^{2+} to DREAM allows it to dissociate from its DNA binding site (Carrion et al. 1999; Ledo et al. 2000, 2002). Thus, nuclear Ca^{2+} acting through DREAM can function as a signal for transcriptional disinhibition. New research implicates DREAM also in synaptic plasticity and memory consolidation. For example, DREAM knockout mice show enhanced CREB-dependent gene transcription, enhanced LTP, and improved performance in a variety of behavioral assays for transcription-dependent long-term memory (Lilliehook et al. 2003; Alexander et al. 2009; Fontan-Lozano et al. 2009). Notably, these mice continued to show improved memory formation during aging, and were found to manifest a marked decrease in aging-associated

pathological changes in the hippocampus (Fontan-Lozano et al. 2009). Moreover, using electrophoretic mobility shift assays with hippocampal nuclear extracts, it was observed that DREAM binding to DNA decreased following training on a hippocampus-dependent behavioral task (Fontan-Lozano et al. 2009). These findings underline the critical involvement of nuclear Ca^{2+} -dependent control of genomic responses through direct interactions with transcriptional regulators like DREAM in the coupling of excitatory stimuli to memory formation and cognitive functioning.

EPIGENETIC MECHANISMS IN SYNAPTIC ACTIVITY AND Ca^{2+} -DEPENDENT TRANSCRIPTIONAL REGULATION

Chromatin remodeling is now emerging as a powerful means by which synaptic activity and intracellular Ca^{2+} signaling can induce genomic responses (Fig. 5). Dynamic changes in chromatin structure are brought about by an array of histone posttranslational modifications including phosphorylation, methylation, and acetylation. These changes are implicated in gene transcription, synaptic plasticity, memory consolidation, and neuronal survival (Alarcon et al. 2004; Korzus et al. 2004; Jiang et al. 2006; Oliveira et al. 2007; Lubin et al. 2008; Koshibu et al. 2009), and their dysregulation is causatively linked to both developmental and neurodegenerative disorders (Petrij et al. 1995; Jorgensen and Bird 2002; Alarcon et al. 2004; Jiang et al. 2006; Zhou et al. 2006; Fischer et al. 2007; Duclot et al. 2010).

Histone acetylation, which results in chromatin expansion and increased access to transcription factor binding sites, is controlled by histone acetyltransferases (HATs) and HDACs. One of the means by which neuronal activity-dependent Ca^{2+} signaling can influence transcription factor activity is through the dynamic regulation of these enzymes. For example, synaptic activity-dependent $[\text{Ca}^{2+}]_i$ increases act through CaMKIV to stimulate CBP, a CREB coactivator and HAT that interacts with numerous transcription factors (Chawla et al. 1998; Sterner and Berger 2000; Impey et al. 2002;

Bedford et al. 2010). In a similar vein, NMDAR-mediated Ca^{2+} signaling through the Ras/MAPK pathway may stimulate gene transcription via p300, a CBP analog HAT (Sterner and Berger 2000; Legube and Trouche 2003; Li et al. 2003; Oliveira et al. 2006, 2007; Bedford et al. 2010). Synaptic activation of NMDARs and L-type VDCCs shapes transcriptional responses also by triggering the CaMK-dependent nuclear export of the class II HDAC and MEF2 corepressor, HDAC5, an effect that is blocked either by costimulation of ES-NMDARs or by pharmacological induction of cyclic AMP signaling (McKinsey et al. 2000; Chawla et al. 2003; Belfield et al. 2006). These and other findings suggest that transcription factor phosphorylation and histone acetylation may represent parallel targets of synapse-to-nucleus Ca^{2+} -dependent signaling through the CaMK and Ras/MAPK pathways. Indeed, a number of recent studies have established CBP-, p300-, CaMK-, and/or NMDAR/Ras/MAPK-dependent histone modifications as critical regulatory mechanisms controlling the synaptic plasticity gene *BDNF*, the induction of LTP, and the consolidation of memory (Hardingham et al. 1999; Impey et al. 2002; Chawla et al. 2003; Chwang et al. 2006, 2007; Oliveira et al. 2006, 2007; Wood et al. 2006; Chandramohan et al. 2008; Brami-Cherrier et al. 2009; Tian et al. 2009, 2010a,b; Duclot et al. 2010).

Synaptic activity and Ca^{2+} -dependent regulation of gene expression may further be achieved via the modulation of cofactors that facilitate the association of HATs and HDACs with DNA. An example is methyl-CpG binding protein 2 (MeCP2), a transcriptional regulator that has been shown to suppress gene expression by recruiting HDAC-containing protein complexes to the genome (Jones et al. 1998; Nan et al. 1998; Jorgensen and Bird 2002; Chen et al. 2003; Martinowich et al. 2003; Zhou et al. 2006; Tao et al. 2009). Synaptic activity and Ca^{2+} -dependent regulation of MeCP2 can be accomplished via its phosphorylation by CaMKs (Zhou et al. 2006; Tao et al. 2009). In particular, the Ca^{2+} -dependent phosphorylation of MeCP2 has been shown both to trigger transcriptional derepression of known

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Figure 5. Epigenetic mechanisms in synaptic activity and Ca^{2+} -dependent transcriptional regulation. Synaptic activity-dependent $[Ca^{2+}]_i$ increases may influence chromatin structure—and therewith access of transcription factors and regulatory enzymes to their specific interaction domains—through influences on histone acetylation and DNA methylation. Synaptic activity-dependent Ca^{2+} signals acting through CaM and $CaMK$ and $Ras/MAPK$ signaling cascades can, for instance, activate HATs such as CBP and $p300$. These transcriptional coactivators catalyze the posttranslational acetylation of histones, leading to chromatin relaxation, increased access of transcription factors to their respective DNA binding domains, and up-regulation of gene transcription in affected genomic regions. Alternately, nuclear Ca^{2+} increases associated with synaptic activity may trigger the $CaMK$ -dependent phosphorylation and dissociation of methyl CpG-binding proteins like $MeCP2$ from methylated sequences of DNA as well as the nuclear export of the HDACs with which they interact. HDAC activity results in the deacetylation of histones and the subsequent compression of chromatin, leading to a suppression of transcriptional activity. $MeCP2$ dissociation and HDAC export thus induce a derepression of gene transcription. Ca^{2+} influx associated with synaptic activity is linked also to de novo DNA methylation via DNMTs such as DNMT3a, and to active DNA demethylation via dMTases such as GADD45a. Note that, although not shown here, histone phosphorylation, ubiquitination, and methylation also contribute to the epigenetic regulation of gene expression (Levenson and Sweatt 2006), and may likewise be involved in Ca^{2+} -dependent synapse-to-nucleus communication.

plasticity-associated genes via a mechanism that involves its dissociation from the genome followed by an up-regulation of histone acetylation (Chen et al. 2003; Martinowich et al. 2003; Zhou et al. 2006; Tao et al. 2009) and to activate gene transcription by recruiting transcription factors such as $CREB1$ to the genome (Chahrouh et al. 2008).

An additional mechanism by which synaptic activity and associated $[Ca^{2+}]_i$ increases might stimulate the genomic responses required for neuronal activity-induced acquired neuroprotection, synaptic plasticity, and long-term memory is via the dynamic regulation of DNA methylation (Levenson et al. 2006; Barreto et al. 2007; Miller and Sweatt 2007; Zhang

et al. 2007b, 2009; Lubin et al. 2008; Miller et al. 2008, 2010; Feng et al. 2010). De novo DNA methylation mediated by DNA methyltransferases (DNMTs) such as DNMT3a has, for instance, been shown to have a critical function in the molecular signaling cascades that underlie synaptic plasticity and memory formation (Levenson et al. 2006; Feng et al. 2010). Moreover, it has been reported that LTP-inducing stimulation in vitro and fear conditioning training in vivo induce rapid methylation changes in the promoter regions of specific plasticity regulated genes such as protein phosphatase 1, brain-derived neurotrophic factor, and reelin (Martinowich et al. 2003; Miller and Sweatt 2007; Lubin et al. 2008). Importantly, pharmacological disruption of Ca^{2+} signaling via NMDARs or of DNMTs was observed not only to compromise the induction of LTP and the consolidation of long-term memory but also to block stimulus-induced methylation changes (Levenson et al. 2006; Miller and Sweatt 2007; Lubin et al. 2008; Miller et al. 2008, 2010). In combination with the recent identification of growth arrest and DNA damage inducible protein 45 α (GADD45 α), a putative stress-induced nuclear DNA demethylase (DMTase) reported to relieve gene silencing by erasing methylation marks (Barreto et al. 2007; Rai et al. 2008; Ma et al. 2009), as a target of synaptic activity-dependent nuclear Ca^{2+} /CaM signaling (Zhang et al. 2007a, 2009), these findings suggest that Ca^{2+} may indeed participate in the regulation of DNA methylation. Clearly, much work remains in identifying the particular signaling pathways linking neuronal activity-dependent $[\text{Ca}^{2+}]_i$ increases to dynamic DNA methylation and chromatin remodeling. We nonetheless anticipate that this developing field will yield many exciting and important insights into the mechanisms underlying synapse-to-nucleus communication.

Ca^{2+} REGULATION OF NUCLEAR PORE PERMEABILITY

Next to its function as a second messenger in the governance of neuronal activity-dependent genomic responses, Ca^{2+} entering the nucleus

may have the added function of regulating nuclear permeability to second messengers. Nucleocytoplasmic transport of soluble molecules takes place at the nuclear pore, a large macromolecular complex consisting of eight ion channels and a large central passage (Akey 1989; Otis et al. 2006). Passage of molecules through this complex depends both on size and on the presence or absence of appropriate localization sequences that enable interaction with nuclear importing proteins. Accordingly, molecules larger in size than 40–60 kD need a signaling sequence to cross the nuclear envelope, and molecules smaller than 4–10 kD diffuse freely between cytosol and nucleus. Intermediate-sized molecules (10–40 kD) do not require a targeting signal, although their passage may be regulated at the level of the nuclear pore (reviewed in O'Brien et al. 2007). Two Ca^{2+} -dependent mechanisms have been proposed for such regulation. On one hand, the filling state of the nuclear lumen, which is contiguous with the ER lumen, may influence the size of the nuclear pore. Accordingly, depletion of nuclear Ca^{2+} stores in a variety of cell types has been shown to induce a conformational change of the nuclear pore complex such that it excludes molecules greater in size than approximately 10 kD (Greber and Gerace 1995; Stehno-Bittel et al. 1995; Perez-Terzic et al. 1999; Wang and Clapham 1999; Erickson et al. 2006; Stoffler et al. 2006). Alternately, a recent study suggests that Ca^{2+} may alter nuclear permeability cytoplasmically: stimulation of $\text{G}_{q/11}$ -coupled receptors and subsequent internal Ca^{2+} release were shown to rapidly and briefly increase nuclear permeability in a liver cell line (O'Brien et al. 2007). Interestingly, this increase in permeability—for which an increase in $[\text{Ca}^{2+}]_i$ near the nuclear envelope was both necessary and sufficient—was unidirectional from cytosol to nucleus. These findings raise the very intriguing possibility that, in addition to regulating genomic responsiveness via interactions with nuclearly localized effectors, somatonuclear Ca^{2+} signals may simultaneously promote the facilitated diffusion of second messengers into the nucleus.

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GENERATING NUCLEAR Ca^{2+} SIGNALS

With respect to the generation of nuclear Ca^{2+} signals, it is important to note that the nuclear envelope does not present a spatial barrier for the transmission of Ca^{2+} transients between somatic and nuclear compartments (Danker et al. 2001; Shahin et al. 2001; Eder and Bading 2007). Cytoplasmic $[\text{Ca}^{2+}]_i$ increases that reach the nuclear envelope are thus poised to participate in nuclear Ca^{2+} -dependent transcriptional regulation. Likely the most obvious candidates for generating robust nuclear Ca^{2+} signals are L-type VDCCs (Fig. 3B). In fact, somatic action potentials, which generate robust L-type VDCC-mediated Ca^{2+} transients in the cytoplasm and nucleus (Johanning and Holthoff 2007), have been reported to induce CREB phosphorylation, CREB-dependent up-regulated gene expression, and transcription-dependent synaptic plasticity (Dudek and Fields 2002). Investigations aimed at identifying specific Ca^{2+} sources involved in the induction of synaptic plasticity also point to L-type VDCCs and somatic Ca^{2+} increases specifically as critical mediators of transcription-dependent plasticity (Raymond and Redman 2002, 2006). By way of their subcellular localization on neuronal somata and proximal dendrites, these channels are appropriately positioned to generate robust somato-nuclear $[\text{Ca}^{2+}]_i$ increases in response to neuronal activity-dependent depolarizations of the plasma membrane (Westenbroek et al. 1990; Obermair et al. 2004; Leitch et al. 2009). Interestingly, the activation kinetics of L-type channels has been suggested to enable their preferred responsiveness to trains of EPSPs over action potentials (Mermelstein et al. 2000; Liu et al. 2003). This proposed ability of L-type VDCCs to discriminate between different forms of depolarizing stimuli could explain why synaptic activity has been observed to be more effective in causing Ca^{2+} -dependent CREB phosphorylation than action potentials alone (Deisseroth et al. 1996; Mermelstein et al. 2000), and suggests that L-type channels on the somatic membrane might contribute to synapse-to-nucleus communication in the form

of a synaptic activity-dependent nuclear Ca^{2+} signal.

Another particularly interesting candidate for the Ca^{2+} -dependent conveyance of information between synapse and nucleus is mGluR-mediated, IP_3R -dependent Ca^{2+} release from intracellular stores (Fig. 3C). IP_3R -dependent internal Ca^{2+} release has been implicated in CREB-mediated gene transcription (Hardingham et al. 2001b; Hu et al. 2002; Carrasco et al. 2004; Mao et al. 2008) as well as in the long-term potentiation and depression of synaptic strength, the stimulation of neurite outgrowth, and the activation of trophic and apoptotic signaling cascades (Berridge 1998; Verkhratsky and Petersen 1998; Korkotian and Segal 1999; Yeckel et al. 1999; Berridge et al. 2000; Rose and Konnerth 2001; Vanderklish and Edelman 2002; Raymond and Redman 2006). Neuronal $[\text{Ca}^{2+}]_i$ increases caused by the release of Ca^{2+} from IP_3 -sensitive intracellular stores are unique when compared to $[\text{Ca}^{2+}]_i$ increases generated by VDCC- or NMDAR-dependent Ca^{2+} influx in a number of important ways. Perhaps the most notable of these is the ability of internal Ca^{2+} release to propagate as a wave from its dendritic site of initiation to distant regions of the neuron including the soma and nucleus (Jaffe and Brown 1994; Pozzo-Miller et al. 1996; Power and Sah 2002, 2007; Larkum et al. 2003; Watanabe et al. 2006; Hagenston et al. 2008). These waves of Ca^{2+} release are predominantly observed in the primary apical dendrites of pyramidal neurons, in which they regularly cover distances upward of 50 μm (Nakamura et al. 1999, 2002; Power and Sah 2007; Hagenston et al. 2008). In contrast, $[\text{Ca}^{2+}]_i$ increases resulting from NMDAR activation are predominantly observed in highly spinous apical oblique and basal dendrites, and are almost negligible in the primary apical dendrite or soma (Schiller et al. 2000; Nakamura et al. 2002; Raymond and Redman 2006). Moreover, Ca^{2+} waves can regularly attain amplitudes of up to 10 μM , approximately 5- to 15-fold greater than $[\text{Ca}^{2+}]_i$ increases evoked by trains of action potentials (Nakamura et al. 1999; Power and Sah 2002, 2007; Larkum et al. 2003). Additionally,

whereas VGCC- and NMDAR-associated $[\text{Ca}^{2+}]_i$ increases turn on at the start of a stimulus or spike train and typically begin to decay at the end of that train (Pozzo-Miller et al. 1996), the rising phase of synaptically activated Ca^{2+} release generally initiates with a delay of tens to hundreds of milliseconds, can easily outlast the duration of synaptic stimulation, and may even be as great as hundreds of milliseconds in any one location (Pozzo-Miller et al. 1996; Kapur et al. 2001; Larkum et al. 2003; Power and Sah 2007). The decay of release-associated $[\text{Ca}^{2+}]_i$ transients is similarly prolonged, presumably because of the slow inactivation kinetics of the IP_3 receptor (Li et al. 1995; Taylor 1998; Foskett et al. 2007). Thus, the total duration of internal Ca^{2+} release-associated $[\text{Ca}^{2+}]_i$ increases is typically on the order of hundreds of milliseconds to longer than one second (Nakamura et al. 1999; Larkum et al. 2003). In sum, mGluR-mediated IP_3 -dependent Ca^{2+} waves have the combined characteristics of large amplitude, long duration, and ability to propagate long distances along the primary apical dendrite into the soma and nucleus. These features make Ca^{2+} waves ideally suited to evoke large, long-lasting nuclear Ca^{2+} signals and robust transcriptional responses in response to synaptic activity (Chawla and Bading 2001; Power and Sah 2002, 2007; Hagenston et al. 2008).

Under what conditions are Ca^{2+} waves likely to play a role in nuclear Ca^{2+} signaling? Investigations of IP_3 R function in reduced cellular and bilayer preparations, modeling studies, and examinations of Ca^{2+} waves in nonneuronal cells describe a number of possible influences on the extent of Ca^{2+} wave propagation (e.g., Parker and Ivorra 1990; Bezprozvanny et al. 1991; Bootman et al. 1997; Callamaras et al. 1998; Verkhratsky and Petersen 1998; Solovyova and Verkhratsky 2002; Friel 2004; Foskett et al. 2007). These include $[\text{Ca}^{2+}]_i$ at the time of IP_3 R activation by IP_3 , the concentration and distribution of mobilized IP_3 in the cytosol, the size of the readily releasable ER Ca^{2+} pool, and the biophysical state of IP_3 Rs. These potential influences translate into a number of different factors likely to regulate the propagation of

mGluR-mediated, IP_3 -dependent Ca^{2+} waves toward and into the somata of neurons, many of which have been validated by Ca^{2+} imaging data in neurons. These factors include the generation of action potentials and VDCC-dependent $[\text{Ca}^{2+}]_i$ increases coincident with IP_3 -mobilizing stimuli (Nakamura et al. 1999; Yamamoto et al. 2000; Larkum et al. 2003; Hagenston et al. 2008), the number and distribution of activated synapses and the activity of neuromodulatory G protein-coupled receptors linked to IP_3 generation (Lezcano and Bergson 2002; Nakamura et al. 2002; Tang et al. 2003; Watanabe et al. 2006; Dai et al. 2008; Hagenston et al. 2008; Fitzpatrick et al. 2009), the activity history of stimulated neurons (Jaffe and Brown 1994; Pozzo-Miller et al. 1996; Morikawa et al. 2000; Rae et al. 2000; Larkum et al. 2003; Stutzmann et al. 2003; Gullledge and Stuart 2005; Power and Sah 2005; Hong and Ross 2007; Hagenston et al. 2008), and the balance of activated kinases and phosphatases that target the IP_3 R. Protein kinase A in particular is promising in this respect, as its activity is linked not only to IP_3 R phosphorylation, but also to increased IP_3 R sensitivity to IP_3 and to augmented internal Ca^{2+} release (Wojcikiewicz and Luo 1998; Bugrim 1999; Tang et al. 2003; Patterson et al. 2004; Straub et al. 2004; Bezprozvanny 2005; Foskett et al. 2007; AM Hagenston and M Yeckel, unpubl.). Following from these studies, we predict that IP_3 -dependent Ca^{2+} waves are most likely to contribute to nuclear Ca^{2+} signaling when elicited by the robust and simultaneous activation of synapses on many proximal apical oblique branches during and/or following a train of action potentials, and particularly when protein kinase A signaling to IP_3 Rs has been engaged.

An additional mechanism has recently emerged by which synaptic activity may give rise to nuclear $[\text{Ca}^{2+}]_i$ increases. This means of synapse-to-nucleus communication involves the import of glutamate through excitatory amino acid transporters (EAATs) and the subsequent activation of mGluRs located on the inner nuclear membrane (Fig. 1) (O'Malley et al. 2003; Jong et al. 2005, 2007; Sheldon and Robinson 2007; Kumar et al. 2008). More

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specifically, synaptically released glutamate is proposed to be transported by extra- and perisynaptic EAATs into the cytosol and diffuse to the cell soma, in which it is transported by nuclear EAATs into the nuclear lumen. There it binds to and activates nuclear resident mGluRs, leading to the liberation of IP₃ into the nucleus where it can bind IP₃Rs on the inner nuclear envelope. Thus, glutamate uptake at the synapse is proposed to give rise to Ca²⁺ release from the nuclear lumen directly into the nucleus (O'Malley et al. 2003; Jong et al. 2005, 2007; Sheldon and Robinson 2007; Kumar et al. 2008). This model is bolstered by data documenting the presence and functional responsiveness of EAATs, mGluRs, and IP₃Rs on the inner nuclear membranes of a variety of cell types including dissociated neurons (Humbert et al. 1996; Echevarria et al. 2003; Gerasimenko et al. 2003; O'Malley et al. 2003; Jong et al. 2005, 2007; Marchenko et al. 2005; Quesada and Verdugo 2005; Marchenko and Thomas 2006; Sheldon and Robinson 2007; Kumar et al. 2008; Bootman et al. 2009; Rodrigues et al. 2009). It remains to be seen, however, whether and under which conditions internal Ca²⁺ release mediated by intranuclear mGluRs and IP₃Rs can be evoked in intact brain tissue. One possibility is that particularly robust stimulus trains such as those known to induce LTP lead to spillover of glutamate, which is then taken up by perisynaptic and extrasynaptic EAATs and shuttled to the nucleus. Subsequent intranuclear Ca²⁺ release might act to ensure the generation of a Ca²⁺ signal concomitant with the import of synaptically activated second messengers. As such, this pathway could support NMDAR- and Ras/MAPK-mediated stimulation of CREB-dependent transcription, synaptic plasticity, and neuronal activity-dependent neuroprotection. Alternatively, this proposed signaling pathway to the nucleus might be most robustly induced when extrasynaptic glutamatergic signaling is elevated. As such, it could contribute to the genomic responses and prodeath activity associated with ES-NMDAR activation, ischemia, and seizure (Hardingham et al. 2002; Liu et al. 2007; Sierra-Paredes and Sierra-Marcuno 2007; Zhang et al.

2007b; Leveille et al. 2008; Scimemi et al. 2009; Wahl et al. 2009).

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ER in neurons, the “neuron within a neuron,” forms a continuous network that extends into all parts of the cell from the nuclear envelope to the most distal dendritic and axonal processes (Berridge 1998). In addition to enabling the propagation of Ca²⁺ waves over long distances in the dendrites and soma, this ubiquitous distribution of ER may allow for postsynaptic signal propagation either via the diffusion of second messengers embedded in or attached to its membranes (Jordan and Kreutz 2009) or in the form of rapid intraluminal Ca²⁺ redistributions within and between dendritic and somatonuclear compartments (Park et al. 2000, 2008; Choi et al. 2006). This latter transit system, which is called Ca²⁺ tunneling, has been credited with the ability of dendrites and spines sparse in ER to persistently respond to repetitive Ca²⁺ mobilizing inputs (Park et al. 2000; Choi et al. 2006). Conversely, ER Ca²⁺ tunneling is suggested to result in depletion of the somatonuclear internal store following strong and long-lasting stimulation of Ca²⁺ release in multiple dendritic compartments (Choi et al. 2006; Park et al. 2008). In view of the influence exerted by luminal Ca²⁺ on nuclear pore permeability (Greber and Gerace 1995; Stehno-Bittel et al. 1995; Lee et al. 1998; Danker et al. 2001), IP₃R activity (Missiaen et al. 1992; Bezprozvanny and Ehrlich 1994; Thrower et al. 2000), and the driving force of Ca²⁺ ions leaving the ER (e.g., Solovyova et al. 2002), and of the potential for somatonuclear internal Ca²⁺ release to regulate CaMKIV activity and nuclear pore permeability, such a signal could have important consequences for the regulation of gene expression programs.

A recent study introduces another particularly intriguing ER-dependent mechanism by which signals may be transmitted from synapse to nucleus: as passively propagating electrotonic potentials along ER membranes (Fig. 3D) (Shemer et al. 2008). This proposal is grounded

on the basis that, like the plasma membrane, the ER membrane is an effective charge separator and may thus support the generation and propagation of trans-ER depolarizations and hyperpolarizations. Such potential fluctuations are likely to occur at ER in synaptic spines and dendrites either as a result of capacitive conduction of plasma membrane potential fluctuations combined with Ca^{2+} uptake into the ER via sarcoendoplasmic reticulum Ca^{2+} ATPases, or as a consequence of the release of Ca^{2+} via RyRs and IP_3 Rs localized to spines and dendrites. Alternately, ER potentials may be evoked in the soma during action potentials and in response to internal Ca^{2+} release. Using a computational “cable in cable” model, it was shown that electrotonic potentials across the ER—and associated current flow within the ER—can be rapidly and effectively transmitted both from synapse to soma, and from the soma into the dendritic arbor (Shemer et al. 2008). Significantly, the investigators observe that these two modes of signal propagation have opposite effects on the transmembrane potential across the nuclear envelope and suggest on this basis that electrotonic signal propagation along ER membranes may account for the ability of the nucleus to differentiate between synaptic signals originating at dendritic spines and backpropagating action potentials generated in the soma (Shemer et al. 2008). That said, it remains to be determined what the specific consequences of nuclear envelope depolarizations or hyperpolarizations might be. One possible scenario involves the activation of putative intracellular voltage-dependent cation channels (Schmid et al. 1990; Martin and Ashley 1993; Mazzanti et al. 2001; Bkaily et al. 2009; Matzke et al. 2010). Alternatively, nuclear envelope depolarizations may regulate signaling proteins that have been proposed to lead to intranuclear IP_3 mobilization (Billups et al. 2006; Ryglewski et al. 2007; Bootman et al. 2009; Liu et al. 2009; see above). Among other possibilities, changes in nuclear potential might also modulate nuclear pore permeability (Matzke and Matzke 1991; Mazzanti et al. 2001; Matzke et al. 2010). Although these possible consequences of a changing nuclear potential remain

to be tested, their potential to influence nuclear Ca^{2+} signaling and neuronal activity-dependent gene transcription nonetheless makes the conduction and summation of electrotonic potentials along ER and nuclear membranes a compelling prospective route for synapse-to-nucleus communication.

CONCLUDING REMARKS

We have attempted here to provide a brief overview of the means by which synaptic excitation may be conveyed to the nucleus to influence neuronal activity-dependent gene transcription, particularly as it relates to synaptic plasticity, learning and memory, and neuronal survival and death processes. Just as the findings we describe inform our understanding of basic neuronal functions and functional responses, so too do they serve the greater aims of neuroscience and cellular signaling research to unravel the causes of neurocognitive disorders and to provide direction for the eventual development of possible therapeutic interventions. Indeed, dysregulations of the many of the proteins and processes involved in the generation of neuronal activity-dependent genomic responses we have described here have already been implicated in a wide range of psychiatric, developmental, and neurodegenerative disorders, including schizophrenia, depression, drug addiction, Rett syndrome, fragile X mental retardation, Alzheimer’s disease, Huntington’s disease, and ischemic stroke (Hong et al. 2005; Tsankova et al. 2007; Abel and Zukin 2008; Cohen and Greenberg 2008; Graff and Mansuy 2009; Kramer and van Bokhoven 2009; Reichenberg et al. 2009). Given the importance of nuclear calcium for the health of neurons and their ability to undergo activity-induced adaptations, a dysfunction in the generation of calcium transients and/or propagation to the nucleus (termed “nuclear calciopathy”; Zhang et al. 2011) may be a common denominator of both cognitive impairments and neurodegenerative processes. Thus, just as we are motivated to continue developing a more complete understanding of intracellular Ca^{2+} signaling and its role in the dialog between synapse and nucleus,

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so too can we be driven by the knowledge that our findings may lead the way to an improved understanding of those changes responsible for the altered emotional and conceptual responses that define mental illness, the impaired learning and memory that accompanies developmental cognitive disorders, and the cell death associated with neurodegenerative diseases.

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