Regulation of Dendritic Development by Neuronal Activity

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ABSTRACT: Proper development of dendrites is essential for the establishment of neuronal circuitry. The elaboration of the dendritic tree is a highly dynamic and regulated process, which involves the formation of new branches as well as the maintenance or elimination of pre-existing branches. This review describes recent advances in our understanding of the molecular mechanisms of activity-dependent dendritic development. Neuronal activity triggers calcium-mediated signaling events that affect the structural components of dendrites and adhesion molecules. These calcium-induced signaling pathways also target nuclear transcription factors thereby controlling expression of genes required for dendritic development. Thus, a coordinated response to calcium-regulated signaling pathways mediates activity-dependent dendritic development. © 2005 Wiley Periodicals, Inc. J Neurobiol 64: 4–10, 2005

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Neurons extend dendrites to receive and integrate information from a vast number of synaptic inputs. The specific branching pattern or morphology of dendrites determines not only the number and type of synaptic contacts but also influences the back propagation of action potentials. Because dendritic morphology plays such a critical role in synaptic integration and information processing, it is important to understand how the development of dendrites is regulated.

Different types of neurons in the central nervous system exhibit different dendritic morphologies. This type-specific morphology appears to be specified by genetic programs (Jan and Jan, 2003). These intrinsic programs act in concert with extracellular signals to specify the mature dendritic arbor. The extracellular influences include various protein factors as well as neuronal activity (Wong and Ghosh, 2002; Miller and Kaplan, 2003). The effects of neuronal activity on dendritic development are mediated by intracellular calcium signals, and recent studies indicate that calcium-induced signaling events have both cytoplasmic and nuclear targets. In this review, we will focus on advances in our understanding of the regulation of dendritic arbor development by neuronal activity. Specifically, we will discuss the calcium-dependent signaling events that affect the dendritic cytoskeleton and gene expression. Studies supporting a role of neuronal activity in dendritic spine development have been reviewed elsewhere (Nimchinsky et al., 2002; Yuste and Bonhoeffer, 2004).

REGULATION OF DENDRITIC BRANCH STABILITY BY NEURONAL ACTIVITY

The development of dendritic arbors is a highly dynamic process. As evident by time-lapse imaging studies using different experimental models, it involves both the addition of new branches, as well

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as elongation, maintenance, retraction, and elimination of pre-existing branches (Cline, 2001). Neuronal activity plays a key role in the growth of dendritic arborization (Wong and Ghosh, 2002). In *Xenopus*, light-induced visual activity increases the growth of new dendritic branches and stability of existing branches of tectal neurons (Sin et al., 2002). Other forms of experience, such as exposure to an enriched environment, have also been reported to influence dendritic growth. Faherty et al. (2003) examined the morphology of neurons in motor cortex, striatum, and hippocampus in brains from adult (4–5 months) mice raised in different housing conditions after weaning. These conditions included standard cages, cages with exercise wheels only, and ''enriched environment'' cages containing more numbers of animals, exercise wheels, nesting materials, and interchangeable tunnels, which facilitate social interactions, physical activity, and learning. Despite the small sample size of neurons analyzed (ranging from four to eight neurons per condition) the authors reported detectable effects of rearing on dendritic morphology. Hippocampal neurons, but not neurons in the motor areas, from mice housed in an enriched environment showed larger dendritic trees and increased dendritic growth compared to littermates raised in standard or exercise cages. Thus, it appears that alterations in neural network activity as a result of enhanced social interactions and learning can affect dendritic development within hippocampus, which is functionally associated with learning and memory.

Consistent with a role for neuronal activity in dendritic development, blockade of activity leads to an impairment of dendritic branching. Tetanus toxin inhibits neurotransmitter release thereby blocking synaptic transmission. *In vivo* blockade of neural activity during the first postnatal week by injecting tetanus toxin into the CA1 region of mouse brains reduced the number of basal dendritic branches of pyramidal neurons (Groc et al., 2002).

Even after the initial formation of neuronal connections, activity continues to control the stability of dendritic branches. Mizrahi and Katz (2003) used two-photon laser scanning microscopy to repeatedly image, through cranial windows, the apical dendrites of YFP (yellow fluorescent protein)-expressing mitral and tufted (M/T) cells in the olfactory bulb over days and weeks in adult mice (>8 weeks of age). These apical dendrites are aspinous and contain both inhibitory and excitatory synapses formed on the dendritic branches. Despite a constant turnover of these synapses in the adult, the apical dendrites of M/T cells are remarkably stable structurally over both short (1 day) and long (1–4 weeks) imaging intervals. Further, the dendritic branches of M/T cells remained highly stable under conditions such as an odor-enriched environment or an olfactory-based learning experience. Only when activity was pharmacologically increased with bicuculline was there a change in dendritic dynamics, indicating structural destabilization. Thus, the stability of existing connections can be changed in response to large alterations in the overall level of neuronal activity.

ACTIVITY-DEPENDENT MODULATION OF LOCAL CYTOSKELETON AND ADHESION MOLECULES

Neuronal activity has been shown to regulate dendritic morphology by affecting the dendritic cytoskeleton. Lohmann et al. (2002) demonstrated that in chick retinal ganglion cells perturbation of local calcium signaling, that is, calcium-induced calcium release, causes the dendrites to retract within minutes. This study demonstrates that local calcium signaling is essential for dendritic stability *in vivo*. In addition, the instantaneous effect of calcium blockade on dendrite stability indicates that local calcium signaling most likely exerts effects directly on dendritic cytoskeleton. Rho family GTPases, which are key regulators of the actin cytoskeleton (Hall and Nobes, 2000), appear to mediate the effects of neuronal activity on dendritic development (Luo et al., 1996; Threadgill et al., 1997; Wong et al., 2000; Li et al., 2002; Sin et al., 2002).

The actin cytoskeleton and microtubules are major structural components of dendrites. Although previous studies have focused on the ability of neuronal activity to regulate dendritic patterning via Rho-family GTPase signaling to the actin cytoskeleton, recent studies have implicated the importance of activity-dependent events in promoting microtubule assembly and dendritic stability. Microtubule-associated proteins (MAPs) act to stabilize microtubules. In sympathetic neurons, depolarization induces dendrite formation via calcium/calmodulin-dependent protein kinase II (CaMKII) and MEK-ERK pathways to enhance MAP2 phosphorylation and MAP2 interaction with microtubules, thereby facilitating microtubule stability (Vaillant et al., 2002; Miller and Kaplan, 2003). Also, a guanine deaminase called cypin has been shown to regulate dendrite formation in hippocampal neurons by promoting microtubule assembly (Akum et al., 2004). Overexpression of cypin leads to an increase in dendrite formation. By contrast, knock down of cypin protein levels by inhibiting the maturation of *cypin* mRNA using a *cypin*-specific 5′ end-mutated U1 small nuclear RNA

results in decreased dendritic growth. Because cypin expression is greatly induced following depolarization, cypin may function in activity-dependent dendritic development by promoting microtubule polymerization and branch elongation and stability.

The influence of afferent innervation on the development of postsynaptic dendrites has been demonstrated in many developing systems (Wong and Ghosh, 2002). Physical interactions between pre- and postsynaptic contacts are thought to stabilize newly formed branches (Hua and Smith, 2004). This raises the possibility that activity might regulate dendritic growth by affecting adhesion molecules that mediate synaptic contacts. A potential regulator of such interactions is β-catenin. Beta-catenin interacts with the intracellular domain of N-cadherin, which is a transmembrane protein that has homophilic interactions with other N-cadherin molecules on the adjacent cells. Beta-catenin links N-cadherin to the actin cytoskeleton. Aside from its role in cell adhesion by stabilizing the actin cytoskeleton, β-catenin also participates in Wnt-dependent transcription. Yu and Malenka (2003) showed that overexpression of N-cadherin or β-catenin can increase dendritic complexity in hippocampal neurons and that β-catenin levels correlate with the degree of branching. Overexpression of the intracellular domain of N-cadherin [Ncad(intra)] can act in a dominant negative fashion by sequestering endogenous β-catenin. Overexpression of Ncad(intra) attenuates the ability of membrane depolarization to induce dendritic growth, suggesting that β-catenin might mediate the effects of activity on dendrites. The effect of β-catenin on activity-dependent dendritic development most likely does not involve its function in Wnt-mediated transcription. This is based on the observations that a transcriptionally defective β-catenin is still capable of inducing dendritic growth, and the expression of the transcriptional partner of β-catenin (LEF) fails to enhance dendritic arborization. Because β-catenin links cadherins at the membrane to the actin cytoskeleton, Yu and Malenka (2003) propose that increasing β-catenin could facilitate the anchoring of motile actin to the membrane of the developing dendrites, thereby stabilizing newly formed branches.

REGULATION OF DENDRITIC DEVELOPMENT BY ACTIVITY-DEPENDENT GENE EXPRESSION

While activity-dependent regulation of cytoplasmic targets is crucial, there is emerging evidence that neuronal activity-triggered calcium signaling to the nucleus also contributes to regulation of dendritic development. The transcription factor cAMP-responsive element binding protein (CREB) is known to play an important role in synaptic plasticity and memory. Calcium signaling via CaMKIV to CREB is required for calcium-dependent dendritic growth in cortical neurons (Redmond et al., 2002). The Rap1 small GTPase also functions in calcium-mediated dendritic development, at least in part, via a CREB-dependent mechanism. Chen et al. (2005) have shown that inhibiting endogenous Rap1 function by expressing the dominant negative version of Rap1 (Rap1N17) attenuated the ability of primary cortical neurons to extend dendrites in culture. Rap1 inhibition also reduced the complexity of basal dendritic trees of layer 5 pyramidal neurons in postnal cortical slice cultures. Similarly, another inhibitor of Rap1 signaling, Rap1GAP, suppressed calcium-induced dendritic growth in primary cortical neurons. These results indicate that Rap1 signaling is important for calcium regulation of dendritic growth and branching. Furthermore, pharmacological blockade studies have revealed that in cortical neurons depolarization-induced calcium influx via voltage-sensitive calcium channels (VSCC) and *N*-methyl-D-aspartate (NMDA) receptors triggers the cGMP- and cAMP-dependent signaling cascades resulting in Rap1 activation (Chen et al., 2004). This cGMP- and cAMP-mediated activation of Rap1 is required for calcium regulation of dendrite morphogenesis (Y. Chen and A. Ghosh, unpublished results).

Rap1 signaling is necessary for calcium activation of ERK1/2, CREB, and CBP in cortical neurons. The authors further showed that inhibition of ERK activation and CREB function suppressed dendritic growth induced by the constitutively active form of Rap1 (Rap1V12) (Chen et al., 2004). Thus, Rap1 functions in calcium-dependent dendritic development and the effects of Rap1 are mediated by downstream ERK1/2 signaling and CREB-dependent transcription.

Recently, a novel calcium-responsive nuclear transcriptional activator called CREST (calcium-responsive transactivator) was cloned and found to be involved in the transcriptional control of dendritic development (Aizawa et al., 2004). Calcium influx following VSCC and NMDA receptor activation leads to CREST-mediated transcription in cortical neurons. CREST expression peaks at birth and declines substantially by P20 in the cortex. This transient expression of CREST during early postnatal age coincides with the period of vast dendritic growth (Miller, 1981; Miller and Peters, 1981). In order to characterize the *in vivo* function of CREST, mice that have a target-disruption of the *crest* gene were gener-

ated. In P7 *crest* mutant mice, there was a dramatic reduction in the growth and branching of cortical layer 5 pyramidal neurons compared to wild-type animals, indicating that CREST is required for dendritic growth and branching.

Because dendritic development is regulated in part by calcium-dependent transcription, and CREST is induced by calcium, the authors also examined whether CREST function was necessary for calcium-induced dendritic growth. Cortical neurons from wild-type or *crest* mutant mice were cultured *in vitro* and tested for their ability to extend dendrites in response to depolarization. Under unstimulated conditions, cultured neurons from wild-type and *crest* mutant mice showed comparable dendritic growth and branching. However, depolarization induced dendritic growth and branching in wild-type neurons but not in *crest* mutant neurons. This defect in depolarization-induced dendritic growth and branching in *crest* mutant neurons could be restored by overexpressing CREST in these neurons. Thus, CREST is required for calcium regulation of dendritic development in cortical neurons.

The mechanism by which CREST-dependent transcription regulates dendritic growth is not known. However, the ability of CREST to interact with the calcium-regulated transactivator CREB-binding protein (CBP) is of interest given the previously demonstrated role of CBP in calcium-induced dendritic growth (Redmond et al., 2002). Aside from CBP, CREST also interacts with the chromatin remodeling proteins BAF250 and BRG-1 (S.–C. Hu, H. Aizawa, A. Ghosh, unpublished results). Although CREST and CBP do not bind DNA sequences, CBP is known to interact with several DNA binding proteins. CREST may be recruited to specific promoters via its interaction with CBP. Together with BAF250 and BRG-1, the CREST-CBP containing complex may regulate gene expression in response to calcium by modifying the chromatin structures within promoter regions of the target genes involved in dendritic development.

The bHLH protein *neuroD2* was identified as another putative calcium-regulated transactivator in the same screen used to clone *crest* (Aizawa et al., 2004). Recently, a NeuroD2-related factor called NeuroD was shown to be necessary for activity-dependent dendritic morphogenesis in cerebellar granule cells. Gaudillière et al. (2004) used an RNAi-mediated knock down approach to examine the role of NeuroD. Neurons transfected with a plasmid encoding NeuroD hairpin RNAs (hpRNAs) showed defects in dendritic, but not axonal, growth. Moreover, this defect in dendritic growth caused by NeuroD RNAi expression could be rescued by transfecting a mutant NeuroD that was resistant to RNA interference. This strongly supports a role for NeuroD in the development of dendrites in granule neurons.

Gaudillière et al. (2004) also examined whether NeuroD was involved in activity-dependent dendritic growth by examining the effect of NeuroD knock down in granule neurons treated with either KCl or the $GABA_A$ receptor antagonist bicuculline. KCl and bicuculline induced dendritic growth of granule neurons in cultures and cerebellar slices, respectively. This activity-induced dendritic growth was inhibited by NeuroD RNAi, suggesting that neuronal activity regulates dendritic development via NeuroD-mediated transcription. The activity-dependent effects of NeuroD appear to require CaMK II-mediated phosphorylation of NeuroD at serine 336.

POSSIBLE MECHANISMS OF ACTIVITY-DEPENDENT GENE EXPRESSION

Although CREB, CREST, and NeuroD are calcium-regulated transcription factors that play a role in activity-dependent dendritic development, their mechanisms of action are largely unknown. In the case of CREB, BDNF may be a target gene that mediates activity-dependent dendritic growth (Wong and Ghosh, 2002). Neuronal activity has been shown to induce the neurotrophin BDNF expression and release (Lu, 2003). Jin et al. (2003) studied changes in the growth of dendritic branches over a 5 day period by imaging live GFP-labeled neocortical non-pyramidal interneurons in cultured cortical slices. The authors showed that depolarization-induced dendritic growth and branching were blocked by anti-BDNF antibody treatment, suggesting that activity-dependent dendritic development in neocortical interneurons may be mediated by BDNF.

CBP serves as a common coactivator for a variety of transcription factors, including CREB and CREST. This ability of CREST to interact with CBP might provide a mechanism by which CREST controls the expression of a large set of genes, including those required for dendritic morphogenesis. Because CREB has already been shown to contribute to calcium-dependent dendritic growth (Redmond et al., 2002), it would be interesting to find out whether CREST-CBP interaction plays any role in CREB-mediated transcription. Moreover, by identifying genes differentially expressed in wild-type and *crest* mutant mice we should be able to learn more about the mechanism by which CREST functions in activity-dependent dendritic patterning.

The target genes regulated by NeuroD that mediate dendritic growth in response to calcium have not

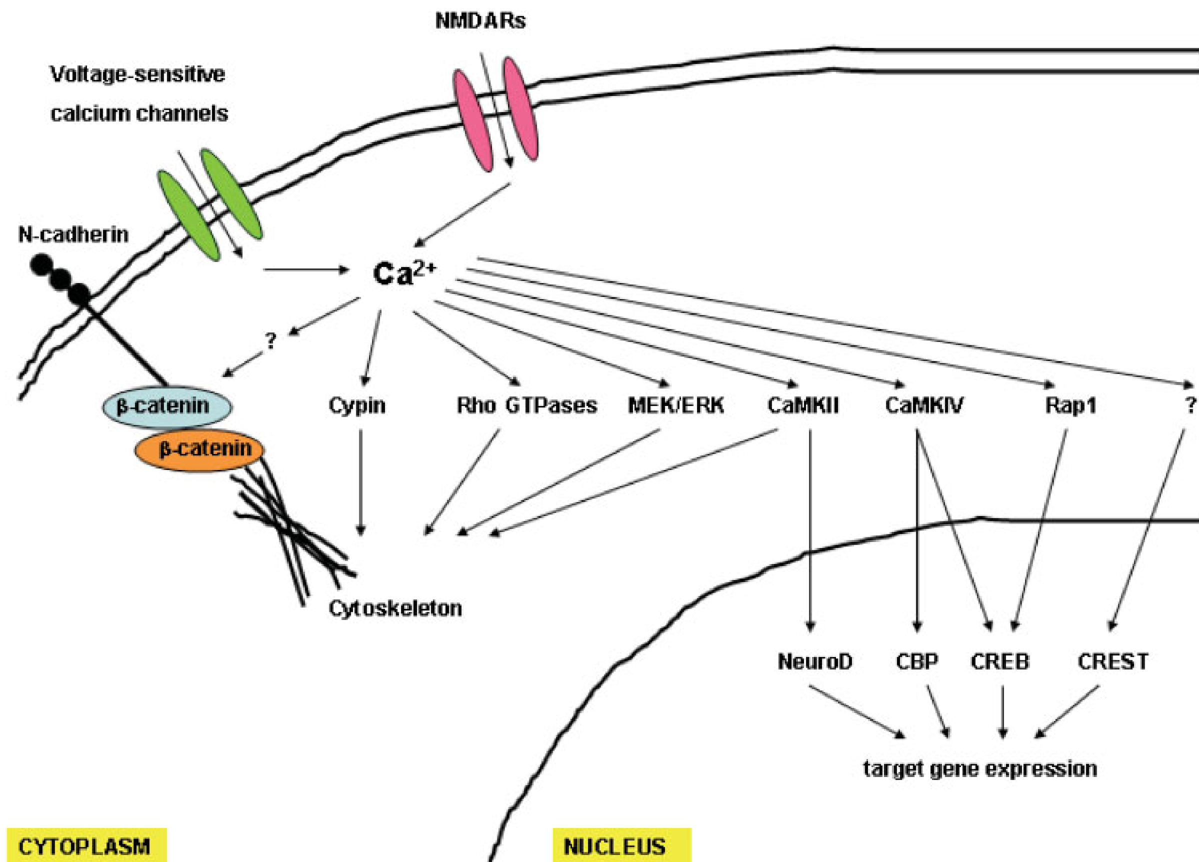

Figure 1 Neuronal activity regulates dendritic development via multiple signal transduction pathways that target the structural components of dendrites, adhesion molecules, and transcription factors. Neuronal activity can lead to calcium influx via voltage-sensitive calcium channels and *N*-methyl-D-aspartate receptors (NMDARs), resulting in an increase in intracellular calcium concentration. Calcium triggers multiple signaling pathways that act via signal transducers such as cypin, Rho GTPases, MEK/ERK, and CaMKII, which ultimately exert their effects on the dendritic cytoskeleton. These signaling intermediates have been shown to affect actin reorganization as well as microtubule assembly and interactions. Beta-catenin represents another site of regulation by calcium-dependent pathways. Beta-catenin may mediate dendritic growth and branching by facilitating N-cadherin interaction with actin filaments, which is essential for the adhesive property of cadherin. Recently, calcium-induced signaling pathways such as those mediated by CaMKII, CaMKIV, and Rap1 have been reported to regulate the activity of several transcription factors including NeuroD, CREB, CBP, and CREST, which are involved in activity-dependent dendritic development. The intermediate signaling cascades are not shown.

been identified, but potential targets include NCAM and N-tubulin. NCAM is a neuronal cell adhesion molecule and N-tubulin is a component of microtubules critical for maintaining neuronal processes. Ectopic expression of the *Xenopus* homologues of NeuroD (XNeuroD) induces NCAM and N-tubulin expression in *Xenopus* embryos (Bao et al., 2000). Although it is not clear whether XNeuroD induction of NCAM and N-tubulin occurs beyond neuronal-fate determination, it is tempting to speculate that NeuroD could exert its effect on activity-dependent dendritic development by regulating NCAM and N-tubulin expression. This view is consistent with the proposed role of NeuroD in the maintenance of pre-existing dendritic branches, which is based on the observation that knocking down NeuroD expression leads to branch retraction (Gaudillière et al., 2004).

CONCLUSIONS

The development of dendrites is a highly dynamic process that is regulated by neuronal activity. As mentioned earlier, *in vivo* time-lapse imaging reveals

that large scale neuronal activity can lead to destabilization of dendrites in the olfactory bulb of adult mice (Mizrahi and Katz, 2003). In addition, real-time live imaging of the hippocampus of adult animals to study spine turnover shows that loss of spines on dendrites caused by epileptic activity can occur within a few hours (Mizrahi et al., 2004). Therefore, even in adult brains dendrites continue to be sites of activity-dependent structural plasticity.

Neuronal activity triggers intracellular calcium signaling. Calcium acts via multiple molecular mechanisms to regulate dendritic development. Figure 1 summarizes signal transduction pathways activated by calcium influx. How these calcium-regulated pathways are integrated to trigger a coordinated response in dendrites is a challenging question and should be the subject of future studies. Because dendrites are made up of various cytoskeletal elements, calcium-dependent signaling events controlling dendritic patterning must ultimately exert their effects on these structural components.

Because dendrites are sites of synaptic connections and integration of information, defects in the morphological development of dendrites could impair neuronal network activity and directly affect neuronal function. Dendritic abnormalities have been associated with mental retardation (Kaufmann and Moser, 2000; Ramakers, 2002), demonstrating the fundamental importance of dendritic patterning in cognitive function. In addition, alterations in dendritic structures have been reported in pathological conditions including stress and schizophrenia (Broadbelt et al., 2002; Radley et al., 2004). Therefore, understanding the molecular mechanisms controlling normal morphogenesis of dendrites should not only provide insights into the defects underlying mental retardation, but should also further our understanding of human cognition, thus improving therapies for treating pathological conditions associated with cognitive impairments.

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