Chapter 2
CREB at the Crossroads of Activity-Dependent Regulation of Nervous System Development and Function

Yesser H. Belgacem and Laura N. Borodinsky

Abstract The central nervous system is a highly plastic network of cells that constantly adjusts its functions to environmental stimuli throughout life. Transcription-dependent mechanisms modify neuronal properties to respond to external stimuli regulating numerous developmental functions, such as cell survival and differentiation, and physiological functions such as learning, memory, and circadian rhythmicity. The discovery and cloning of the cyclic adenosine monophosphate (cAMP) responsive element binding protein (CREB) constituted a big step toward deciphering the molecular mechanisms underlying neuronal plasticity. CREB was first discovered in learning and memory studies as a crucial mediator of activity-dependent changes in target gene expression that in turn impose long-lasting modifications of the structure and function of neurons. In this chapter, we review the molecular and signaling mechanisms of neural activity-dependent recruitment of CREB and its cofactors. We discuss the crosstalk between signaling pathways that imprints diverse spatiotemporal patterns of CREB activation allowing for the integration of a wide variety of stimuli.

Keywords Spatiotemporal integration • Crosstalk • Plasticity • Activity-dependent transcription factors • CREB cofactors

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R. von Bernhardi et al. (eds.), *The Plastic Brain*, Advances in Experimental Medicine and Biology 1015, DOI 10.1007/978-3-319-62817-2_2

Abbreviations

AC	Adenylate cyclase
ATF1	Activating transcription factor 1
BDNF	Brain-derived neurotrophic factor
b-zip	Basic leucine zipper domain
CaMKII/IV	Ca^{2+}/Calmodulin dependent Kinase II and IV
cAMP	3′,5′-cyclic adenosine monophosphate
CaRE	Ca^{2+} Responsive Element
CBP	CREB Binding Protein
Cn	Calcineurin
CRE	cAMP-responsive elements
CREB	cAMP responsive element binding protein
CRTC	cAMP-regulated transcriptional coactivator
CREM	cAMP responsive element modulator ERK
DARPP	Dopamine and cAMP–regulated phosphoprotein
ERK	Extracellular signal-regulated kinase
IP3	Inositol 1,4,5-trisphosphate
KID	Kinase Inducible Domain
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinase
MSK-I	Mitogen/Stress Activated Kinase I
NGF	Nerve growth factor
NMDA	N-Methyl-D-Aspartate
NMDAR	N-Methyl-D-Aspartate ionotropic glutamate receptor
PDGF	Platelet-derived growth factor
PI3K	Phosphatidylinositol 3-kinase
PIP3	(3,4,5)-trisphosphate
PKA	cAMP-dependent Protein Kinase
PKB	Protein Kinase B
PKC	Protein Kinase C
pp90RSK	pp90 ribosomal S6 kinase
Shh	Sonic hedgehog
SIK1	Salt-inducible kinase 1
TORC	Transducer of regulated CREB
TRPC	Transient receptor potential canonical channel
VGCC	Voltage-gated Ca^{2+} channel

Introduction

During development of the nervous system, numerous cascades of transcription factors are the means of a genetic program governing a wide variety of critical events such as neural cell proliferation, migration, differentiation and synapse formation.

As mentioned in Chap. 1, until recently, the dogma has been that genetic programs determine the fate of different neural cells. However, emerging studies provided by multiple research groups indicate that the cell environment allows for plasticity in the process of neural cell specification. This phenomenon often involves activity-dependent mechanisms that add a homeostatic dimension to nervous system development. Once development concludes, control of gene expression by activity-dependent mechanisms becomes a predominant feature of neurons. Interestingly, these mechanisms resemble those occurring during development.

In this chapter, we review prominent examples of activity-induced molecular mechanisms modulating gene expression in the developing and adult central nervous system. We particularly focus on 3′,5′-cyclic adenosine monophosphate (cAMP) responsive element binding protein (CREB) as the paradigmatic model of an activity-dependent transcription factor that participates in diverse processes of the developing and mature nervous system by regulating expression of crucial target genes.

We present some of the classical intracellular signaling cascades that transduce extracellular activity-dependent stimuli to CREB activation and the crosstalk among them. We also present the more recently discovered mechanisms controlling CREB expression and activity.

Molecular Structure of CREB

The CREB family of transcription factors is composed of several members, including CREB itself, the activating transcription factor 1 (ATF1), and the cAMP responsive element modulator CREM, among others (Altarejos and Montminy 2011; Flavell and Greenberg 2008; Mayr and Montminy 2001). There is a high level of redundancy between members of the CREB family that act as homo- or heterodimers to bind to cAMP-responsive elements (CRE) found in the regulatory regions of target genes (Altarejos and Montminy 2011; Flavell and Greenberg 2008; Mayr and Montminy 2001).

CREB is mainly activated or inactivated through phosphorylation or dephosphorylation of key serine amino acids, a mechanism characterized by a quick response rate leading to transcription of target genes, peaking 30 min to 1 h after stimulation (Michael et al. 2000). Several kinases have been shown to phosophorylate Ser133, such as cAMP-dependent Protein Kinase (PKA), Protein Kinase C (PKC), Akt, MAPKAP Kinase 2, Ca^{2+}/Calmodulin dependent Kinase II and IV (CaMKII/IV) and Mitogen/Stress Activated Kinase I (MSK-I) (Mayr and Montminy 2001). Ser133 is dephosphorylated by such phosphatases as serine/threonine phosphatases PP-1 (Bito et al. 1996; Alberts et al. 1994) and PP-2A (Wadzinski et al. 1993).

Once phosphorylated at Ser 133, CREB is able to recruit transcription coactivators such as the histone acetyltransferase CREB Binding Protein (CBP) and its paralogue p300; it thus upregulates transcription of target genes (Parker et al. 1996;

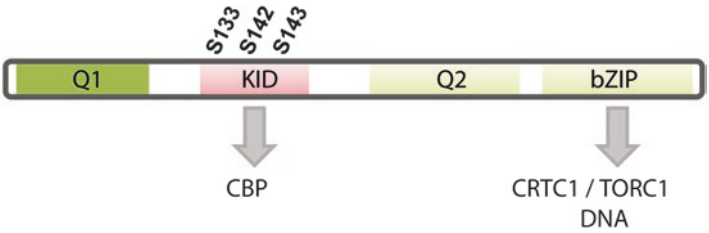

Fig. 2.1 CREB structure and function. Main domains of CREB are represented by *colored boxes*. The C-terminal basic leucine zipper domain (b-zip) is important for CREB homodimerization and for binding to the CRE element on target gene enhancer regions. The KID domain contains several serines (S) that, depending on their phosphorylation status, control the interaction between CREB and cofactors such as CBP. Two glutamine-rich domains (Q1 and Q2) are constitutive activators of transcription and interact with several co-activators and members of the transcriptional machinery. *Arrows* indicate the binding potential of KID and bZIP domains

Mayr and Montminy 2001). While Ser133 phosphorylation is the main way of activating CREB, other phosphorylation sites are important for the regulation of CREB activity (Kornhauser et al. 2002; Sakamoto et al. 2011) such as Ser142, which depending on the context, can activate or inhibit CREB's promotion of transcription (Wu and McMurray 2001; Gau et al. 2002).

CREB1 is a 43 kD soluble protein, which is constitutively expressed and is mainly found in the nucleus. It is a member of the basic leucine zipper domain (b-zip) transcription factor family (Mayr and Montminy 2001) (Fig. 2.1). The C-terminal b-zip domain is important for CREB homodimerization and for binding to the specific DNA palindromic consensus sequences of CRE "TGACGTCA" (Montminy and Bilezikjian 1987). However, CREB is capable, though with a five-fold reduced affinity, to bind on half CREs "CGTCA" (Fink et al. 1988; Craig et al. 2001). Phosphorylation of CREB does not seem to affect binding on CRE (Mayr and Montminy 2001). Methylation of the CpG present in CRE (Iguchi-Ariga and Schaffner 1989; Zhang et al. 2005) as well as the sequence of DNA surrounding CRE are important regulators of CREB binding on CREs (Connor and Marriott 2000; Mayr and Montminy 2001).

Upon binding to DNA and activation by phosphorylation on the Kinase Inducible Domain (KID), CREB recruits cofactors and members of the transcriptional machinery. The KID domain is surrounded by two glutamine-rich domains (Q1 and Q2) (Fig. 2.1) that are constitutive activators of transcription (Felinski et al. 2001; Brindle et al. 1993; Quinn 1993) and interact with several co-activators and members of the transcriptional machinery (Felinski and Quinn 1999).

While more than 750,000 potential binding sites for CREB have been identified in the human genome (Zhang et al. 2005), CREB stimulation leads to the expression of specific set of genes (Impey et al. 2004; Zhang et al. 2005), highlighting the importance of the regulation of CREB's action. This is done at multiple levels ranging from the type of ligand and signaling mechanism triggering CREB phosphorylation/dephosphorylation, the cell type and subcellular localization of the transducing machinery, the presence of cofactors, and the methylation level of target DNA sequences.

Mechanisms of CREB Activation

Researchers in the field of learning and memory have been major contributors to the discovery of how electrical activity is translated into gene expression. Stimulation of sensory neurons activates specific neuronal networks through synaptic connections that, under specific conditions, are reinforced and stabilized in time (for reviews see Kandel et al. 2014; Flavell and Greenberg 2008).

The cAMP/PKA Axis

The first described signaling pathway involving CREB as playing a role in central nervous system physiology was discovered while studying learning and memory. The studies done on the mollusk *Aplysia californica* identified a model for simple forms of procedural memories such as habituation, dishabituation and sensitization (Kandel et al. 2014). Aplysia has a simple reflex called the gill withdrawal reflex: if the siphon of the animal is mechanically stimulated, sensory neurons innervating motor neurons trigger the withdrawal of the gill. Sensitization occurs if, before stimulating the siphon, an electric shock is applied to the tail of the animal, resulting in a stronger depolarization of motor neurons during the gill withdrawal reflex. Eric Kandel's group discovered that this sensitization is due to a release of serotonin by modulatory neurons, resulting in synthesis of cAMP in sensory neurons (Brunelli et al. 1976) thus activating PKA (Castellucci et al. 1980). Other groups also identified the cAMP signaling axis as a component in various forms of learning and memory in *Drosophila melanogaster* (Dudai et al. 1976; Byers et al. 1981). Interestingly, when a single shock is applied to the Aplysia's tail, the sensitization does not last more than few hours. However, if multiple shocks are delivered, the sensitization lasts several days, suggesting that a long-term memory has been acquired. This long term facilitation is dependent on mRNA and protein synthesis (Montarolo et al. 1986). The mechanism linking cAMP and activity to gene transcription in sensory neurons during long-term facilitation remained elusive until Montminy and colleagues' breakthrough while investigating the mechanisms by which cAMP regulates somatostatin gene transcription. By analyzing the regulatory sequences of the somatostatin gene, they found a short palindromic sequence (5′-TGACGTCA-3) responsive to cAMP (CRE) that is highly conserved in the regulatory regions of other genes for which transcription is controlled by cAMP (Montminy et al. 1986). Shortly after, Marc Montminy and Louise Bilezikjian identified a nuclear protein that binds to CRE and named it CREB (Montminy and Bilezikjian 1987). Using an elegant approach, Dash and colleagues (Dash et al. 1990) injected oligonucleotides coding for CRE and abolished long-term but not short-term facilitation in *Aplysia* sensory neurons, suggesting a prominent role for CREB in transducing activity into gene transcription necessary for long-term memory. In summary, the serotonin receptor, a G-protein-coupled membrane receptor recruits an adenylate cyclase (AC), leading to production of cAMP and activation of PKA that phosphorylates CREB on the KID domain, particularly at the Ser133, activating it (Figs. 2.1 and 2.2).

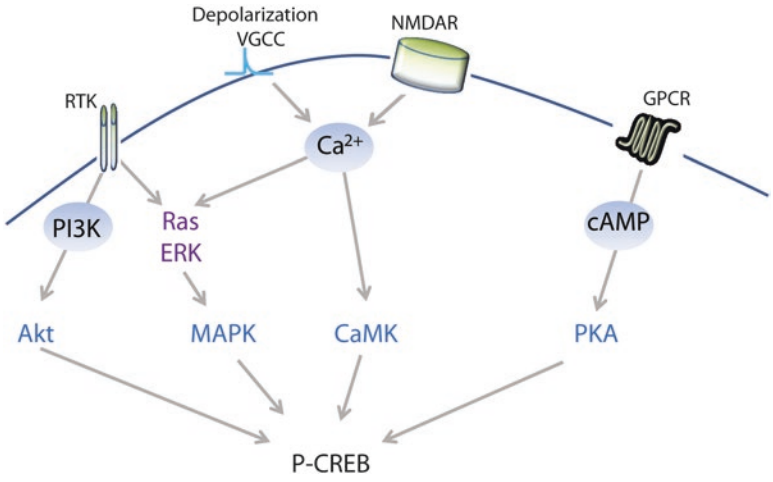

Fig. 2.2 Classical signaling pathways that lead to CREB activation. Membrane depolarization (voltage-gated Ca^{2+} channels, VGCC) and glutamate receptors (NMDAR) lead to cytosolic and nuclear Ca^{2+} elevations recruiting the CaMK or Ras/MAPK signaling pathways. G-protein-coupled receptors (GPCR) activate the cAMP/PKA axis, while Receptor Tyrosine Kinases (RTKs) generally recruit the Ras/MAPK or Akt signaling cascades

Calcium as Second Messenger

Ca^{2+} is a very important second messenger implicated in the transduction of numerous signaling pathways and playing a wide variety of roles in the central nervous system development and physiology (Bito and Takemoto-Kimura 2003; Flavell and Greenberg 2008; Ghosh et al. 1994; Carlezon et al. 2005; Lonze and Ginty 2002; Mayr and Montminy 2001; Sakamoto et al. 2011; Rosenberg and Spitzer 2011; Spitzer 2006). Increases in cytosolic Ca^{2+} concentration occur through a wide variety of mechanisms (Ghosh et al. 1994; Kornhauser et al. 1990; Averaimo and Nicol 2014; Brini et al. 2014), including voltage-gated Ca^{2+} channels (VGCCs) upon depolarization, and ligand-gated Ca^{2+} channels such as the N-Methyl-D-Aspartate (NMDA) ionotropic glutamate receptor (NMDAR), which upon glutamate binding allows Ca^{2+} influx (Fig. 2.2). Transient increases in Ca^{2+} are followed by recruitment of different signaling pathways, which will modify the activation status of CREB.

Ca^{2+}/CaMK Axis

Long-term synaptic plasticity is triggered by depolarization of the postsynaptic membrane and, consequently, transcription of immediate early genes (Flavell and Greenberg 2008; Kandel et al. 2014; Mayr and Montminy 2001; Shaywitz and Greenberg 1999). The Greenberg and Kandel groups simultaneously discovered the mechanisms controlling the immediate early gene *c-fos* expression by membrane

depolarization (Sheng et al. 1990; Dash et al. 1991; Sheng et al. 1991). Sheng and colleagues first found that in the rat pheochromocytoma cell line PC12, c-fos responds to potassium chloride-induced depolarization through a cis-regulating element present in the c-fos promoter (Sheng et al. 1990). This element, called CaRE (for Ca^{2+} Responsive Element), is responsive to depolarization and Ca^{2+} influx through voltage-gated Ca^{2+} channels. CaRE (-TGACGTTT-) is very similar to CRE (-TGACGTCA-) as it is recognized by cAMP/PKA-activated CREB (Sheng et al. 1990). In PC12 cells, depolarization and Ca^{2+} influx do not activate the cAMP/PKA axis, suggesting that another kinase transduces the depolarizing signal to CREB (Sheng et al. 1990). Instead, CREB activation is mediated by CaMKI and II (Sheng et al. 1991) (Fig. 2.2). This depolarization/Ca^{2+}/CaMK axis is independent but synergistic to the effects of the cAMP/PKA axis on CREB activation and subsequent c-fos transcription (Sheng et al. 1990, 1991).

Ca^{2+}/MAPK Axis

Another source of Ca^{2+} influx is the set of ligand-controlled Ca^{2+} channel receptors including the NMDAR. Ginty and collaborators (Ginty et al. 1993) discovered that these receptors are capable of activating CREB while studying the molecular basis of circadian rhythms in the suprachiasmatic neurons of the hypothalamus. The pacemaker cells in this structure regulate the circadian rhythms of the whole organism. Rhythms can be shifted by inputs of environmental information such as light: during the subjective night, a pulse of light activates retinal ganglionic cells that project axons to the suprachiasmatic nuclei establishing glutamatergic synapses. Interestingly, this signal triggers expression of immediate early genes such as c-fos, similarly to what is observed in long-term memory. Taking this analogy in consideration, Ginty et al. (1993) investigated the possibility that CREB transduces the signal of light pulses to the transcription of the early gene c-fos. They first isolated an antibody recognizing specifically phosphorylated CREB at the Ser133 and then, found, in vivo, that a pulse of light during the subjective night induces rapid CREB phosphorylation at Ser133 (Ginty et al. 1993). Trying to understand the mechanism responsible for the light-induced CREB phosphorylation, they found that in vitro, a 7-min NMDA incubation or depolarization induces a very strong phosphorylation of CREB at Ser133. Furthermore, the effect observed with NMDA but not with depolarization was prevented by APV, a potent NMDAR antagonist (Ginty et al. 1993). These results suggest that NMDARs are capable of activating CREB through a mechanism other than depolarization. It has been shown that an increase in cytosolic Ca^{2+} concentration is responsible for the recruitment of the extracellular signal–related protein kinase/mitogen-activated protein kinase (ERK/MAPK) pathway and subsequent CREB phosphorylation (Impey et al. 1998; Rosen et al. 1994). Obrietan et al. (1998) later showed that CREB activation by NMDAR in the suprachiasmatic nucleus, is, at least partially, mediated through the Ras/ERK/MAPK signaling pathway (Obrietan et al. 1998) (Fig. 2.2).

Receptor Tyrosine Kinases

Ras /MAPK

Neurotrophins and their tyrosine kinase receptors play important roles in the central nervous system development and homeostasis. Nerve growth factor (NGF) is a member of this family that induces expression of immediate early genes, particularly c-fos. Greenberg's group, using PC12 cells, investigated how NGF activates c-fos transcription (Ginty et al. 1994). They ruled out the implication of cAMP/PKA and Ca^{2+}/CamK axes. Instead, by using an inducible dominant-negative mutant of Ras, they identified a 105 kD CREB kinase (Ras-dependent p105 kinase) under the control of Ras that transduces the NGF-dependent phosphorylation of CREB on Ser 133 (Ginty et al. 1994) (Fig. 2.2). Xing et al. (1996) later identified the Ras-dependent p105 kinase as RSK2 (Xing et al. 1996), a member of the pp90 ribosomal S6 kinase (pp90RSK) family. Numerous extracellular signals mediated via receptor tyrosine kinases trigger MAP kinases and subsequently CREB kinases, such as MAPKAP-K2/3, MSK1 or MSK 1–3 (Shaywitz and Greenberg 1999; Flavell and Greenberg 2008; Carlezon et al. 2005; Lonze and Ginty 2002; Mayr and Montminy 2001; Sakamoto et al. 2011).

PI3K/Akt-PKB

The serine/threonine protein kinase Akt is mainly known for its anti-apoptotic and cell survival roles following growth factor stimulation. Upon binding to their receptors, growth factors trigger a signaling cascade involving the phosphatidylinositol 3-kinase (PI3K), which synthesizes the second messenger phosphatidylinositol (3,4,5)-trisphosphate (PIP3) at the plasma membrane. Akt (also called Protein kinase B (PKB)) is consequently recruited and docked to the membrane, where it is activated. Akt is then translocated to the cytosol and then to the nucleus to phosphorylate its targets (see Manning and Cantley 2007 for review). Du and Montminy demonstrated in 293 T cells that serum induces CREB phosphorylation at Ser 133 via recruitment of the PI3K/Akt axis, thus promoting cell survival (Du and Montminy 1998). Later, the PI3K/Akt/CREB signaling was also implicated in cell survival in the central nervous system (Chong et al. 2005) (Fig. 2.2).

Crosstalk Between CREB-Activating Pathways

Since the identification of the classical signaling cascades described previously in this chapter, numerous studies in multiple models discovered that combinations of these pathways work together, whether in parallel, synergistically or in an antagonistic manner to modulate CREB phosphorylation and activation.

CREB-induced immediate early genes are important for long-term potentiation (LTP), and both cAMP and Ca^{2+} second messengers play an important role in

activating CREB (Impey et al. 1996). Moreover, the CRE element present in immediate early gene promoters is responsive to both Ca^{2+} and cAMP in a synergistic manner (Deutsch et al. 1987; Sheng et al. 1990; Impey et al. 1994). Late phase LTP (L-LTP) is a good example of the dual action of Ca^{2+} and cAMP (Impey et al. 1996). Indeed, Ca^{2+} induces phosphorylation of CREB at Ser133, an event necessary but not sufficient to promote sustained transcription of target genes (Brindle et al. 1995; Wagner et al. 2000; Ravnskjaer et al. 2007; Ginty et al. 1994; Impey et al. 1996). Impey and colleagues discovered that in PC12 cells and hippocampal neurons, Ca^{2+} influx recruits the ERK signaling cascade leading to CREB phosphorylation at Ser133. Remarkably, cAMP-induced PKA activation is mandatory for translocation of activated ERK in the nucleus where it promotes CREB phosphorylation. These studies demonstrate crosstalk between the cAMP-PKA and Ca^{2+}-MAPK signaling pathways in neurons important for L-LTP (Impey et al. 1998).

Another example of crosstalk between signaling pathways has come from a study on brain-derived neurotrophic factor (BDNF) signaling in neurons. In cultured cortical neurons and hippocampal slices, BDNF induces release of Ca^{2+} from intracellular stores and subsequent activation of CaMKIV. In parallel, BDNF triggers the Ras/ERK/RSK pathway. Both the Ca^{2+}/CaMKIV and Ras/ERK signaling lead to CREB phosphorylation at Ser133 (Finkbeiner et al. 1997). The study suggests that the two signaling pathways may induce different spatiotemporal dynamics for CREB activation given the distinct kinetics and localization of the Ras pathway and the IP3-induced mobilization of intracellular Ca^{2+} (Finkbeiner et al. 1997).

Platelet-derived growth factor (PDGF) promotes a neuroprotective action against toxicity induced by HIV-1 in primary midbrain neurons and in vivo on dopaminergic neurons of the *substantia nigra*, also by a crosstalk between pathways converging in CREB. PDGF activates the PI3K/Akt and Ca^{2+}/ERK signaling through IP3-mediated intracellular Ca^{2+} release and Ca^{2+} influx through transient receptor potential canonical (TRPC) channels leading to CREB phosphorylation (Yao et al. 2009). Whether both pathways are additive in CREB activation remains unclear.

Another example of signaling crosstalk converging on CREB activation comes from our recent study on the Sonic hedgehog (Shh) pathway in the developing *Xenopus laevis* spinal cord (Belgacem and Borodinsky 2015). Shh stimulation of embryonic spinal neurons elicits a non-canonical, Ca^{2+} spike-dependent pathway that regulates neurotransmitter specification (Belgacem and Borodinsky 2011). Shh activation of its coreceptor Smoothened, recruits a phospholipase C, inducing inositol 1,4,5-trisphosphate (IP3) oscillations in the primary cilium of embryonic spinal neurons and enhancing Ca^{2+} spike activity that relies on both IP3 receptor (IP3R)-regulated intracellular Ca^{2+} stores and Ca^{2+} influx through voltage-gated Ca^{2+} channels and TRPC1 (Belgacem and Borodinsky 2011) (Fig. 2.3). This Ca^{2+} spike-dependent, non-canonical Shh pathway results in PKA activation, which activates CREB that, in turn, represses gli1 transcription and contributes to the switch off of the Shh canonical, Gli transcription factor-mediated pathway during spinal cord development (Belgacem and Borodinsky 2015) (Fig. 2.3).

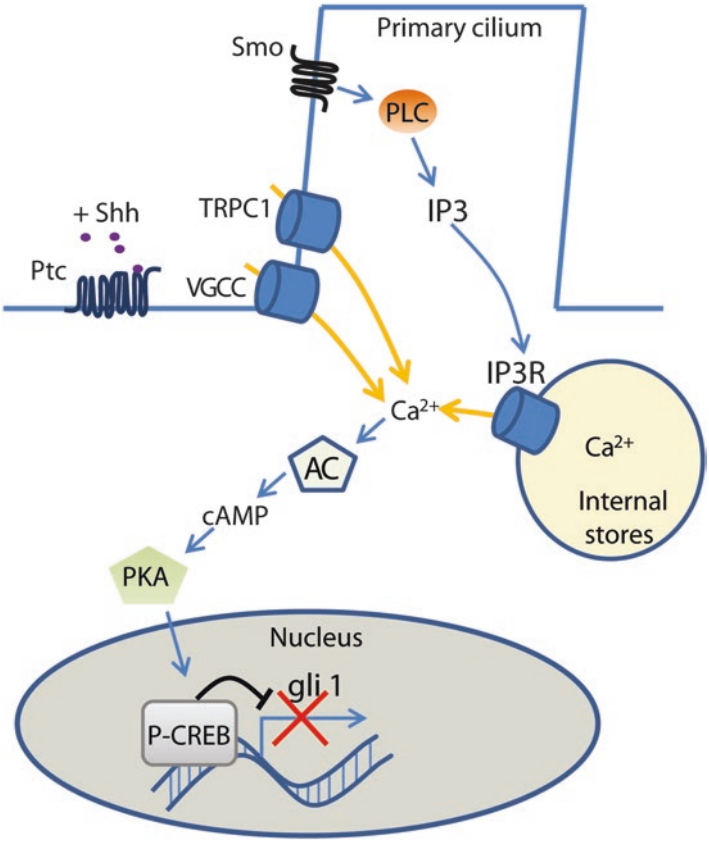

Fig. 2.3 CREB contributes to the Shh-calcium signaling axis-dependent switch off of the canonical Shh pathway in the embryonic spinal cord. In embryonic spinal neurons, Smo-dependent Shh signaling activates the synthesis of IP3 second messenger at the primary cilium. IP3 transients trigger the release of intracellular Ca^{2+} from intracellular stores that, in conjunction with Ca^{2+} influx through voltage-gated Ca^{2+} channels (VGCC) and transient receptor potential canonical (TRPC) channels lead to activation of Ca^{2+}-sensitive adenylate cyclase (AC) and an increase in cAMP levels. In turn, this leads to PKA-dependent CREB phosphorylation at serine 133. CREB represses expression of the canonical Shh transcription factor Gli1

Activation of CREB Cofactors by Activity Dependent Signaling Pathways: Consequences for CREB Function

CREB phosphorylation on key amino acids is a crucial step in its activation and recruitment of cofactors allowing for specific gene transcription. Activity-dependent signaling controls all the steps from CREB phosphorylation to recruitment and activation of the cofactors. In this section, we will focus particularly on two important CREB cofactors: CBP and TORC/CRTC1.

CBP

The most studied site of phosphorylation by serine/threonine kinases is the Ser133 that controls the binding of CREB to CBP/p300 (Gonzalez et al. 1989; Gonzalez and Montminy 1989; Altarejos and Montminy 2011; Parker et al. 1996). However, it has been observed that growth factor and stress pathways, while promoting CREB phosphorylation at Ser133, do not promote gene transcription as efficiently as the cAMP-induced Ser133 phosphorylation does (Mayr and Montminy 2001; Hardingham et al. 2001; Chawla et al. 1998; Altarejos and Montminy 2011; Brindle et al. 1995; Ravnskjaer et al. 2007; Bito et al. 1996; Mayr et al. 2001). This difference could be due to subcellular events such as the presence of nuclear Ca^{2+} waves as observed in hippocampal neurons (Hardingham et al. 2001) or the activation of other factors that could act as positive or negative regulators and that are preferentially activated by Ras or cAMP (discussed in (Mayr and Montminy 2001)). For instance, Chawla et al. (1998) in mouse pituitary cell line AtT20 show that CBP is activated by nuclear Ca^{2+}, CaMKIV and cAMP (Chawla et al. 1998) (Fig. 2.4). Receptor tyrosine kinase-mediated growth factors and stress pathways that do not elevate intracellular Ca^{2+} and cAMP might then fail to efficiently recruit CBP and, consequently, prevent the phosphorylated CREB from promoting gene transcription.

Activity-dependent signaling can negatively or positively regulate CREB activity by recruiting CaMKII or CaMKIV, respectively (Matthews et al. 1994). Sun et al. (1994) investigated the mechanisms responsible for this difference. They demonstrated, in vitro in GH3 pituitary tumor cells using mutagenesis studies and phosphopeptide mapping analysis, that, while both CaMKII and IV phosphorylate CREB at Ser133, CaMKII also phosphorylates Ser142 (Fig. 2.1) (Sun et al. 1994). Additionally, they showed that Ser 142 has an inhibitory effect on CREB-induced gene transcription. Wu and McMurray (2001) later showed in human neuroblastoma cells (SK-N-MC) and African green monkey kidney cells (CV-1) that phosphorylation of Ser142 by CaMKII prevents CREB dimerization and binding to CBP (Wu and McMurray 2001), explaining its negative effect on CREB transcriptional capability (Sun et al. 1994). These results have been confirmed in vivo (Flavell and Greenberg 2008; Carlezon et al. 2005; Lonze and Ginty 2002; Mayr and Montminy 2001; Sakamoto et al. 2011), highlighting the importance of CREB phosphorylation status, as well as the fact that Ca^{2+} can be a positive or a negative regulator of CREB activity depending on the subtype of CaMK recruited in the cell.

Although in general Ser142 phosphorylation inhibits CREB-dependent gene transcription, Kornhauser and colleagues showed that in rat cortical neurons in vitro and in vivo, Ca^{2+} influx through VGCCs or NMDAR triggers CREB triple phosphorylation at Ser133, 142 and 143, promoting CREB transcriptional action (Kornhauser et al. 2002). Strikingly, this triple phosphorylation disrupts CBP binding on CREB, suggesting that CBP is not always necessary to transduce CREB-dependent signaling.

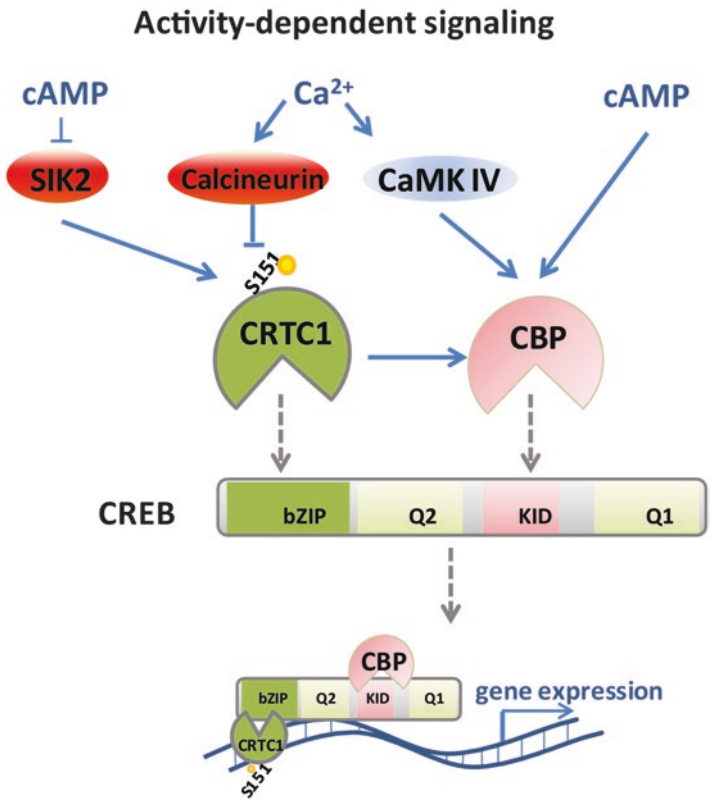

Fig. 2.4 Model of activity-dependent recruitment of CREB co-activators. Binding of cofactors to CREB and DNA is modulated by Ca^{2+} and cAMP second messengers. Activity-induced signaling leads to increases in cAMP and Ca^{2+}, which inhibit Salt-induced kinase 2 (SIK2) and activate calcineurin. This results in dephosphorylation of serine 151 (S151) on the cofactor CRTC1 and its translocation to the nucleus, where it promotes binding of CREB to the TFIID complex. In parallel, Ca^{2+}-activated CaMKIV and cAMP lead to CBP recruitment and a reciprocal synergism between CBP and CRTC1

TORC/CRTC1

Another important CREB coactivator called cAMP-regulated transcriptional coactivator (CRTC) or transducer of regulated CREB (TORC) was discovered simultaneously by two groups (Iourgenko et al. 2003; Conkright et al. 2003). Three genes code for this evolutionarily conserved cofactor: CRTC1–3, with CRTC1 as the prevalent isoform found in the brain. Contrary to CBP, CRTC binds to the bZIP domain of CREB (Altarejos and Montminy 2011; Xue et al. 2015). Under basal conditions, TORC1 phosphorylated at Ser 151 is maintained in the cytosol by 14–3-3 proteins (Screaton et al. 2004). Upon Ca^{2+} influx in the cell, calcineurin dephosphorylates TORC and, thus, allows its translocation to the nucleus, where it

promotes binding of CREB to the TFIID complex, enhancing CREB DNA binding activity independently of CREB's phosphorylation status (Bittinger et al. 2004; Screaton et al. 2004). cAMP elevation also leads to CRTC dephosphorylation and nuclear translocation by inhibiting the TORC2 kinase SIK2 (Screaton et al. 2004) (Fig. 2.4).

TORC is essential for CRE-dependent transcription of numerous genes triggered by Ca^{2+} or cAMP elevation (Altarejos and Montminy 2011; Xue et al. 2015). For instance, TORC plays a crucial role in long term memory: Zhou et al. (2006) showed that, in hippocampus, neuronal activity elicits CRTC1 translocation to the nucleus, leading to CRE-mediated gene expression necessary for L-LTP (Zhou et al. 2006). Interestingly, Kovacs et al. (2007) later showed that CRTC1 was acting as an integrator of neuronal activity by detecting the coincidence of Ca^{2+} and cAMP increases in hippocampal neurons, thus leading to activation of the genetic machinery responsible of L-LTP (Kovacs et al. 2007) (Fig. 2.4). These studies illustrate the role of signaling pathway crosstalk in CREB function via regulating its cofactors.

CBP and TORC Interaction

CBP and TORC2 interact in an activity-dependent synergistic way. cAMP signaling that leads to TORC dephosphorylation and translocation to the nucleus also promotes its association with CBP/p300 and subsequently increases CBP occupancy on promoters of target genes (Ravnskjaer et al. 2007). Interestingly, CBP/p300 has a reciprocal effect on TORC2 recruitment. This interaction participates in the specificity of CRE-driven gene expression by favoring cAMP-dependent signaling over other pathways such as the stress cascade (Ravnskjaer et al. 2007) (Fig. 2.4).

Spatiotemporal Patterns of CREB Activation

Regulation of gene expression through CREB is fast and transitory; for instance, in PC12 cells cAMP-induced somatostatin expression peaks 15–30 min after stimulation and goes back to baseline after 4 h (Hagiwara et al. 1992). The decay in CREB activity is controlled by specific serine/threonine protein phosphatases such as protein phosphatase PP1 and PP2A that dephosphorylate CREB at Ser133 (Flavell and Greenberg 2008). The duration of CREB activation is key for the efficiency of target gene expression. Bito et al. (1996) showed in hippocampal neurons that a short stimulation of synaptic activity was translated into a transient CREB phosphorylation that was not sufficient to cause gene expression (Bito et al. 1996). This might be due to activation of CaMKIV, which phosphorylates CREB, followed by calcineurin (Cn) or PP2B, a Ca^{2+}/calmodulin-dependent serine/threonine phosphatase, and PP1-mediated CREB dephosphorylation (Fig. 2.5a). However, when synaptic stimulation is prolonged, the effects of Cn/PP1 are strongly reduced, allowing for a

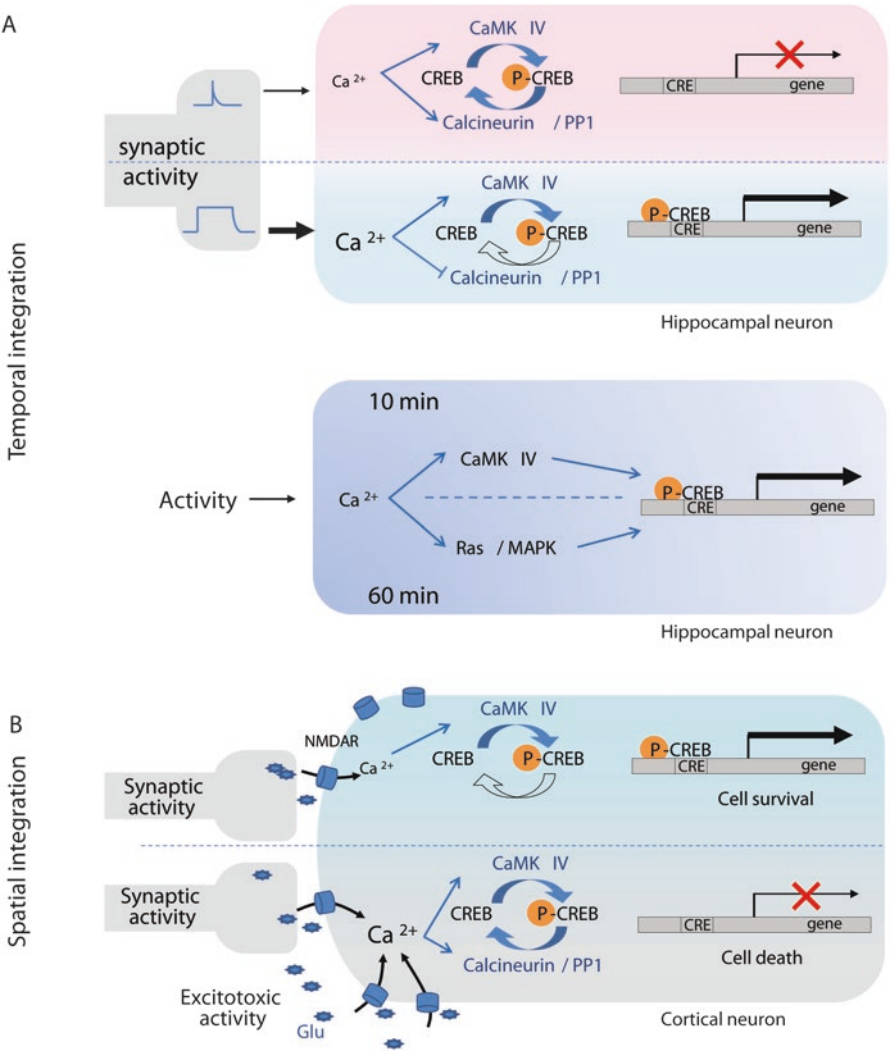

Fig. 2.5 Spatiotemporal control of CREB activation. (**a**) Temporal integration of activity through CREB. *Upper panel*: The duration of synaptic activity influences the duration of CREB phosphorylation. Short stimulation induces a low increase in cytosolic [Ca^{2+}] and transient CREB phosphorylation that does not lead to expression of target genes. Longer synaptic stimulation triggers a large increase in cytosolic [Ca^{2+}] and sustained CREB activation, enhancing expression of target genes. *Lower panel*: In hippocampal neurons, synaptic activity triggers a fast acting signaling that recruits CaMKIV and CREB phosphorylation within 10 min. This signal is then replaced by a slower and long lasting Ras/MAPK-dependent pathway that dominates 60 min after the initial stimulation, thus both fast and long-lasting CREB activation are ensured. (**b**) Spatial integration of Ca^{2+}-mediated activity through CREB. In cortical neurons, glutamatergic synaptic activity triggers CREB phosphorylation through recruitment of CaMKIV leading to expression of target genes and cell survival. Excitotoxic levels of glutamate (Glu), also lead to recruitment of phosphatases such as calcineurin, with consequent CREB dephosphorylation, inactivation and cell death

sustained activation of CREB and expression of target genes (Mayr and Montminy 2001). Moreover, Cn can be activated and inactivated by Ca^{2+} and Calmodulin (Stemmer et al. 1995), which might result in varied temporal patterns of CREB activation.

Another example of dynamic temporal control of CREB activity comes from the work of Wu et al. (2001), who showed in hippocampal neurons in vitro that within 10 min of stimulation, the Ca^{2+}-induced CaMKIV signaling phosphorylates CREB at Ser133. Then, the slower intracellular Ca^{2+}-sensitive Ras/MAPK pathway follows and predominates after 60 min of stimulation, extending CREB phosphorylation and promoting gene expression (Wu et al. 2001) (Fig. 2.5a). The fast CaMKIV signaling may convey acute and precise information to the nucleus, while MAPK signaling might code information about the duration of the stimulation.

The expression of phosphatases is cell specific, allowing for different responses in CREB-mediated gene expression depending on the neuronal subtype. Liu and Graybiel (1996) compared the convergence of Ca^{2+} and cAMP signaling on CREB phosphorylation by activating the D1/D5 dopamine receptor (D1/D5R) and L-type VGCC at the same time in two populations of striatal neurons in organotypic slices (Liu and Graybiel 1996). The two neuronal populations differ in their expression of two phosphatases: while neurons present in the striosomes express the phosphatase dopamine and cAMP–regulated phosphoprotein (DARPP-32) and Ca^{2+}/PP2B, which are induced by cAMP and Ca^{2+} respectively, neurons found in the striatal matrix do not. While both D1/D5R and L-type VGCC were able to transiently stimulate CREB phosphorylation, only D1/D5R promoted sustained CREB phosphorylation in DARPP-32-expressing cells, while L-type VGCC did it in DARPP-32-lacking cells (Liu and Graybiel 1996). This is interesting because only sustained CREB phosphorylation leads to c-fos expression, highlighting the importance of the spatiotemporal control of CREB activation. Thus, the duration of CREB phosphorylation is not only controlled by the coincidence of the synaptic stimulation, but also by the cell-specific presence of CREB phosphatases.

Strong activation of the NMDAR can lead to an excitotoxic cell death signal, while exerting a cell survival role or mediating synaptic plasticity when activated within the synapse. This divergent effect seems to be due, at least partially, to the duration of CREB phosphorylation following NMDAR activation. In cortical neurons, synaptic NMDAR stimulation leads to a sustained phosphorylation of CREB at the Ser133 that lasts 3 h, while excitotoxic activation of NMDAR leads to a transient, shorter activation of CREB. This difference on the effects of NMDAR activation on CREB phosphorylation is due to the recruitment of Cn after excitotoxic activation of NMDAR and therefore CREB dephosphorylation (Lee et al. 2005). This effect could be, at least partially, due to the activation of extrasynaptic NMDAR during excitotoxic glutamatergic stimulation (Fig. 2.5b).

Dynamic control of CREB activity also occurs at the CREB coactivator level. For instance, in rat developing cortical neurons, CRTC1/TORC is dephosphorylated via calcineurin following depolarization-induced Ca^{2+} influx, leading to CRTC1 nuclear translocation. This promotes CREB activation and expression of genes such as the salt-inducible kinase 1 (SIK1). In turn, SIK1 phosphorylates CRTC1

in response to persistent depolarization and therefore inactivates CRTC1 and CREB-driven transcription (Li et al. 2009).

Examples of spatially restricted CREB activation include the regulation of CREB in axons. In embryonic dorsal root ganglia cultures, CREB mRNA is translated in axons under the control of NGF in an activity-dependent manner; CREB is then retrogradely transported to the nucleus by endosomes containing the NGF receptor TrkA and phosphorylated in endosomes by this receptor through a MEK5-ERK5 signaling. CREB is finally translocated in the nucleus where it promotes cell survival (Cox et al. 2008).

Additional Regulatory Mechanisms of CREB Activation/ Recruitment

CREB can be regulated independently of phosphorylation through such mechanisms as ubiquitination (Comerford et al. 2003) and glycosylation (Lamarre-Vincent and Hsieh-Wilson 2003), and also through activity-dependent epigenetic modifications of CREB mRNA. Rajasethupathy et al. (2009) showed that in Aplysia the small RNA miR-124 inhibits CREB translation. In turn, serotonin signaling in presynaptic sensory neurons relieves this negative effect enabling long-term facilitation (Rajasethupathy et al. 2009). Similarly, miR-134 exerts a negative effect on CREB translation and synaptic plasticity (Gao et al. 2010). These studies present alternative mechanisms for activity-dependent regulation of CREB in the central nervous system.

Concluding Remarks

Long-term plasticity of the central nervous system relies on a molecular machinery that in neurons transduces extracellular stimuli into long lasting structural and functional modifications. In the context of a living organism, changes in the environment lead to the activation of numerous intracellular signaling cascades that need to be integrated to achieve the appropriate neuronal response. The crosstalk among different signaling pathways allows for spatiotemporal integration of multiple signals converging at CREB and its cofactors. In addition to regulation of the level of phosphorylation of CREB, several other mechanisms, such as activity-dependent epigenetic modifications of CREB mRNA, are emerging as crucial in controlling CREB activity and target gene transcription. Future studies will likely reveal novel activity-dependent mechanisms that utilize CREB to integrate diverse stimuli that generate complex neuronal responses.

Acknowledgements Research in the laboratory has been supported by the Basil O'Connor Starter Scholar Research Award Grant 5-FY09-131 from the March of Dimes Foundation, Klingenstein Foundation Award in Neuroscience, NSF 1120796, NIH-NINDS R01NS073055 and

Shriners Hospital for Children 86500-NCA and 85220-NCA grants to LNB and Shriners Hospital for Children Fellowship, Brain and Behavior foundation NARSAD grant #25356, IMERA grant and fellowship with the support of INSERM / Labex RFIEA / ANR (Investissements d'avenir), and Prestige / Marie Curie fellowship #PRESTIGE-2016-3-0025 to YHB.

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http://www.springer.com/978-3-319-62815-8

The Plastic Brain
von Bernhardi, R.; Eugenín, J.; Muller, K.J. (Eds.)
2017, IX, 284 p. 47 illus., 26 illus. in color., Hardcover
ISBN: 978-3-319-62815-8