Review

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Macromolecular transport in synapse to nucleus communication

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Local signaling events at synapses or axon terminals must be communicated to the nucleus to elicit transcriptional responses. The lengths of neuronal processes pose a significant challenge for such intracellular communication. This challenge is met by mechanisms ranging from rapid signals encoded in calcium waves to slower macromolecular signaling complexes carried by molecular motors. Here we summarize recent findings on macromolecular signaling from the synapse to the nucleus, in comparison to those employed in injury signaling along axons. A number of common themes emerge, including combinatorial signal encoding by post-translational mechanisms such as differential phosphorylation and proteolysis, and conserved roles for importins in coordinating signaling complexes. Neurons may integrate ionic flux with motor-transported signals as a temporal code for synaptic plasticity signaling.

Communication between synapse and soma

Neurons communicate at synaptic contacts by signaling events, yet their long-term responses to such stimuli require changes in gene expression at the nucleus. In contrast to many other cell types, the intracellular distances that separate synapse from soma in neurons are well beyond the effective range of diffusion-dependent mechanisms [1–4]. How then are distant stimuli sensed and decoded by the nucleus? Conversely, how are changes in transcription or translation in the soma conveyed to specific synapses or terminals? A series of events, including membrane depolarization and calcium influx, was shown to contribute to information transfer in neurons via electrophysiological encoding, while the physical transport of macromolecules was thought to serve secondary roles [5–7]. In contrast, long-distance transport of protein messengers in axons is well established as being essential for neuronal maintenance, survival, and regeneration [8–10]. Can localized activation of macromolecules combined with intracellular trafficking also enable communication between the synapse and the soma [11]? Here we review recent advances in the understanding of macromolecular communication between the synapse and the nucleus, and discuss how these advances can be integrated with the more established fast coupling mechanisms underlying synaptic plasticity.

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Nuclear integration of synaptic events by fast coupling mechanisms

The prevailing viewpoint in the literature is that calcium signals are the major route for communication of synaptic activity to the nucleus [7,12]. According to this model, the activation of receptor-gated calcium channels in the distal dendrites is propagated by action potentials or calcium waves to the soma, thereby enabling the local activation of calcium-dependent pathways connected to gene transcription. The fast genomic response to sustained rises in nuclear calcium is generally believed to be important for the induction of immediate early gene expression (IEG) within a few minutes of the stimulus [5,7,13,14]. It has been suggested that IEG transcription can be subdivided into rapid versus delayed transcription [15]. A distinctive feature is the near-instantaneous transcription by the stalling of RNA polymerase II directly downstream of the transcription start site and it is likely that very rapid transcription events require fast calcium signaling [15,16].

In the electrochemical coupling model, the activation of calcium-permeable ion channels in distal dendrites generates back-propagating action potentials or regenerative calcium waves that are conveyed along the endoplasmic reticulum (ER) to the soma [12]. Their arrival at the nucleus enables the local activation of calcium-dependent pathways connected to gene transcription. This mode of synapse to nucleus communication has been intensively studied for excitatory synapses and calcium influx generated by activation of synaptic NMDA receptors, L-type calcium channels, or intracellular calcium release [17–20]. The resulting action potentials generated at the initial axon segment may propagate retrogradely in the soma, and spread into dendrites [21]. Propagation of such signals is influenced by the geometry of the dendritic arbor as well as spatiotemporal integration of excitatory and inhibitory inputs in the system and back-propagating action potentials were suggested to complement and enhance synaptic calcium influx [22,23].

Many forms of long-term potentiation (LTP) require NMDA receptor (NMDAR) activation and postsynaptic calcium entry [24]. Interestingly, the calcium transients generated upon synaptic activation of NMDARs are spatially restricted in spines, with low diffusion into the

dendritic shaft [25,26]. However, although calcium signals are dampened by uptake and clearance systems, regenerative wave mechanisms may allow them to cover distances of hundreds of micrometers in a number of milliseconds, bridging the gap between the synapse and the nucleus. Thus, synaptic activation can mobilize calcium from internal stores like the ER [27–29], which extends from the nucleus into the distal processes in both axons and dendrites [30,31]. Regenerative calcium waves may be initiated by calcium signals arising from voltage-gated ion channels, NMDARs, or the activation of metabotropic glutamate receptors (mGluRs) [32], and propagated by calcium-induced calcium release mediated by the activation of inositol-1,4,5-triphosphate (IP3) and ryanodine receptors (RyRs) located on the ER [33].

Although waves represent a plausible mechanism to convey calcium signals to the nucleus, the source of nuclear calcium and the mechanism of its elevation by synaptic activity are still a matter of debate [7,34]. Of note, the nucleus can generate autonomous calcium transients and a very recent study suggests that BK-type calcium-sensitive potassium channels reside on the nuclear envelope and regulate the coupling between synaptic activity and gene expression [35]. BK channels are typically plasma membrane proteins that contain a large conserved C-terminal extension, which is involved in channel gating by intracellular ions or second-messenger systems [36]. Li *et al.* [35] demonstrated the presence of BK channels on the nuclear envelope of rodent hippocampal neurons. Pharmacological blockade of nuclear BK channels in both intact neurons and isolated nuclei induced calcium release from the nuclear envelope and cAMP response element-binding protein (CREB)-dependent transcription [35]. These results suggest that local signaling at the nuclear envelope could link synaptic activity to nuclear calcium transients.

The rapid mechanisms described above have been a primary focus for most of the field in recent years. A considerably slower process that depends on the nuclear import of proteins released from synapses may be of particular importance in coupling local synaptic activity to specific gene expression programs and potentially more sustained and delayed gene transcription [11,37]. What is the evidence for such macromolecular signaling in synapse to nucleus communication?

ERK signaling from synapse to nucleus requires macromolecular trafficking

Although diverse signaling molecules have been proposed to physically translocate from synapse to soma [11], the functional significance of such transport events has been contentious. NMDARs play a pivotal role in regulation of activity-dependent gene expression and the multi-protein NMDAR complex is a potentially rich source for long-distance protein messengers [38–40]. The mitogen-activated protein kinase (MAPK) cascade plays an important role in transducing synaptic signals to the nucleus, and the MAPK extracellular signal-regulated kinase (ERK) regulates gene transcription in learning and memory [41]. ERK activation occurs both at the vicinity of the stimulated synapse [4,42] and at the nucleus [6]. Strikingly, two very recent studies have now combined advanced imaging with biochemical approaches to provide convincing evidence of the need for transport of ERK signaling complexes in specific paradigms of synapse to nucleus communication [43,44].

Zhai *et al.* [43] used a fluorescent ERK activity reporter to examine spatial parameters of signaling under different parameters of LTP. They evaluated the effect of inducing LTP in single versus multiple dendritic spines of rat CA1 hippocampal pyramidal neurons on the propagation of ERK signaling to the nucleus. Stimulation of three or more spines generated a signal that propagated to the nucleus, if the stimulated spines were located in at least two distinct dendritic branches (Figure 1A). Moreover, Zhai *et al.* further showed that this mechanism allows both spatial integration of signals from multiple branches and temporal summation of spatially distinct signals separated by intervals of 30 min. The onset of the nuclear response was delayed by tens of minutes, in correlation with the distance of the stimulation, suggesting that propagation was via a relatively slow mechanism [43].

The effective diffusion range of ERK has been estimated to be approximately 30 μm in hippocampal dendrites [2] and, moreover, the signaling range might be additionally constrained by phosphatase activity in the cytoplasm [3]. How then might a phosphorylated signaling molecule such as ERK traverse distances of a few hundred microns in a phosphatase-rich environment from synapse to nucleus while maintaining its signaling capacity over periods of tens of minutes or more? Karpova *et al.* [44] characterized such a mechanism in the course of a study aimed at understanding how the nucleus can distinguish between signaling of synaptic versus extrasynaptic NMDARs. Synaptic and extrasynaptic NMDARs have distinct roles in synaptic plasticity, transcription, and cell death [45,46]. The transcriptional response to synaptic NMDAR activation is biased toward cell survival and plasticity genes, whereas extrasynaptic NMDAR signaling primarily induces expression of transcripts involved in cell death pathways [44,47]. ERK activity was found to be required for nuclear translocation of the protein Jacob after specific activation of synaptic NMDARs. Although activation of extrasynaptic NMDARs also induced accumulation of Jacob in the nucleus, ERK activity was not required in the latter case. A series of biochemical, proteomic, and cell biological analyses then showed that Jacob is an ERK substrate, and that synaptic, but not extrasynaptic, NMDAR activation leads to the phosphorylation of Serine180 in Jacob by ERK. Phosphorylated Jacob was protected from dephosphorylation *en route* to the nucleus by association with proteolytic cleavage fragments of the intermediate filament α-internexin, together with ERK (Figure 1B). The phosphorylation state of Jacob upon arrival in the nucleus then determines the transcriptional response and physiological outcome (Figure 1C), and it is tempting to speculate that Jacob operates as a mobile hub that docks NMDAR-derived signalosomes to CREB and potentially other nuclear target sites [44]. This transport mechanism is strikingly analogous to that previously described for protected transport of phosphorylated ERK from injured peripheral axons to the soma in association with proteolytic fragments of the intermediate filament