Chapter 22
Calcium Signaling and Gene Expression

Basant K. Puri

Abstract Calcium signaling plays an important role in gene expression. At the transcriptional level, this may underpin mammalian neuronal synaptic plasticity. Calcium influx into the postsynaptic neuron via: *N*-methyl-D-aspartate (NMDA) receptors activates small GTPase Rac1 and other Rac guanine nucleotide exchange factors, and stimulates calmodulin-dependent kinase kinase (CaMKK) and CaMKI; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors that are not impermeable to calcium ions, that is, those lacking the glutamate receptor-2 subunits, leads to activation of Ras guanine nucleotide-releasing factor proteins, which is coupled with activation of the mitogen-activated protein kinases/extracellular signal-regulated kinases signaling cascade; L-type voltage-gated calcium channels activates signaling pathways involving CaMKII, downstream responsive element antagonist modulator and distinct microdomains. Key members of these signaling cascades then translocate into the nucleus, where they alter the expression of genes involved in neuronal synaptic plasticity. At the post-transcriptional level, intracellular calcium level changes can change alternative splicing patterns; in the mammalian brain, alterations in calcium signaling via NMDA receptors is associated with exon silencing of the CI cassette of the NMDA R1 receptor (*GRIN1*) transcript by UAGG motifs in response to neuronal excitation. Regulation also occurs at the translational level; transglutaminase-2 (TG2) mediates calcium ion-regulated crosslinking of Y-box binding protein-1 (YB-1) translation-regulatory protein in TGFβ1-activated myofibroblasts; YB-1 binds smooth muscle α-actin mRNA and regulates its translational activity. Calcium signaling is also important in epigenetic regulation, for example in respect of changes in cytosine bases. Targeting calcium signaling may provide therapeutically useful options, for example to induce epigenetic reactivation of tumor suppressor genes in cancer patients.

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22.1 Introduction

Gene expression is the process by which the information in a DNA sequence in a gene is used to biosynthesize an RNA or polypeptide [1]. In turn, this involves transcription, that is, the synthesis of an RNA copy from a DNA template, and, in the case of polypeptides, translation, that is, protein synthesis on a messenger RNA (mRNA) template [1]. It has recently become increasingly apparent that calcium signaling is relevant to the regulation of eukaryotic transcription, alternative splicing patterns, and translation. In this chapter, the roles of calcium ion signaling in these processes and in the regulation of epigenetic mechanisms will be discussed.

Calcium ion binding, and associated phosphorylation, are associated with changes in protein electrical charge, conformation and interactions; phosphate moieties can be removed by protein kinases from adenosine-5′-triphosphate (ATP) and attached covalently to the three common amino acid residues which have free hydroxyl groups, namely the polar amino acids serine, threonine and tyrosine [2, 3]. Thus, calcium ions and phosphate ions can effect signal transduction [2, 3]. Aside from its role in gene expression, calcium ion signaling, both intercellular and intracellular, has numerous other important functions, ranging from mitochondrial functioning and innate immunity to apoptosis and cell death pathways [2, 4, 5]. Other chapters of this work deal with many of these. An excellent review from the year 2000 which considers the versatility and universality of calcium signaling is that of Berridge, Lipp and Bootman [6], while Putney and Tomita review the role of phospholipase C signaling and calcium influx [7]; in this chapter, the focus is on the role of calcium ion signaling in respect of gene expression.

22.2 Pre-translation

22.2.1 Eukaryotic Transcription

Eukaryotic transcription occurs on a chromatin template (unlike the case for prokaryotes, in which a DNA template is used for transcription); the following three classes of RNA polymerase are involved: RNA polymerase I, which transcribes 18S/28S ribosomal RNA (rRNA); RNA polymerase II, which transcribes mRNA and certain small RNAs; and RNA polymerase III, which transcribes transfer RNA (tRNA), 5S rRNA and certain small RNAs [1].

22.2.2 Calcium-Related Transcriptional Regulation

Calcium-dependent gene expression regulation at the transcriptional level is thought to underlie animal neuronal synaptic plasticity and thereby mediate learning and adaptation to the environment [8]. In mammalian neurons, such regulation involves a complex cascade of signaling molecules, beginning with influx of calcium ions into the postsynaptic neuron via *N*-methyl-D-aspartate (NMDA) receptors (for glutamate), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (also for glutamate), or L-type voltage-gated calcium channels (VGCCs) [9–11]. Each of these three possibilities will be briefly considered in turn.

Calcium ion influx through NMDA receptors activates small GTPase Rac1 (also known as Ras-related C3 botulinum toxin substrate 1), which acts as a pleiotropic activator of actin, and also activates other Rac guanine nucleotide exchange factors (GEFs) such as kalirin-7 and betaPIX (βPIX) [12, 13]. It also stimulates calmodulin-dependent kinase kinase (CaMKK) and CaMKI, which in turn phosphorylates βPIX [13]. Kalirin-7 interacts with AMPA receptors, controlling their synaptic expression [12]. While most AMPA receptors are calcium impermeable, those lacking the glutamate receptor-2 (GluR2) subunits do allow calcium ion flow. Calcium ion influx through such calcium-permeable AMPA receptors leads to activation of Ras guanine nucleotide-releasing factor (RasGRF) proteins, which in turn is coupled with activation of the mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK; also known as the Ras-ERK or Ras-Raf-MEK-ERK) signaling cascade [14]. Finally, calcium ion influx through L-type VGCCs appears to activate signaling pathways involving CaMKII, downstream responsive element antagonist modulator (DREAM), distinct microdomains (MD-I and MD-II), and possibly the distal C-terminal (dCT) fragment of the L-type receptor and beta subunits [15]. These consequences of calcium ion influx through NMDA, AMPA receptors and VGCCs are summarized in Table 22.1.

In turn, key members of the above signaling cascades, such as CAMKII, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), MAPK/ERK, GTP-Rac, DREAM, MD-I, MD-II, and possibly dCT and β4c, cross from the cytoplasm into the nucleus [8, 15]. Here, they alter the expression of, amongst others, the non-

Table 22.1 Primary activated molecules following calcium ion influx through NMDA and AMPA receptors and VGCCs

Type of calcium ion receptor or channel	NMDA receptors	AMPA receptors	VGCCs
Primary activated molecules	Small GTPase Rac1	RasGRF	CaMKII
	Kalirin-7		DREAM
	βPIX		MD-I
	CaMKK		MD-II
	CaMKI		dCT
			β subunits

coding RNA (ncRNA) miR-132 (which is a microRNA), *CREM* (which encodes the protein cyclic adenosine monophosphate (cAMP) responsive element modulator), *BDNF* (which encodes brain-derived neurotrophic factor), the proto-oncogene *c-Fos*, *PDYN* (which encodes a preproprotein which, following proteolysis, gives rise to several opioid peptides), *WNT2* (wingless-type MMTV integration site family, member 2; encoding signaling proteins relating to the Wnt signal transduction pathways), *BCL2* (encoding B-cell lymphoma 2 or Bcl-2), *SOD2* or *MnSOD* (encoding superoxide dismutase 2, mitochondrial), *XIAP* (X-linked inhibitor of apoptosis family of proteins), *NR4A1* or *Nur77* (nuclear receptor subfamily 4 group A member 1 or nerve growth factor IB), *ARC* (which encodes activity-regulated cytoskeleton-associated protein), HOMER1 (Homer scaffold protein 1 or Homer1a), *SLC8A1* or *NCX1* (solute carrier family 8 member A1 or sodium/calcium exchanger), and *SLC8A3* or *NCX3*. These are involved in synaptic development, dendritic growth, and neuronal plasticity; changes in their expression, as well as mutations in some of these loci, may be associated with neurocognitive disorders [8, 15]. Furthermore, EphB receptor tyrosine kinases, localized at excitatory synapses, cluster with NMDA receptors and modulate the function of the latter during early synaptogenesis [16].

A similar picture exists in respect of the mammalian heart, from which efflux of calcium ions normally takes place via plasma membrane calcium ATPases (PMCAs). Sustained increase in intracellular calcium ion concentration in cardiac cells activates the calcineurin moiety of PMCA4, which in turn dephosphorylates nuclear factor of activated T-cells (NFAT), which then translocates to the nucleus where it activates genes involved in cardiac hypertrophy [17].

The above examples have been drawn from animal cells. Calcium-related transcriptional regulation has also been shown to be important in plants. This has been studied in the unicellular green alga *Chlamydomonas reinhardtii*, which has a relatively short life-cycle and a fully sequenced genome [18–20]. In chloroplasts of this alga, calcium ion signaling and the calcium ion-binding protein CAS, acting in response to cues such as biotic and abiotic stress and carbon dioxide concentrating mechanisms, ultimately act upon a number of nuclear targets, including: *APX* (encoding ascorbate peroxidase); flg22 (flagellin 22); *HSF*s (heat shock transcription factors); *HSP*s (heat shock proteins); and *LHCRS3* (light-harvesting complex stress-related protein 3) [21]. These result in changes in basal defense responses and carbon dioxide concentration mechanisms [21].

22.2.3 Changes in Alternative Splicing Patterns

At the post-transcriptional, but pre-translational, level, intracellular calcium ion level changes can also alter gene expression by causing changes in alternative splicing patterns, whereby the same pre-mRNA generates mRNAs (post-splicing) which have different exon combinations [1].

In the mammalian brain, it has been shown that alterations in calcium ion signaling via NMDA receptors is associated with exon silencing of the CI cassette (exon 19) of the NMDA R1 receptor (*GRIN1*) transcript by UAGG motifs in response to neuronal excitation [22]. CI mediates targeting of NMDA R1 to the plasma membrane, has an endoplasmic reticulum retention signal, and contains a binding site for calcium/calmodulin [23, 24]. This may offer a powerful strategy for neuronal adaptation to hyperstimulation and may explain the diverse properties of NMDA receptors in different groups of neurons [22, 24].

Mechanical stimulation of hair cells of the basilar papilla of the avian inner ear, which is homologous to the organ of Corti, or spiral organ, of mammals, is associated with changes in intracellular calcium ion concentration via changes in the kinetic properties of calcium-ion-activated potassium ion channels; in turn, changes in calcium concentration have been found to be associated with alternative mRNA splicing patterns which tune individual hair cells to specific auditory frequencies [25–27].

In a similar vein, it is also noteworthy that GH3 pituitary cell depolarization has been shown to repress *KCNMA1* or *STREX* (potassium calcium-activated channel subfamily M alpha 1, previously stress-axis regulated exon) exon splicing in BK (big potassium, also known as Maxi-K, Kcal.1 or slo1) potassium ion channel transcripts via CaMKs [28].

Mammalian VGCCs are able to be activated over a relatively wide range of electrical potential differences, whereas the activation voltage dependence of calcium channel isoforms found in different tissues are tuned to their specific corresponding physiological functions. For example, the type known as 1.1 is the VGCC least responsive to depolarization and it has been found to achieve this electrical property through alternative splicing [29]. It acts both as a calcium ion channel in embryonic muscle and as a sensor of electrical potential difference in mature skeletal muscle for excitation-contraction coupling, and its relative lack of responsiveness to depolarization serves these functions well [29, 30]. On the other hand, the type of VGCC known as 1.2, which is the main type found in the brain and the cardiovascular system, is more responsive to depolarization; interestingly, the adjustment of its optimum activation voltage-dependency has recently been shown not to result from alternative splicing, showing that more than one mechanism is involved in fine tuning VGCCs [30].

22.3 Translation

Calcium regulation of gene expression at the translational level has been demonstrated in human cultured cells. The peptide transforming growth factor beta (TGFβ) controls cell proliferation in many tissues, including connective tissue [31]. In particular, repair of mammalian tissue injury can be initiated by TGFβ1 receptor signaling [32–35]. Indeed, poor regulation of this process may lead to dysfunctional cardiopulmonary fibrosis and chronic myofibroblast differentiation [36–38]. In

2013, it was shown, by Willis and colleagues, that the protein cross-linking enzyme transglutaminase-2 (TG2) mediates calcium ion-regulated crosslinking of Y-box binding protein-1 (YB-1) translation-regulatory protein in TGFβ1-activated myofibroblasts; YB-1 binds smooth muscle α-actin (*SMαA*) mRNA and regulates its translational activity [39].

22.4 Epigenetics

22.4.1 Epigenetic Mechanisms

Tollefsbol has defined epigenetic processes as 'changes of a biochemical nature to the DNA or its associated proteins or RNA that do not change the DNA sequence itself but do impact the level of gene expression' [40]. These biochemical changes are reversible and include DNA methylation, modifications in chromatin, nucleosome positioning, and ncRNA profile alterations [41]. The study of epigenetics is a rapidly developing field of research, which is of relevance to the study of diseases and, at a fundamental level, to a deeper understanding of intracellular communication [40–42]. It has recently become increasingly clear that calcium ion signaling plays an important role in epigenetic regulation.

22.4.2 Calcium-Related Epigenetic Regulation

A few recent examples are given to illustrate the important role of calcium signaling in epigenetic regulation.

Regarding DNA methylation, it has been shown that changes in the calcium content of murine diets can induce methylation changes in DNA cytosine bases. For example, a calcium-deficient diet in pregnant and nursing rats is associated with hypomethylation of the pup hepatic *HSD11B2* promoter region; this gene encodes the NAD^+-dependent enzyme corticosteroid 11-β-dehydrogenase isozyme 2 (also known as 11-β-hydroxysteroid dehydrogenase 2), and such pups have higher serum corticosterone levels than matched control pups from mothers fed a normal diet [43].

Raynal and colleagues tested a number of drugs which re-activate silenced gene expression in human cancer cells [44]. They found 11 newly identified pharmacological agents, such as cardiac glycosides, which induce methylated and silenced CpG island promoters which drive *GFP*, the gene for green fluorescent protein, and endogenous tumor suppressor genes in cancer cell lines. Surprisingly, rather than causing local DNA methylation changes or global histone changes, all 11 agents were found to alter calcium ion signaling and trigger CaMK activity; in turn, this released methyl CpG binding protein 2 (MeCP2), a methyl-binding protein, from silenced promoters, thus causing gene activation [44–46]. Given

that epigenetic changes are, in principle, reversible, this suggests that a potential therapeutic approach to the treatment of cancer might involve targeting calcium signaling in order to induce epigenetic reactivation of tumor suppressor genes [44].

It has been pointed out that the calcium ion influx through postsynaptic NMDA receptors and VGCCs mentioned above, which can lead to changes in *BDNF* expression, for example, also cause epigenetic changes such DNA hypomethylation (unmethylated cytosines) and histone acetylation; indeed, histone modification and changes in DNA methylation appear to be important features of the mediation of the risk of the development of major depressive disorder [47].

It should also be noted that epigenetic changes can also regulate calcium ion homeostasis. For example, epigenetic modification of the promoter region of *SERCA2a*, which encodes sarcoplasmic reticulum Ca^{2+}-ATPase and which is rich in CpG islands, changes the expression of this gene and is associated with alterations in calcium ion homeostasis; indeed, it has been suggested that demethylation in this promoter region, induced by the hydrazinophthalazine antihypertensive pharmacological agent hydralazine, may lead to modulated cardiomyocytic calcium homeostasis and consequent improved cardiac functioning [48].

22.5 Discussion

The examples given above have shown that calcium signaling has an important role in gene expression. This may involve regulation at the level of gene transcription; it may involve the regulation of alternative splicing; it may occur at the level of gene translation; and it may entail epigenetic mechanisms. Furthermore, these regulatory processes are bidirectional, in that changes in gene expression can themselves affect calcium ion homeostasis and calcium ion signaling. These findings offer important potential therapeutic avenues for the treatment of numerous diseases.

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