Biological Psychiatry: Celebrating 50 Years

Synapse-to-Nucleus Signaling in Neurodegenerative and Neuropsychiatric Disorders

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ABSTRACT

Synapse-to-nucleus signaling is critical for converting signals received at synapses into transcriptional programs essential for cognition, memory, and emotion. This neuronal mechanism usually involves activity-dependent translocation of synaptonuclear factors from synapses to the nucleus resulting in regulation of transcriptional programs underlying synaptic plasticity. Acting as synapse-to-nucleus messengers, amyloid precursor protein intracellular domain associated-1 protein, cAMP response element binding protein (CREB)-regulated transcription coactivator-1, Jacob, nuclear factor kappa-light-chain-enhancer of activated B cells, RING finger protein 10, and SH3 and multiple ankyrin repeat domains 3 play essential roles in synapse remodeling and plasticity, which are considered the cellular basis of memory. Other synaptic proteins, such as extracellular signal-regulated kinase, calcium/calmodulin-dependent protein kinase II gamma, and CREB2, translocate from dendrites or cytosol to the nucleus upon synaptic activity, suggesting that they could contribute to synapse-to-nucleus signaling. Notably, some synaptonuclear factors converge on the transcription factor CREB, indicating that CREB signaling is a key hub mediating integration of synaptic signals into transcriptional programs required for neuronal function and plasticity. Although major efforts have been focused on identification and regulatory mechanisms of synaptonuclear factors, the relevance of synapse-to-nucleus communication in brain physiology and pathology is still unclear. Recent evidence, however, indicates that synaptonuclear factors are implicated in neuropsychiatric, neurodevelopmental, and neurodegenerative disorders, suggesting that uncoupling synaptic activity from nuclear signaling may prompt synapse pathology, contributing to a broad spectrum of brain disorders. This review summarizes current knowledge of synapse-to-nucleus signaling in neuron survival, synaptic function and plasticity, and memory. Finally, we discuss how altered synapse-to-nucleus signaling may lead to memory and emotional disturbances, which is relevant for clinical and therapeutic strategies in neurodegenerative and neuropsychiatric diseases.

Keywords: Alzheimer's disease, Dementia, Gene expression, Memory, Mental disorders, Neurodegeneration, Synapse

https://doi.org/10.1016/j.biopsych.2019.01.006

The most prominent feature of the brain is the ability to sense, adapt, and respond to external stimuli and internal body changes. A century ago, Ramón y Cajal (1) postulated that the brain's adaptability to experiences and daily activities depends on the strength of and modifications in neuronal connections and that these changes could contribute to mental and memory processes. This view was extended by Hebb (2), who proposed that changes in synaptic efficacy could mediate memory storage. At the present time, structural and functional synapse remodeling is considered a dynamic process regulated by synapse-to-nucleus communication, which underlies a wide range of brain processes, including synaptic plasticity and memory (3). Thus, synapse-to-nucleus signaling is essential for converting signals received at synapses into transcriptional programs mediating synapse function and plasticity. This mechanism involves local activation of synaptic *N*-methyl-D-aspartate receptors (NMDARs), calcium influx, and nuclear translocation from dendrites or synapses of synaptonuclear factors (e.g., amyloid precursor protein intracellular domain associated-1 protein [AIDA-1], CREB-regulated transcription coactivator-1 [CRTC1], extracellular signal-regulated kinase [ERK], Jacob, nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB], RING finger protein 10 [RNF10], and SH3 and multiple ankyrin repeat domains 3 [Shank3]) (Figure 1). Nuclear translocation of these factors is a rapid process that occurs within minutes and seems to be mediated by nuclear localization signal sequences contained in these proteins (4). Despite the enormous progress that has been made toward understanding the biology and regulatory mechanisms of synaptonuclear factors [for recent reviews, see (5,6)], the relevance of synapse-to-nucleus signaling in brain pathologies remains largely unknown. Remarkably, dysfunction and genetic mutations of synaptonuclear factors have been recently associated with a number of neurodevelopmental, psychiatric, and neurodegenerative disorders (Table 1). Specifically, dysfunction of

ISSN: 0006-3223

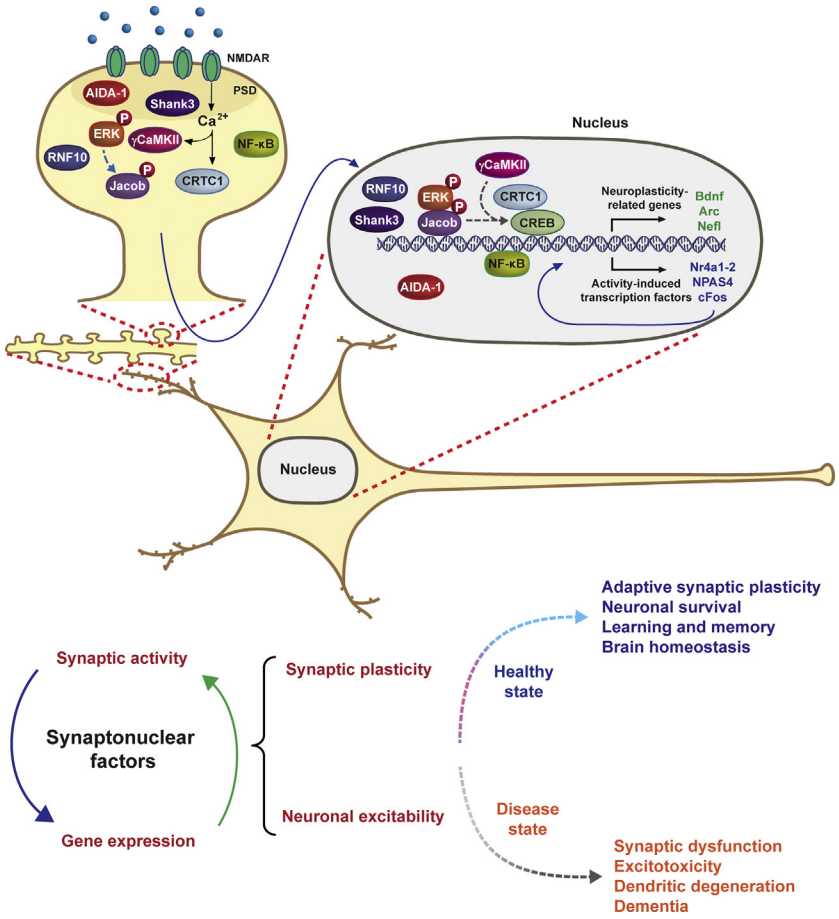

Figure 1. Synapse-to-nucleus signaling regulates neuronal excitability and synapse plasticity. (Top panel) Several synaptic factors (e.g., CREB-regulated transcription coactivator-1 [CRTC1], extracellular signal-regulated kinase [ERK], Jacob, nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB], RING finger protein 10 [RNF10], SH3 and multiple ankyrin repeat domains 3 [Shank3], calcium/calmodulin-dependent protein kinase II gamma [γCaMKII]) are activated by synaptic activity at distal dendrites, including synapses, and translocate to the nucleus to regulate cAMP-response element binding protein (CREB)-mediated transcription. By contrast, activity-dependent synapse-to-nucleus amyloid precursor protein intracellular domain associated-1 protein (AIDA-1) translocation does not affect CREB-mediated transcription. Blue lines indicate signals traveling from dendritic spines or dendrites to the nucleus to regulate gene expression. (Bottom panel) Synaptonuclear factors regulate synaptic plasticity and neuronal excitability by affecting synaptic activity and gene expression. Imbalance of synaptic plasticity and neuronal excitability can affect health and disease states. Some brain physiological and pathological states that are directly or indirectly regulated by synapse-to-nucleus signaling are indicated on the right. NMDAR, *N*-methyl-D-aspartate receptor; P, phosphorylation; PSD, postsynaptic density region.

synaptonuclear factors occurs in neurodegenerative diseases, and genetic mutations in some of these factors are associated with cognitive and mental disorders, including autism, intellectual disability, and schizophrenia. Although the current picture suggests that uncoupling synaptic activity from nuclear signaling may prompt synapse pathology in a broad spectrum of brain disorders, the significance of synapse-to-nucleus signaling to brain function and dysfunction is still largely unclear. In this review, we summarize recent evidence indicating that synapse-to-nucleus signaling plays a role in synapse function and plasticity and describe how its deregulation may lead to cognitive and emotional alterations in neurodegenerative and neuropsychiatric disorders.

SYNAPSE-TO-NUCLEUS SIGNALING IN NEURODEGENERATIVE AND DEMENTIA DISEASES

CRTC1 Synapse-to-Nucleus Signaling

CRTC1 is a critical modulator of cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) transcriptional activity in the brain (7). Synaptic and neuronal activities promote CRTC1 translocation from synapses and dendrites to the nucleus, a process that requires dephosphorylation of CRTC1 triggered by NMDARs and L-type voltage-gated calcium channels (8). Activity-dependent synaptonuclear translocation of CRTC1 is a rapid process (approximately 1–2 minutes) mediated by dynein, as revealed by imaging analysis using photoconvertible fluorescent CRTC1 and uncaged synaptic glutamate (9). Synaptic potentiation stimuli and memory training also trigger CRTC1 nuclear translocation and CREB-dependent gene transcription (8,10,11). Neuronal activity and associative learning promotes recruitment of a CREB/CREB binding protein/CRTC1 complex to cAMP-response element–containing promoters that together with histone acetylation induce transcription of CREB target neuroplasticity genes (e.g., brain-derived neurotrophic factor *[Bdnf]*, *Fos*, *Fgf1*, *Zif268/Egr1*, *Arc*, *Nr4a1*, *Nr4a2*) (10,12,13). CRTC nuclear translocation cooperates with histone acetylation to regulate gene expression programs mediating formation, maintenance, and extinction of memory (14,15). In agreement, CRTC1 is required for hippocampus-dependent synaptic plasticity and memory in mammals (10–12,16,17). This evidence indicates that by regulating synapse-to-nucleus signaling, CRTC1 may be crucial for transforming synaptic activity signals into gene programs essential for long-term synaptic plasticity and memory.

Recent evidence indicates that CRTC1/CREB signaling plays a role in several neurodegenerative diseases. In Alzheimer's disease, CRTC1 promoter methylation correlates

Table 1. Synaptonuclear Factors and Associated Brain Physiological and Pathological Functions

Synaptonuclear Factor	Activation Mechanism	Downstream Targets	Physiological Functions	Related Pathologies	References
ANKS1B/AIDA-1	NMDAR, CaMKII	Protein synthesis	Synaptic plasticity, regulation of nucleolar number	Schizophrenia, ASD, Alzheimer's disease	(46,47,57)
γCaMKII	Calmodulin	CREB target genes	Synaptic plasticity, learning and memory	Intellectual disability	(83,85)
CRTC1	Calcineurin/PP2B	CREB target genes (*BDNF*, *FOS*, *NR4A1/2*)	Synaptic plasticity, learning and memory, neuronal survival	Alzheimer's disease, neurodegeneration, mood and affective disorders	(10,19,29–31)
ERK	NMDAR	CREB target genes	Synaptic plasticity	Mood disorders, neurodegeneration	(103,104)
Jacob	ERK	CREB target genes	Synaptic plasticity, dendritic morphology, learning and memory	Kallmann syndrome, Alzheimer's disease	(38–40)
NF-κB	NMDAR, CaMKII	*BDNF*, *HTT*, CREB target, independent genes	Synaptic plasticity, learning and memory, neuronal survival	Huntington's disease, Alzheimer's disease	(42,44,45)
RNF10	NMDAR	*MMP-9*, *ARHGEF6*, *ARHGAP4*, *OPHN1*	Synapse morphology	Fragile X syndrome	(58)
Shank3	NMDAR	CREB target genes	Synapse morphology, excitatory/inhibitory balance	ASD, intellectual disability, schizophrenia, Phelan-McDermid syndrome	(67,73,74)
CREB2/ATF4	Importin-α, NMDA/LTD	CREB target genes	Synaptic plasticity	Alzheimer's disease, Parkinson's disease	(79,80,82)

AIDA-1, amyloid precursor protein intracellular domain associated-1 protein; ANKS1B, ankyrin repeat and sterile alpha motif domain containing 1B; ASD, autism spectrum disorder; ATF4, activating transcription factor 4; cAMP, cyclic adenosine monophosphate; CREB, cAMP-response element binding protein; CRTC1, CREB-regulated transcription coactivator-1; γCaMKII, calcium/calmodulin-dependent protein kinase II gamma; *HTT,* huntingtin; LTD, long-term depression; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMDAR, *N*-methyl-D-aspartate receptor; PP2B, protein phosphatase-2B; RNF10, RING finger protein 10; Shank3, SH3 and multiple ankyrin repeat domains 3.

inversely with phosphorylated tau suggesting a link between pathological changes and downregulation of CRTC1 during progression of the disease (18,19). Impaired CRTC1 activation and dendrite-to-nucleus translocation in the hippocampus is associated with early intracellular Aβ accumulation and memory deficits in Alzheimer's disease and/or neurodegeneration mouse models (10,19–21). These results are in agreement with deregulation of CRTC1/CREB signaling at moderate Alzheimer's disease pathological stages (19). Notably, the CRTC1 target gene Nurr1 (*Nr4a2*) regulates negatively amyloid accumulation and neurodegeneration in Alzheimer's disease transgenic mice, which suggests that CRTC1 signaling modulates Alzheimer's disease pathology (22). In Parkinson's disease, CRTC1 function seems to be reduced as revealed by low levels of active phosphorylated CRTC1 (Ser215) in the substantia nigra of patients and 6-hydroxydopamine and α-synuclein rat models (23). CRTC1 mediates protection against neurodegeneration by activating CREB target genes (*Bcl-2*, *Bdnf*, and *Pgc-1α*) in Parkinson's disease animal models (23). CRTC1 levels are also reduced in the striatum of patients with Huntington's disease, likely contributing to neurodegeneration caused by trophic factor deficits (e.g., BDNF) (24,25). In agreement, CRTC1 inactivation results in neurodegeneration in mutant huntingtin (*Htt*) transgenic mice, whereas its overexpression protects against mitochondrial toxicity (25). Interestingly, long-term memory deficits are associated with reduced levels of hippocampal CRTC1/CREB binding protein/CREB target genes in Huntington's disease mice (26). Whether CRTC1 deregulation causes synapse dysfunction, or, alternatively, altered CRTC1 synapse-to-nucleus signaling is a consequence of synapse dysfunction or loss in these diseases is still unclear. Deregulation of CRTC1/CREB-mediated transcription is a common pathological mechanism in neurodegeneration, but the significance of CRTC1 synapse-to-nucleus signaling in neurodegenerative diseases requires further investigation.

Psychiatric alterations caused by changes in the brain reward circuitry are postulated to underlie mood disorders, including depression, anxiety, and addiction (27). In agreement with the established role of CREB and BDNF in depression (28), CRTC1-deficient mice develop depressive-like symptoms associated with reduced CREB-target neuroplasticity genes (e.g., BDNF) in the frontal cortex (29). Antidepressant pharmacological treatments ameliorate depressive-like symptoms by increasing CRTC1 nuclear translocation and BDNF levels in the cortex and hippocampus (30–32). Interestingly, CRTC1 mutant mice show reduced cortical levels of agmatinase, an enzyme that is reduced in postmortem brain of patients with depression (31). Acute agmatine or ketamine treatments improved depressive-like symptoms in this mutant mouse model suggesting a causal role of the agmatinergic system in CRTC1-dependent regulation of depression (31). The association of CRTC1 polymorphisms with major depressive disorders further supports a role of CRTC1 in mood disorders (33). Moreover, CRTC1 protects against cocaine consumption in a rat model of addiction (34). In summary, CRTC1-dependent transcription regulates memory, mood, and reward circuits, but the role of CRTC1 synapse-to-nucleus signaling in neurodegeneration, dementia, and psychiatric disorders still merits further investigation.

Jacob Synapse-to-Nucleus Signaling

Jacob is encoded by the *NSMF* gene. Jacob, first identified as a binding protein of the postsynaptic calcium sensor caldendrin, translocates to the nucleus by a mechanism involving both synaptic and extrasynaptic GluN2B-containing NMDARs (35). Synaptic NMDAR activation and subsequent sustained calcium levels induce ERK-mediated Jacob phosphorylation (Ser180) and nuclear translocation (35,36). Advanced imaging analysis using photoconvertible Jacob constructs demonstrated that synaptic activation induces rapid (5–15 minutes) trafficking of Jacob from distal dendrites, including synapses, to the nucleus (36). Similarly, NMDAR-dependent long-term potentiation, but not long-term depression, increases Jacob phosphorylation and nuclear import. Phosphorylated Jacob promotes CREB signaling and transcription of neuroplasticity genes resulting in enhanced synaptic strength, whereas its inactivation impairs CREB signaling (36,37). Consistent with the role of Jacob in synapse-to-nucleus signaling in synaptic plasticity and memory, genetic inactivation of Jacob impairs CREB signaling, reduces the number of synapses, and causes hippocampal-dependent synaptic plasticity and memory deficits in mice (38).

Alternatively, extrasynaptic NMDARs induce Jacob nuclear import independently of Ser180 phosphorylation, reduce CREB phosphorylation and synapse and dendritic complexity, and elicit neuron death (35). Nuclear phosphorylated Jacob, however, potentiates CREB phosphorylation and prevents extrasynaptic NMDA-induced synapse loss and neuron death (35,36). Other pathogenic agents that induce accumulation of Jacob into the nucleus (e.g., amyloid-β [Aβ] oligomers) impair hippocampal synaptic transmission and plasticity (39). These results elegantly demonstrate that the phosphorylation state of a synaptonuclear factor may determine its function as cell survival or death factor. Interestingly, mutations in *NSMF* are linked to Kallmann syndrome, a disease of idiopathic hypogonadotropic hypogonadism with anosmia or hyposmia (40). Jacob, whether its function is dependent or independent of synapse-to-nucleus signaling, is critical for synaptic efficacy and plasticity and neuron survival.

NF-κB Synapse-to-Nucleus Signaling

The transcription factor NF-κB is present as p65/p50 heterodimers in postsynaptic compartments, where it is activated and transported to the nucleus (41–43). Fluorescence recovery after photobleaching assays showed basal and rapid (<1 minute) NMDA-mediated and depolarization-mediated disappearance of dendritic/synaptic NF-κB resulting in its translocation to the nucleus (41,42). Interestingly, activity-dependent synaptonuclear NF-κB trafficking is mediated by huntingtin/importin-α2 and impaired by a pathogenic *Htt* mutation, suggesting that altered synaptonuclear NF-κB trafficking may contribute to Huntington's disease (42). It is surprising that *Htt* is an NF-κB target gene and that a single nucleotide polymorphism (SNP) in the human *HTT* gene promoter impairs NF-κB binding affecting its expression and the age of disease onset (44). Despite this evidence suggesting a clear association between *Htt* dysfunction and altered synaptonuclear NF-κB signaling, further studies are needed to elucidate the specific role of synaptic NF-κB in Huntington's disease pathology. Notably, NF-κB has been extensively involved in neuron death and memory deficits in several neurodegenerative diseases through regulation of a subset of target genes that are also regulated by CREB (e.g., *BDNF*), suggesting transcriptional convergence of both factors (45). The role of synaptonuclear NF-κB signaling in these pathological conditions warrants further investigation.

SYNAPSE-TO-NUCLEUS SIGNALING IN NEUROPSYCHIATRIC AND MENTAL DISORDERS

ANKS1B/AIDA-1 Synapse-to-Nucleus Signaling

Ankyrin repeat and sterile alpha motif domain containing 1B (ANKS1B), also known as AIDA-1, is a postsynaptic density protein 95/NMDAR binding protein required for NMDAR-mediated synaptic transmission and plasticity (46). In turn, synaptic NMDAR activation results in dendrite-to-nucleus translocation of ANKS1B/AIDA-1, which increases nucleoli number and protein synthesis (47). Thus, in contrast to most synaptonuclear factors that regulate gene expression by modulating CREB-dependent transcription, ANKS1B/AIDA-1 synapse-to-nucleus signaling seems to enable protein synthesis triggered by synaptic activity independently of CREB. Additional insights on ANKS1B/AIDA-1 synaptic function come from analysis of mutant mice. Genetic inactivation of *Anks1b* in mice results in deficits in hippocampal-dependent synaptic transmission and plasticity deficits and prepulse inhibition and increased locomotor activity and stereotypies (46,48).

The physiological and behavioral alterations of *Anks1b* mutant mice are consistent with the association of ANKS1B with human neuropsychiatric disorders. Genome-wide studies have revealed genetic variants in ANKS1B associated with bipolar disorder, pediatric obsessive-compulsive disorder, and antipsychotic treatment response (49–51). Rare copy number variants and SNPs in the *ANKS1B* gene are also found in autism spectrum disorder (ASD) (52,53). ANKS1A and ANKS1B variants have been suggested as risk factor alleles for schizophrenia (54,55). Furthermore, a recent study suggested that ANKS1B is a candidate risk gene for late-onset Alzheimer's disease (56), and AIDA-1 inhibits Aβ generation by modulating γ-secretase-mediated amyloid precursor protein processing (57). Together, these studies indicate an association of ANKS1B/AIDA-1 gene variants with mental and psychiatric disorders. Molecular characterization of *Anks1b* mutant mice may shed light on the mechanisms and significance of AIDA-1 synapse-to-nucleus signaling in neuropsychiatric disorders.

RNF10 Synapse-to-Nucleus Signaling

RNF10 is a postsynaptic protein that links glutamate receptor signaling with nuclear gene expression in excitatory neurons of the hippocampus. Upon synaptic NMDAR activation and potentiation stimuli, RNF10 shuttles from dendritic spines to the nucleus in an importin-α1-dependent manner (58). Activity-induced RNF10 synapse-to-nucleus translocation is a rapid process (approximately 15 minutes) that depends on synaptic

GluN1/GluN2A receptors. RNF10 is essential for synaptic plasticity, likely by modulating the expression of genes regulating synaptic function (58). For instance, RNF10 regulates the expression of Rho guanosine triphosphatases (e.g., *ARHGEF6*, *ARHGAP4*, and *OPHN1*) that are localized at the postsynaptic density of excitatory synapses, where they regulate actin cytoskeleton and spine morphology (59). The fact that mice lacking these genes develop deficits in synaptic plasticity and memory is consistent with the idea that synapse dysfunction may lead to cognitive deficits in mental retardation (60,61). Importantly, these genes are mutated in X-linked intellectual disability syndrome (59,62,63), the most common cause of mental retardation and global cognitive and skill deficiencies in childhood. Notably, RNF10 was downregulated in the brain of a mouse model and blood samples of patients with fragile X–associated tremor/ataxia syndrome (64), a neurodegenerative disorder characterized by cognitive and psychiatric symptoms, including anxiety, mood changes, and depression (65). In summary, RNF10 synapse-to-nucleus signaling seems essential for maintaining synapse function and plasticity by regulating expression of synaptic genes involved in mental processes.

Shank3 Synapse-to-Nucleus Signaling

Shank3, also known as proline-rich synapse-associated protein 2, is an abundant synaptic protein that regulates synapse formation, morphology, and function presumably by interacting with postsynaptic density proteins, such as homer, cortactin, dynamin, insulin receptor substrate p53, and Abelson interacting protein 1 (66). A recent study showed that Shank3 undergoes activity-dependent nuclear transport in hippocampal neurons, but specific synapse-to-nucleus trafficking of Shank3 has not been fully confirmed (67). Abelson interacting protein 1 is also translocated to the nucleus on synaptic NMDAR activation, a process that regulates dendrite and synapse morphology (68). These results suggest that nuclear transport of assembled synaptonuclear complexes, such as Shank3/Abelson interacting protein 1, can be relevant in synapse-to-nucleus communication to mediate gene transcription.

In humans, genetic missense, deletion, and duplication mutations in the *SHANK3* gene are linked to ASD, schizophrenia, and Phelan-McDermid syndrome (69). These mutations generally lead to loss of Shank3 function resulting in altered synapse morphology and presynaptic and/or postsynaptic signaling and autistic-like behaviors in animal models (70–72), whereas Shank 3 overexpression leads to manic behavior caused by excitatory/inhibitory imbalance (73). In particular, a schizophrenia-linked mutation that alters the synaptic localization of Shank3 resulting in nuclear localization independent of synaptic activity and deregulates transcription of multiple schizophrenia-related synaptic genes, including synaptotagmin and *LRRTM1*, affects synapse number and function (67). Moreover, Shank3 truncated mutations found in individuals with ASD and intellectual disability accumulate in the nucleus resulting in fewer dendritic spines and dendrites (74). Remarkably, Shank3 regulates ERK and CREB by affecting calcium and metabotropic glutamate receptor 5, suggesting that synaptonuclear signaling mediated by Shank3 is also integrated into CREB-regulated transcription (75,76). Together, these results indicate that uncoupling Shank3/proline-rich synapse-associated protein 2 synapse-to-nucleus signaling may contribute to synaptic dysfunction in intellectual disability in mental disorders.

DENDRITIC/CYTOSOL-TO-NUCLEUS SIGNALING IN NEURODEGENERATIVE AND NEUROPSYCHIATRIC DISEASES

CREB2/ATF4 Dendritic-to-Nucleus Signaling

CREB2/activating transcription factor 4 (ATF4) is a transcriptional repressor that modulates synaptic plasticity and memory (77,78). Live neuron imaging analysis showed that CREB2 shuttles from distal dendrites and cytoplasm to the nucleus of hippocampal neurons in an importin-α-dependent manner (79). Specifically, CREB2 undergoes retrograde translocation from dendrites to the nucleus during NMDA-dependent long-term depression, but not during long-term potentiation, suggesting that activity-dependent CREB2/ATF4 synapse-to-nucleus signaling may be critical for synaptic plasticity and memory (79). Recent studies indicate that ATF4 protein and messenger RNA are more frequently localized in axons of Alzheimer's disease brains. Aβ increases local ATF4 synthesis in axons, whereas inhibition of CREB2/ATF4 axonal retrograde transport abolishes Aβ-induced neurodegeneration (80). Notably, ATF4 is upregulated in the brain of patients with Alzheimer's disease and in mouse models expressing the apolipoprotein E ε4 alleles, the most prevalent gene risk factor of Alzheimer's disease. Decreasing ATF4 rescues the hippocampal-dependent memory impairments in humanized apolipoprotein E ε4 mutant mice suggesting that ATF4 may act as a potential risk factor in Alzheimer's disease (81). By contrast, ATF4 is protective against neurotoxicity in Parkinson's disease cellular models (82). The abundance of CREB2/ATF4 at synaptic compartments of excitatory neurons raises the possibility for a role of this factor on synapse-to-nucleus signaling.

γCaMKII Cytosol-to-Nucleus Signaling

Calcium/calmodulin-dependent protein kinase II gamma (γCaMKII) is a member of the CaMK subfamily of serine/threonine protein kinases generated from alternative splicing of a single *CAMK2G* gene. Recent studies have uncovered key molecular mechanisms regulated by γCaMKII during brain function. In glutamatergic neurons, depolarization and high-frequency stimuli induce the γCaMKII-dependent shuttling of CaM from the cytosol to the nucleus leading to the activation of CaMK/CREB and gene transcription, a process essential for synaptic plasticity and learning in mice (83,84). Similarly, γCaMKI, but not γCaMKII, mediates cytosol-to-nucleus CaM translocation, CREB phosphorylation, and gene transcription contributing to dendritic branching in interneurons (85). As γCaMKII is an abundant protein of the postsynaptic density compartment (86), it is possible that besides regulating cytoplasmic-to-nuclear CaM signaling, this factor could play a relevant role in activity-dependent

synapse-to-nucleus signaling in glutamatergic excitatory neurons.

CAMK2G genetic variants are linked with episodic memory deficits, intellectual disability, and mental retardation in humans (87,88). Importantly, a *CAMK2G* point mutation associated with severe intellectual disability and mental retardation impairs γCaMKII-mediated CaM nuclear translocation, CREB transcriptional activity, synaptic plasticity, and memory (84,87). Of interest, SNPs within the *CAMK2G* gene were recently identified in cohorts of patients with Parkinson's disease (89) and late-onset Alzheimer's disease (90,91), in which reduced *CAMK2G* messenger RNA is detected in the cortex (92). There is also compelling evidence linking multiple genes of the γCaMKII pathway (Ca^{2+} channels, CaM, CamKIV, and CREB) with mental and neuropsychiatric disorders, including ASD, schizophrenia, and depression (93,94). In summary, the emerging evidence linking γCaMKII with several neurodegenerative and mental diseases raises the possibility for a role of γCaMKII cytosol/synapse-to-nucleus signaling in the physiopathology of these brain disorders.

MAPK/ERK Synapse-to-Nucleus Signaling

Mitogen-activated protein kinase (MAPK)/ERK mediates excitation-transcription coupling in several forms of glutamate-dependent synaptic plasticity. Synaptic stimulation of specific dendritic spines triggers local phosphorylation and nuclear translocation of ERK resulting in activation of nuclear transcription factors, including CREB and Elk-1 (95). Phosphorylation and nuclear trafficking of ERK occurs during induction of long-term potentiation and requires NMDARs and CaMKIIα, but not voltage-gated Ca^{2+} channels (37,96). As already mentioned, ERK also binds Jacob in response to synaptic activity to mediate its synapse-to-nucleus translocation (36). Although ERK activation occurs in the vicinity of stimulated synapses, there is still a lack of direct experimental evidence for synapse-to-nucleus translocation of ERK. However, consistent with ERK activation at postsynaptic sites, a recent study showed that distinct temporal patterns of neuronal activity induce different gene expression profiles, and indeed an early wave of gene expression is specifically mediated by MAPK/ERK signaling (97).

MAPK/ERK signaling is involved in multiple brain physiological and pathological processes. In neurodegenerative and dementia disorders, ERK1/2 mediates Aβ-induced neurodegeneration and neuropsychiatric symptoms in Alzheimer's disease (98,99). More recent studies showed that tau is phosphorylated by ERK and that ERK/S6 signaling mediates somatodendritic tau accumulation induced by Aβ, suggesting a direct link between ERK signaling and tau pathology (100). In Huntington's disease, mutant *Htt* compromises ERK signaling (101), whereas ERK activation induces neuroprotection in a mouse model of the disease (102). Meanwhile, compelling recent evidence suggests that neuronal MAPK/ERK signaling regulates maladaptive plasticity in mood disorders, including addiction, stress, and emotional pain (103,104). Finally, a recent study reported that SNPs in the *MAP2K1* gene, which encodes MAPK/ERK kinase, is associated with depression (105). In summary, the involvement of ERK in neurodegenerative and psychiatric disorders suggests a possible role of MAPK/ERK dendritic/synaptic-to-nucleus signaling in these brain pathologies.

CONCLUSIONS

Synapse-to-nucleus signaling plays a crucial role in brain plasticity and function, but its contribution to brain pathologies still remains largely unclear. Neurodegenerative and neuropsychiatric disorders are generally characterized by early synaptic and/or neuronal dysfunction, so it is possible that changes in synapse-to-nucleus signaling could be a key mechanism underlying these pathologies. The fact that genetic variants in synaptonuclear genes are associated with brain pathologies points to a causative role of synaptonuclear signaling in these disorders. In addition, synapse-to-nucleus signaling is affected by essential cellular processes (e.g., calcium signaling, energy metabolism, dendritic transport) that are altered in pathological conditions. Whether dysfunction of synaptonuclear factors is a primary pathogenic mechanism or merely a consequence of the disease process is still unclear. Based on the growing evidence linking synaptonuclear factors with brain diseases, an important question still to be addressed is the real significance of synapse-to-nucleus signaling in human brain pathologies.

It is remarkable that the majority of synaptonuclear factors regulate CREB-dependent transcription. This suggests that synapse-to-nucleus signaling integrates synaptic signals into transcriptional programs by converging on CREB signaling. It is possible that synapse dysfunction caused by altered synapse-to-nucleus signaling and CREB-mediated transcription could be a link among some neurodegenerative diseases. Nevertheless, the specific gene programs regulated by these factors in the nucleus remain largely unexplored. One interesting possibility is that each factor may integrate different information traits by coupling specific patterns of synaptic activation to a subset of activity-induced genes (5). This may be relevant, as different patterns of neuronal activity induce distinct gene expression profiles. For instance, early gene expression induced by brief activity is specifically mediated by MAPK/ERK signaling (97), which is consistent with an early activation of ERK at postsynaptic sites. In this context, further studies employing genome-wide sequencing approaches will help to elucidate the gene programs modulated by these factors and how they may contribute to synaptic dysfunction in specific brain disorders.

It is currently unclear whether and how synapse-to-nucleus signaling modulates global excitability, local synaptic plasticity, or both. Synapse-specific modifications of synaptic strength and global neuronal excitability are complementary to mediate superior brain functions, such as memory storage (106). It should be noted that functional differences of synaptonuclear factors at synapses and cytosol may exist based on distinct signaling or activation mechanisms, binding partners, and differential levels of these proteins at these cellular locations. Another puzzling but essential unresolved question is how these synaptonuclear factors transduce signals back to the synapse. It is relevant that CREB, which enhances neuronal excitability and allocation of neurons to memory circuits (107), acts as master regulator that integrates synapse-to-nucleus signals into transcriptional changes (Figure 1).

However, it is unlikely that a single transcription factor mediates synapse-to-nucleus signaling affecting such a variety of physiological effects. One possibility is that specific coactivators or epigenetic factors also contribute to fine-tuning synapse-to-nucleus regulation of target genes. For instance, CRTC1 nuclear translocation cooperates with histone acetylation to regulate memory-related gene programs (12,14). It is therefore possible that formation of alternative transcriptional complexes and/or epigenetic regulators may act downstream of synapse-to-nucleus signaling to regulate specific transcriptional programs.

Despite the remarkable progress in understanding the contribution of synapse-to-nucleus signaling to gene expression at the nucleus, the local effects of synaptonuclear factors at synapses are largely unclear. It is plausible that besides their nuclear functions, they may contribute to synapse morphology and plasticity by acting locally at synapses, for instance, by binding and regulating other synaptic proteins. Interesting in this respect is the recent finding that the serum response factor coactivators megakaryoblastic leukemia 1 and 2, which are linked with schizophrenia and autism, are localized at synapses and regulate spine morphology (108). Nonetheless, a number of synaptonuclear factors were recently linked to synaptopathies, including autism, schizophrenia, and Alzheimer's disease, reinforcing the view that synapse pathology is a common underlying mechanism in brain disorders. For instance, genetic variants or mutations of these factors are associated with neuropsychiatric disorders, and their dysfunction occurs in neurodegenerative diseases (Table 1). How polymorphisms, mutations, or deregulation of these factors, acting distally or locally at synapses, alter synapse-to-nucleus signaling contributing to those pathologies is still unclear. Future research on this topic is needed to understand the role of synapse-to-nucleus signaling in brain pathologies. More importantly, therapeutic strategies targeting synapse-to-nucleus signaling will be essential for developing novel treatments for mental and neurodegenerative disorders.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the Spanish Ministerio de Ciencia, Innovación y Universidades (Grant No. SAF2016-80027-R [to CAS]), Instituto Carlos III (Grant No. CB/06/05/0042 [to José Rodríguez-Alvarez and CAS]), and BrightFocus Foundation (Grant No. A2014417S [to CAS]).

We thank members of Saura's lab for their scientific contribution over the years to the content of this review.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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Received Nov 6, 2018; revised Dec 18, 2018; accepted Jan 4, 2019.

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