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·Review·

Ca^{2+} signaling initiated by canonical transient receptor potential channels in dendritic development

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The spatial patterns of dendritic structures diverge in different types of neurons as adaptations to their unique functions. Although different intracellular mechanisms underlying dendritic morphogenesis have been suggested, it is evident that the elevation in intracellular Ca^{2+} levels plays a major role in the process. Canonical transient receptor potential (TRPC) channels, known to be non-selective Ca^{2+}-permeable cation channels, act as environmental detectors to sense and transduce extracellular signals into different intracellular responses, including the regulation of dendritic growth, *via* Ca^{2+} influx. Here, we review recent advances in the understanding of Ca^{2+} signaling, especially signals mediated by Ca^{2+} influx *via* TRPC channels, and the underlying molecular events in dendritic development.

Keywords: dendrite; calcium; TRPC; neurotrophin

Introduction

Dendrites are predominant neuronal structures that constrain the total input a neuron can receive. Their forms determine the regions with which other neurons can communicate and how the signals received are integrated. Dendritic development includes its growth and retraction by which patterns are formed. Since the branching pattern of a neuron dictates its function to a large extent, there has been a great deal of interest in elucidating the mechanisms by which dendritic growth and retraction are controlled during development. Dendritic growth is typified by the addition and elongation of processes. The arbor is gradually patterned not only by the process of outgrowth but also by the selective maintenance and retraction of terminal dendrites[1]. Besides an autonomous growth program, the activity-dependent growth or modification of dendritic structure has become a focus of research in the past few years, and this has yielded a series of reports on the important role of Ca^{2+} in several aspects of activity-dependent dendritic development. In this review, we discuss how Ca^{2+} signaling participates in the formation of dendritic structures, especially Ca^{2+} influx *via* canonical transient receptor potential (TRPC) channels, and the molecular events underlying this process. In addition, the possible role of TRPC channels in the neurotrophic regulation of dendritic development is also discussed.

Effects of Ca^{2+} Signaling on Dendritic Development

Ca^{2+} signaling plays multiple roles in neuronal development, including axon growth, growth-cone turning, dendrite morphogenesis, and synapse formation[2]. A variety of neuronal functions, including synaptic signaling, short- and long-term plasticity, and gene transcription, can be regulated by Ca^{2+} influx into the cytoplasm of dendrites and dendritic spines[3]. For example, Ca^{2+} accumulation within dendrites is evoked by action potentials and synaptic stimuli, which can then lead to intracellular Ca^{2+} $[Ca^{2+}]_i$

elevation through two major pathways: extracellular Ca^{2+} influx through different Ca^{2+} channels or transporters on the plasma membrane, such as N-methyl-D-aspartate receptors (NMDARs), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), voltage-gated Ca^{2+} channels (VGCCs), and TRP channels; or Ca^{2+} release from internal Ca^{2+} stores, such as the endoplasmic reticulum (ER). When inositol 1,4,5-trisphosphate receptors or ryanodine receptors on the ER are activated by their ligands, the Ca^{2+} stores in the ER are opened and internal Ca^{2+} is released, leading to an increase in $[Ca^{2+}]_i$. The effect of intracellular Ca^{2+} signaling on dendrite development varies with developmental stage, cell type, and Ca^{2+} source[1, 3, 4]. At early developmental stages, neurons require spontaneous Ca^{2+} elevation to promote dendritic growth. Growing neurons in low extracellular Ca^{2+} results in stunted growth. During later stages, Ca^{2+} influx through both NMDARs and AMPARs stabilizes dendritic development. Dendrites retract if extracellular Ca^{2+} levels fall. Thus, increases in $[Ca^{2+}]_i$ lead to dendritic elaboration in relatively immature neurons, while stabilizing the dendritic arbor with maturation[5]. Further, various cell types require different Ca^{2+} sources for dendritic growth. Ca^{2+} influx through NMDARs promotes dendritic outgrowth in tectal neurons in *Xenopus*[6], while Ca^{2+} influx from AMPARs, but not NMDARs, promotes dendritic outgrowth in rat spinal motor neurons *in vivo*[7]. However, even at the same developmental stage and in the same cell type, Ca^{2+} elevation from different sources has different effects on dendritic development, sometimes even opposing each other. For example, Ca^{2+} influx through VGCCs promotes dendritic growth in cultured cortical neurons[8], whereas Ca^{2+} influx through TRPC5 inhibits dendritic morphogenesis in cerebral cortex[9]. Therefore, it is likely that differences in Ca^{2+} sources lead to different outcomes in dendritic development.

Influences of TRPC Channels on Dendritic Development

TRP channels are recognized as a new route leading to $[Ca^{2+}]_i$ elevation. Since the identification, cloning, and characterization of the first *Trp* gene in *Drosophila*[10], many other *Trp* members have been identified. TRP channels are non-selective cation channels conserved from worms to flies and humans. Based on the primary amino-acid sequence, there are now seven subfamilies (TRPC, TRPV, TRPA, TRPN, TRPM, TRPML, and TRPP). They are all proteins with six putative transmembrane domains. Between the fifth and sixth transmembrane domains is an ion pore region[11, 12]. These channels are considered to be critical sensors of external signals, activated by various chemical and physical stimuli; they function in vision, thermosensation, olfaction, taste, hygrosensation, and mechanosensation[12]. Members of the *Trp* superfamily also play pivotal roles during neuronal development including neuronal stem cell differentiation, axon guidance, dendritic outgrowth, and spine formation[13, 14]. For example, perturbation of TRPP2 causes a randomization of heart looping and embryonic turning[15]; BDNF-induced chemoattraction is mediated by TRPC3 and 6[16, 17]; TRPC1 is required for proper growth-cone turning in response to microscopic gradients of netrin-1; and TRPC5 and 6 play different roles in regulating dendritic development[18-21].

Among all its members, the *Trpc* subfamily includes the closest homologues of *trp* genes in mammals. There are seven *Trpc* members, *Trpc1* to *Trpc7*, and *Trpc2* is a pseudogene in *Homo sapiens*. The structure of TRPC channels has not been solved; however, it seems that they function in the form of homo- or hetero-tetramers[22-25]. Based on similarity of amino-acid sequence, TRPC members can be subdivided into three groups: TRPC1; TRPC3/TRPC6/TRPC7, and TRPC4/TRPC5[11]. They are assembled into hetero-tetramers of multiple compositions, usually within the subgroups. Interestingly, although the protein sequences of TRPC members share high similarity, the influences of TRPCs on dendritic development are various. In a recent report, He *et al*. have shown that TRPC5 inhibits while TRPC6 promotes hippocampal dendritic growth. TRPC4, which belongs to the same subfamily as TRPC5, inhibits dendritic growth in hippocampal neurons[18]. However, suppression of TRPC4 by a specific siRNA or shRNA significantly reduces the length of neurites in cultured dorsal root ganglion neurons[26]. Meanwhile, opposing regulatory effects of TRPC1 and TRPC5 on neurite outgrowth in PC12 cells have been reported[27]. Therefore, it seems that Ca^{2+} influx *via* different TRPC channels (e.g. TRPC5/6) or the same

Ca^{2+} influx in different cell types (e.g. TRPC4) is able to determine the specific regulation of dendritic development by Ca^{2+}.

Regulation of Dendritic Development by Neurotrophins *via* TRPC Channels

Neurotrophins trigger a variety of responses, including cell proliferation[28, 29], differentiation, survival of neuroblasts, and adaptive responses of mature neurons. Among the differentiation responses that neurotrophins elicit are alterations in neuronal cell fate[30], regulation of neurite outgrowth and synapse formation, and changes in electrophysiological properties of neurons. There are four major neurotrophins, NGF, BDNF, NT-3, and NT-4/5, the receptors of which include TrkA, TrkB, and TrkC, with P75 as the co-receptor for all of them[31]. The neurotrophins have profound effects on dendritic development in various types of neurons. Since neurotrophins and Trks are expressed differentially in the various cortical layers, their roles in dendritic growth are complicated. For instance, exogenous application of any one of these four neurotrophins to P14 ferret visual cortical slice cultures changes specific patterns of dendritic growth in distinct ways. BDNF stimulates dendrite outgrowth from neurons in layer 4, but inhibits outgrowth from neurons in layer 6. In contrast, NT-4 enhances dendrite outgrowth from layer 6 neurons[32]. BDNF is the most extensively-studied molecule that is known to influence dendritic development from neurons in the central nervous system. It regulates the dendritic complexity of cortical pyramidal neurons by influencing total dendritic length, the number of branch-points, and the number of primary dendrites[33, 34]. Furthermore, using two-photon microscopy, recent studies have shown that BDNF is involved in activity-dependent dendritic plasticity. Local release of BDNF can lead to the maintenance and/or outgrowth of dendrites at the release site. Overexpression of BDNF significantly alters the formation and stability of basal dendritic arbors *via* an autocrine mechanism. In a highly local fashion, paracrine BDNF also alters dendritic branching. This provides a mechanism by which BDNF could participate in the formation of an active neuronal network[35, 36]. The Ca^{2+} signaling initiated by neurotrophins has been reported to be critical for dendrite development.

Activation of TrkB by BDNF leads to a phospholipase C (PLC)-dependent Ca^{2+} elevation through TRPC channels. Further, in hippocampal neurons, both TRPC3 and TRPC6 channels have been shown to promote dendritic growth and spine formation in response to BDNF. More interestingly, stimulation of these neurons by NT-3 induces a nonselective cation conductance and a PLCγ-dependent $[Ca^{2+}]_i$ elevation, both of which are blocked when TRPC5 but not TRPC6 channels are inhibited. Moreover, the Ca^{2+} influx through TRPC5 induced by NT-3 inhibits dendritic growth while the Ca^{2+} influx through TRPC6 induced by NT-4 promotes dendritic growth (Fig. 1). In PC12 cells, NGF markedly up-regulates TRPC1 and TRPC6 expression, but down-regulates TRPC5 expression while promoting neurite outgrowth, which suggests that a balance in TRPC1, TRPC5, and TRPC6 expression determines the neurite extension rate in neural cells[37]. However, TRPC1 and TRPC5 similarly increase Ca^{2+} influx in PC12 cells, but only TRPC1 induces neurite outgrowth. The constitutive STIM1 (D76A) mutant that activates Ca^{2+} influx *via* TRPC and

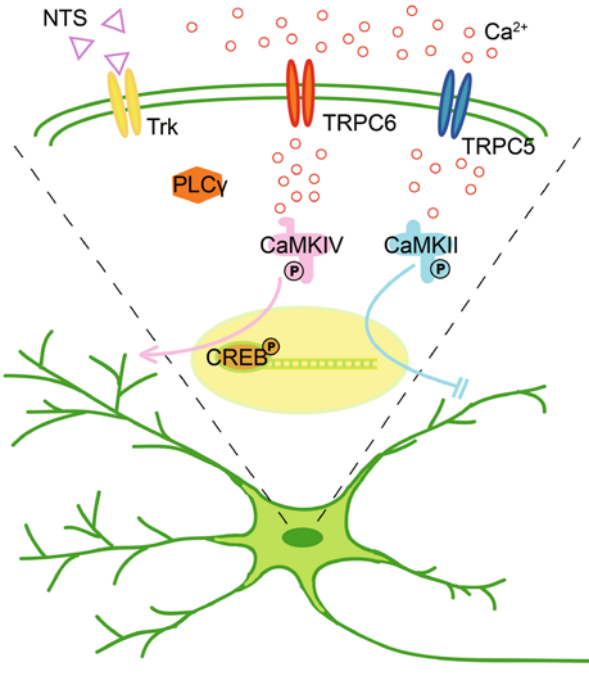

Fig. 1. Different roles of TRPC channels in dendritic development. Ca^{2+} influx through TRPC5 induced by NT-3 inhibits dendritic growth *via* CaMKIIα activation. On the contrary, Ca^{2+} influx through TRPC6 induced by NT-4 promotes dendritic growth by phosphorylation of CaMIV and CREB.

ORAI channels does not increase neurite outgrowth. Co-expression of TRPC5 with TRPC1 suppresses the effect of TRPC1 on neurite outgrowth. Most notably, the channel-dead pore mutant of TRPC1 increases neurite outgrowth to the same extent as TRPC1 (WT). Suppression of TRPC1-induced neurite outgrowth by TRPC5 is due to a marked reduction in the surface expression of TRPC1[27]. All these observations indicate that neurotrophins influence dendritic growth through TRPC channels by regulating either their channel activities or expression levels.

Mechanisms of Action of TRPC Signaling on Dendritic Development

Several mechanisms may account for the differential TRPC regulation of dendritic development. First, the spatial and temporal expression patterns of TRPCs vary with their subunits. For example, TRPC1 does not occur at the synapse in hippocampal neurons, whereas it is expressed in perisynaptic regions and is physically associated with metabotropic glutamate receptor 1 in Purkinje cells and dopaminergic neurons[38-40]. In the hippocampus, TRPC1 and TRPC3 are detectable at postnatal days 7 and 14, respectively, and their expression levels remain high into adulthood. In contrast, the peak expression of TRPC4, TRPC5, and TRPC6 is between postnatal days 7 and 14[18]. Second, distinct upstream regulators of TRPCs may impact their functions. For instance, TRPC3 can be directly phosphorylated by protein kinase G (PKG) [41]. Like PKG, PKC activity negatively regulates TRPC3[42]. $[Ca^{2+}]_i$ stimulates TRPC6 activity and inhibits TRPC7 activity *via* Ca^{2+}/calmodulin[42]. On the other hand, Ca^{2+} influx through TRPCs can be induced by the binding of neurotrophins to Trks as noted above. Thus, the distribution of neurotrophins (BDNF, NT-3, or NT-4/5) and the affinity of their receptors (TrkB or TrkC) may cause the differences in the roles of TRPCs in dendritic outgrowth. Third, the selectivity and the kinetics of cation influx through TRPCs are relatively distinct, and the subcellular localizations of TRPCs are different, which may affect the diversity of downstream signaling following their activation. Also, their effects can differ with the TRPC subunits. Long-term dendritic growth requires the activation of transcription. The calmodulin-dependent kinase (CaMK) II isoforms in dendrites are required to locally regulate dendrite dynamics. Another CaMK isoform, CaMKIV, has recently been implicated in mediating Ca^{2+}-induced transcriptional activation. This kinase, for instance, stimulates histone acetyltransferase and CREB binding protein (CBP). Activated CBP, which interacts directly with numerous transcription factors such as CREB to promote transcription, influences gene transcription by catalyzing histone acetylation and subsequent chromatin decondensation, further promoting dendritic outgrowth[43]. It has been reported that CaMKIIα, CaMKIIβ, and CaMKIV can be activated by Ca^{2+} influx through TRPC channels. Activation of TRPC5 induced by NT-3 inhibits dendritic growth through the activation of CaMKIIα, while TRPC6 activated by BDNF or NT-4 promotes dendritic elongation and arborization *via* CaMKIV. After phosphorylation, CaMKIV is transferred into the nucleus to stimulate CREB, leading to the activation of gene transcription (Fig. 1)[9, 18, 19]. Fourth, the numbers of activated channels and/or their duration of opening likely also determine the positive or negative effects of TRPCs on their functions because a small amount of Ca^{2+} influx may increase the excitability of neurons by depolarizing the membrane potential, but a large amount of persistent Ca^{2+} influx can inactivate Na^+ channels, which results in the reduction of neuronal excitability.

Conclusion and Perspectives

In conclusion, TRPC channels play critical roles in dendritic development as summarized in Table 1[11, 12]. This process can be initiated by neurotrophic factors, and after Trk activates PLCs, it hydrolyses PIP2 into membrane-bound diacylglycerol and soluble inositol triphosphate, and then the latter two activate TRPC channels. The Ca^{2+} influx through TRPC channels further triggers the activation of their downstream kinases. Finally, gene transcription, for example initiated by pCREB, is upregulated to start dendritic growth-related gene expression. Some questions remain unanswered concerning the roles of TRPC channels in dendritic development. Why is Ca^{2+} influx *via* different TRPCs antagonistic in dendritic development? In what circumstances does TRPC5 or 6 outweigh its counterpart in the otherwise “push-pull” balance in dendritic development? Since the members of the TRPC subfamily are non-selective cation channels with similar

Table 1. Properties of vertebrate TRPC channels

Name	Selectivity P_{Na}:P_{Ca}	Proposed regulation	Highest expression	Roles in dendritic outgrowth
TRPC1	Non-selective cation	Receptor-operated (heteromer)	Brain, heart, testis, ovaries	PC12 cells↑[27]
		Store-operated?		
TRPC2	1/2.7	DAG, Store-operated?	Vomeronasal organ, testis,	N.D.
			heart, brain, sperm	
TRPC3	1/1.5–1.6	DAG, $InsP_3R$	Brain, placenta, heart, muscle	Hippocampal neurons↑[14]
TRPC4	1/7	Receptor-operated	Brain, endothelia, adrenal gland,	DRG neurons↑[26]
		Store-operated?	retina, testis	Hippocampal neurons↓[18]
TRPC5	1/9–9.5	Receptor-operated	Brain	PC12 cells↓[27]
		Store-operated?		Hippocampal neurons↓[19]
TRPC6	1/5	DAG	Brain, lung, muscle	Hippocampal neurons↑[13, 19]
TRPC7	1/1.9–2	DAG, store-operated	Eye, heart, lung	N.D.

protein sequences at both the N- and C- termini, it is worth studying the different effects of the transmembrane regions on dendritic development. Another related question is why even the same TRPC channel (e.g. TRPC6) acts differently in various cell types. To some extent, these questions can be explained by the temporal or spatial distribution of these channels, however, more experiments are needed to solve these puzzles. Understanding of these questions is important for exploration of the roles of TRPCs in dendritic development and beyond.

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REFERENCES

[1] Lohmann C, Wong RO. Regulation of dendritic growth and plasticity by local and global calcium dynamics. Cell Calcium 2005, 37: 403–409.

[2] Zheng JQ, Poo MM. Calcium signaling in neuronal motility. Ann Rev Cell Dev Biol 2007, 23: 375–404.

[3] Bloodgood BL, Sabatini BL. Ca^{2+} signaling in dendritic spines. Curr Opin Neurobiol 2007, 17: 345–351.

[4] Higley MJ, Sabatini BL. Calcium signaling in dendrites and spines: practical and functional considerations. Neuron 2008, 59: 902–913.

[5] Lohmann C, Myhr KL, Wong RO. Transmitter-evoked local calcium release stabilizes developing dendrites. Nature 2002, 418: 177–181.

[6] Rajan I, Cline HT. Glutamate receptor activity is required for normal development of tectal cell dendrites *in vivo*. J Neurosci 1998, 18: 7836–7846.

[7] Jakowec MW, Fox AJ, Martin LJ, Kalb RG. Quantitative and qualitative changes in AMPA receptor expression during spinal cord development. Neuroscience 1995, 67: 893–907.

[8] Redmond L, Kashani AH, Ghosh A. Calcium regulation of dendritic growth *via* CaM kinase IV and CREB-mediated transcription. Neuron 2002, 34: 999–1010.

[9] Puram SV, Riccio A, Koirala S, Ikeuchi Y, Kim AH, Corfas G, *et al.* A TRPC5-regulated calcium signaling pathway controls dendrite patterning in the mammalian brain. Genes Dev 2011, 25: 2659–2673.

[10] Cosens DJ, Manning A. Abnormal electroretinogram from a Drosophila mutant. Nature 1969, 224: 285–287.

[11] Montell C. The TRP superfamily of cation channels. Sci STKE 2005, 2005: re3.

[12] Ramsey IS, Delling M, Clapham DE. An introduction to TRP channels. Annu Rev Physiol 2006, 68: 619–647.

[13] Tai Y, Feng S, Du W, Wang Y. Functional roles of TRPC channels in the developing brain. Pflugers Arch 2009, 458: 283–289.

[14] Amaral MD, Pozzo-Miller L. TRPC3 channels are necessary for brain-derived neurotrophic factor to activate a nonselective cationic current and to induce dendritic spine formation. J Neurosci 2007, 27: 5179–5189.

[15] Teilmann SC, Byskov AG, Pedersen PA, Wheatley DN,

Pazour GJ, Christensen ST. Localization of transient receptor potential ion channels in primary and motile cilia of the female murine reproductive organs. Mol Reprod Dev 2005, 71: 444–452.

[16] Shim S, Goh EL, Ge S, Sailor K, Yuan JP, Roderick HL*, et al.* XTRPC1-dependent chemotropic guidance of neuronal growth cones. Nat Neurosci 2005, 8: 730–735.

[17] Wang GX, Poo MM. Requirement of TRPC channels in netrin-1-induced chemotropic turning of nerve growth cones. Nature 2005, 434: 898–904.

[18] Tai Y, Feng S, Ge R, Du W, Zhang X, He Z*, et al.* TRPC6 channels promote dendritic growth via the CaMKIV-CREB pathway. J Cell Sci 2008, 121: 2301–2307.

[19] He Z, Jia C, Feng S, Zhou K, Tai Y, Bai X*, et al.* TRPC5 channel is the mediator of neurotrophin-3 in regulating dendritic growth via CaMKIIα in rat hippocampal neurons. J Neurosci 2012, 32: 9383–9395.

[20] Heiser JH, Schuwald AM, Sillani G, Ye L, Muller WE, Leuner K. TRPC6 channel-mediated neurite outgrowth in PC12 cells and hippocampal neurons involves activation of RAS/MEK/ERK, PI3K, and CAMKIV signaling. J Neurochem 2013, 127: 303–313.

[21] Leuner K, Li W, Amaral MD, Rudolph S, Calfa G, Schuwald AM*, et al.* Hyperforin modulates dendritic spine morphology in hippocampal pyramidal neurons by activating Ca(2+)-permeable TRPC6 channels. Hippocampus 2013, 23: 40–52.

[22] Amiri H, Schultz G, Schaefer M. FRET-based analysis of TRPC subunit stoichiometry. Cell Calcium 2003, 33: 463–470.

[23] Hoenderop JG, Voets T, Hoefs S, Weidema F, Prenen J, Nilius B*, et al.* Homo- and heterotetrameric architecture of the epithelial Ca2+ channels TRPV5 and TRPV6. EMBO J 2003, 22: 776–785.

[24] Kedei N, Szabo T, Lile JD, Treanor JJ, Olah Z, Iadarola MJ*, et al.* Analysis of the native quaternary structure of vanilloid receptor 1. J Biol Chem 2001, 276: 28613–28619.

[25] Kuzhikandathil EV, Wang H, Szabo T, Morozova N, Blumberg PM, Oxford GS. Functional analysis of capsaicin receptor (vanilloid receptor subtype 1) multimerization and agonist responsiveness using a dominant negative mutation. J Neurosci 2001, 21: 8697–8706.

[26] Wu D, Huang W, Richardson PM, Priestley JV, Liu M. TRPC4 in rat dorsal root ganglion neurons is increased after nerve injury and is necessary for neurite outgrowth. J Biol Chem 2008, 283: 416–426.

[27] Heo DK, Chung WY, Park HW, Yuan JP, Lee MG, Kim JY. Opposite regulatory effects of TRPC1 and TRPC5 on neurite outgrowth in PC12 cells. Cell Signal 2012, 24: 899–906.

[28] Confort C, Charrasse S, Clos J. Nerve growth factor enhances DNA synthesis in cultured cerebellar neuroblasts. Neuroreport 1991, 2: 566–568.

[29] Pincus DW, DiCicco-Bloom E, Black IB. Role of voltage-sensitive calcium channels in mitogenic stimulation of neuroblasts. Brain Res 1991, 553: 211–214.

[30] Sieber-Blum M. Role of the neurotrophic factors BDNF and NGF in the commitment of pluripotent neural crest cells. Neuron 1991, 6: 949–955.

[31] Segal RA, Greenberg ME. Intracellular signaling pathways activated by neuropathic factors. Ann Rev Neurosci 1996, 19: 463–489.

[32] McAllister AK, Lo DC, Katz LC. Neurotrophins regulate dendritic growth in developing visual cortex. Neuron 1995, 15: 791–803.

[33] Dijkhuizen PA, Ghosh A. Regulation of dendritic growth by calcium and neurotrophin signaling. Progress in Brain Research 2005, 147: 15–27.

[34] McFarlane S. Dendritic morphogenesis: building an arbor. Mol Neurobiol 2000, 22: 1–9.

[35] Horch HW. Local effects of BDNF on dendritic growth. Rev Neurosci 2004, 15: 117–129.

[36] Li W, Calfa G, Larimore J, Pozzo-Miller L. Activity-dependent BDNF release and TRPC signaling is impaired in hippocampal neurons of Mecp2 mutant mice. Proc Natl Acad Sci U S A 2012, 109: 17087–17092.

[37] Kumar S, Chakraborty S, Barbosa C, Brustovetsky T, Brustovetsky N, Obukhov AG. Mechanisms controlling neurite outgrowth in a pheochromocytoma cell line: the role of TRPC channels. J Cell Physiol 2012, 227: 1408–1419.

[38] Strubing C, Krapivinsky G, Krapivinsky L, Clapham DE. TRPC1 and TRPC5 form a novel cation channel in mammalian brain. Neuron 2001, 29: 645–655.

[39] Kim SJ, Kim YS, Yuan JP, Petralia RS, Worley PF, Linden DJ. Activation of the TRPC1 cation channel by metabotropic glutamate receptor mGluR1. Nature 2003, 426: 285–291.

[40] Tozzi A, Bengtson CP, Longone P, Carignani C, Fusco FR, Bernardi G*, et al.* Involvement of transient receptor potential-like channels in responses to mGluR-I activation in midbrain dopamine neurons. Eur J Neurosci 2003, 18: 2133–2145.

[41] Kwan HY, Huang Y, Yao X. Regulation of canonical transient receptor potential isoform 3 (TRPC3) channel by protein kinase G. Proc Natl Acad Sci U S A 2004, 101: 2625–2630.

[42] Venkatachalam K, Zheng F, Gill DL. Regulation of canonical transient receptor potential (TRPC) channel function by diacylglycerol and protein kinase C. J Biol Chem 2003, 278: 29031–29040.

[43] Hagenston AM, Bading H. Calcium signaling in synapse-to-nucleus communication. Cold Spring Harb Perspect Biol 2011, 3: a004564.