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CREB: a multifaceted regulator of neuronal plasticity and protection

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Abstract

Since its initial characterization over 20 years ago, there has been intense and unwavering interest in understanding the role of the transcription factor cAMP-responsive element binding protein (CREB) in a nervous system physiology. Through an array of experimental approaches and model systems, researchers have begun to unravel the complex and multifaceted role of this transcription factor in such diverse processes as neurodevelopment, synaptic plasticity, and neuroprotection. Here we discuss current insights into the molecular mechanisms by which CREB couples synaptic activity to long-term changes in neuronal plasticity, which is thought to underlie learning and memory. We also discuss work showing that CREB is a critical component of the neuroprotective transcriptional network, and data indicating that CREB dysregulation contributes to an array of neuropathological conditions.

Keywords

transcription; plasticity; memory; cell death; pathophysiology; neuroprotection

CREB structure and regulation

CREB was originally identified in 1987 as a 43kDa, nuclear protein which binds to the cAMP response element (CRE) of the somatostatin gene in PC12 cells (Montminy & Bilezikjian 1987). Further work revealed that CREB is a member of a large functionally- and structurally-related group of transcription factors, termed the basic leucine zipper domain (b-zip domain) family, which includes activation transcription factor 1 (ATF1), and cAMP responsive element modulator (CREM). Of note, a detailed discussion of the various CREB splice variants, as well as other b-zip family members is beyond the scope of this review, and as such, readers are referred to excellent reviews of this topic (Mayr & Montminy 2001, Don & Stelzer 2002).

CREB can be organized into distinct domains that allow it to dimerize, interact with DNA, cofactors, and the basal transcriptional complex. Located at the C-terminus of CREB is the bZIP DNA-binding domain, which binds to the CRE, and the dimerization domain, which allows CREB to homo- and hetero-dimerize (Schumacher *et al*. 2000). Located at the N-terminus of CREB is the glutamine rich 1 (Q1) domain, which is followed by the kinase-inducible domain (KID), and then the Q2 domain. These domains interact with various co-factors (described below) as well as components of the basic transcription complex (Johannessen *et al*. 2004). For example, Q1 and Q2 domains interact with TATA binding protein-associated factor II 135 (TAFII135) which in turn recruits a polymerase complex and stimulates transcription (Felinski & Quinn 2001).

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The KID is a regulatory region that plays a key role in coupling changes in intracellular signaling to CREB-mediated transcription. Central to this region is Serine (Ser) 133, which is targeted by a number of activity-inducible kinases, including Ca2+/CaM-dependent kinase (CaMK) II and IV, protein kinase A (PKA), protein kinase C (PKC), mitogen/stress-activated kinas (MSK), ribosomal S6 kinase (RSK), AKT, and MAPKAP kinase2 (MK2) (Gonzalez & Montminy 1989, de Groot *et al.* 1993, Sun *et al.* 1994, Ginty *et al.* 1994, Deak *et al.* 1998, Xing *et al.* 1996, Du & Montminy 1998, Tan *et al.* 1996). Hence, kinase activity in response to an array of stimuli, including increased intracellular Ca^{2+} and cAMP, triggers the phosphorylation of Ser 133. Once in the Ser 133-phosphorylated state, CREB becomes a binding target of the KIX domain in the transcription co-activators, CREB binding protein (CBP) and p300 (Parker *et al.* 1996), thus allowing induction of CRE-mediated transcription.

In addition to Ser 133, the functionality of CREB can be affected via an array of additional phosphorylation events, which have complex, and context-specific effects on CREB transactivation. For example, the phosphorylation of Ser 142 by CaMKII has been shown to represses CREB transactivation by triggering the dissociation of the CREB dimer and, in turn, inhibiting CBP recruitment (Wu & McMurray 2001, Kornhauser *et al.* 2002). Conversely, using a combination of phosphorylation-specific antibodies, and a CREB Ser 142-to-Alanine 142 knock-in mouse, Gau et al. (2002), showed Ser 142 is phosphorylated in an activity-dependent manner and is required for robust CREB-mediated gene expression in the CNS (Gau *et al.* 2002).

Glycogen Synthase Kinase-3beta (GSK3beta), a kinase implicated in neurodegenerative and psychiatric disorders, phosphorylates CREB at Ser 129. As with Ser 142, the phosphorylation of this site has been shown to both enhance and suppress CREB- mediated gene expression (Fiol *et al.* 1994, Bullock & Habener 1998, Grimes & Jope 2001). Recent work has also revealed that in response to the genotoxic stress, the homeodomain-interacting protein kinase 2 (HIPK2) phosphorylates CREB at Ser 271 and activates CREB-dependent gene transcription through the recruitment of CBP/p300 (Sakamoto *et al.*). Finally, the complexity of CREB phospho-regulation can be appreciated by the work of Shanware et al. (2007), which showed that DNA damage triggers CREB inhibition via a series of intertwined steps initiated by casein kinase (CK) phosphorylation of multiple Ser residues (i.e., Ser 108, 111, 114, and 117), which in turn, allows ataxia telangiectasia mutated (ATM)-dependent phosphorylation on Ser 121, thus leading to a decoupling of CREB and CBP. Given the discussion above, it should not be surprising that CK/ATM phosphorylation has also been shown to stimulate rather than inhibit CREB transactivation (Kim et al., 2010).

In addition to inducible phosphorylation, CREB dephosphorylation can also be regulated in an activity-dependent manner. Along these lines, the dephosphorylation of CREB at Ser 133, which leads to transcriptional repression, is mediated by Ser /Thr-specific protein phosphatases type 1 (PP1) and 2A (PP2A) (Alberts *et al.* 1994, Wadzinski *et al.* 1993). Of note, in hippocampal neurons, synaptic activity can lead to a prolonged period of CREB phosphorylation via the inhibition of PP1 (Bito *et al.* 1996).

Additional CREB regulatory mechanisms

Although CREB is mainly regulated through phosphorylation, alternate CREB regulatory mechanisms have been reported, including acetylation, ubiquitination, sumoylation, and glycosylation (Lu *et al.* 2003, Taylor *et al.* 2000, Comerford *et al.* 2003, Lamarre-Vincent & Hsieh-Wilson 2003). For example, CREB is acetylated by CBP at three lysine residues around the Q1 and KID domains, which enhances CRE-dependent transcription (Lu *et al.* 2003). In addition, CREB can function as a constitutive transcriptional activator,

independent of Ser 133 phosphorylation. This occurs via the transducers of CREB regulatory activity (TORC) family of CREB coactivators. TORCs facilitate CREB-mediated transcription via an association with the bZIP DNA binding domain, which enhances CREB interactions with components of the basal transcriptional complex (Conkright *et al.* 2003a). Within the nervous system, TORCs have been implicated in regulating neuronal development and plasticity (Finsterwald *et al.*, Zhou *et al.* 2006).

CREB is also regulated at the translational level. For example, the non-coding small RNA, miR-34b has been shown to bind to the 3'-UTR of CREB mRNA and repress CREB expression (Pigazzi *et al.* 2009). Interestingly, there is an inverse correlation between miR-34b and CREB expression levels in patients with acute myeloid leukemia (Pigazzi *et al.* 2009). Recently, miR-134, a brain specific miRNA, was also shown to regulate CREB expression levels (Gao *et al.* 2010). Interestingly, within the hippocampus, NAD-dependent deacetylase SIRT1 deficiency causes increased miR-134 expression, leading to the reduction of CREB expression and impaired synaptic plasticity (Gao et al. 2010).

To add a further wrinkle, recent work revealed that CREB mRNA is localized to dorsal root ganglion axons, and, upon nerve growth factor (NGF) stimulation, is translated and retrogradely transported to the nucleus, driving a pro-survival transcriptional response (Cox et al. 2008). Additional work that determines how this relatively small pool of CREB could exert such a profound and specific transcriptional effect will be critical to further this fascinating line of inquiry. Of note, CREB is also expressed within mitochondria and affects mitochondrial gene expression and neuronal viability (Lee *et al.* 2005b).

Finally, CREB transcriptional potential can be regulated at an epigenetic level. Along these lines, cytosine methylation within CRE sites inhibits CREB binding to DNA, which in turn, inhibits CRE-dependent transcription (Iguchi-Ariga & Schaffner 1989, Zhang *et al.* 2005). This process can be dynamically regulated, and appears to contribute to inducible BDNF expression in the CNS (Yossifoff et al. 2008).

CREB target genes

Reporter gene-based methods have been used for years to identify CREB-regulated genes. These approaches have recently been complemented with bioinformatic based-methods, combined with microarrays and ChIP-based chromatin occupancy analysis, such as ChIP-on-chip and the serial analysis of chromatin occupancy (SACO) (Conkright *et al.* 2003b, Fass *et al.* 2003, McClung & Nestler 2003, Zhang *et al.* 2005, Impey *et al.* 2004, Euskirchen *et al.* 2004) to interrogate vast regions of the genome for CREB binding and CRE-regulated gene expression. These studies have revealed a diverse array of both inducible and constitutively expressed genes that are regulated by CREB. For example, using the SACO methods, which is a modified ChIP/serial analysis of gene expression (SAGE)-based approach, Impey et al. (2004) identified 6302 CREB binding regions in forskolin-treated PC12 cells. These data were tested via an affymetrix array, which showed that forskolin induces 1621 genes, half of which were occupied by CREB (Impey et al. 2004). Of note, these studies found that the CRE binding motif can be quite variable, diverging from the 'consensus' TGACGTCA to highly degenerate motifs where little more than a half-cite of site (i.e., TGACG) can effectively bind CREB. Further, these studies have revealed that a large number of neuronally-enriched coding genes are regulated by CREB in an activity-dependent manner. These genes, which include neurotransmitters, growth factors, transcription factors, signal transduction factors, and metabolic enzymes, have critical roles in neuronal development, plasticity and protection (Tao *et al.* 1998, Sgambato *et al.* 1998, Fukuchi *et al.* 2005, St-Pierre *et al.* 2006, Sassone-Corsi *et al.* 1988, Yagita & Okamura 2000), and as such, CREB has been implicated as a key signaling intermediate that couples

neuronal activity to an array of functional outcomes. Of note, recent studies have revealed that non-coding small RNA transcription within the nervous system is also regulated by CREB. Along these lines, the expression from the miR-132/212 locus is tightly regulated by CREB (Vo *et al*. 2005, Remenyi *et al*.). Further, CREB binding is also detected proximal to the miR219 locus, although its functional significance in miR219 expression has not been extensively examined (Cheng *et al*. 2007).

CREB in memory and plasticity

Protein synthesis is an essential step for long term memory formation (Davis & Squire 1984), and work in a number of model systems has clearly established an underlying role for CREB/CRE-mediated transcription in this process. Along these lines, the first definitive work linking CREB to long-lasting changes in neuronal functional plasticity was performed in the mollusk *Aplysia*, where the induction of long-term, but not short-term, facilitation of the gill-withdrawal reflex was associated with CREB-mediated gene expression (Schacher *et al*. 1988, Dash *et al*. 1990, Kaang *et al*. 1993). The phylogenetic conservation of these findings was supported by work in another invertebrate system, the fruit fly *Drosophila melanogaster*, where the overexpression of an inducible dominant negative form of CREB led to a complete blockade of long-term olfactory memory (Yin *et al*. 1994).

These seminal observations provided a framework to begin to dissect the role of CREB in vertebrate synaptic plasticity and memory formation. Some of the most compelling work on this topic was performed using genetically modified loss- and gain-of function mouse models. For example, CREB alpha/delta knockout mice showed impaired memory formation in contextual fear conditioning, the Morris water maze, and social transmitted food preferences (Bourtchuladze *et al*. 1994, Kogan *et al*. 1997). CREB was also shown to be involved in cued and contextual fear memory, spatial memory, olfactory memory, conditioned taste aversion memory, and object and social recognition memory (Bourtchuladze et al. 1994, Kogan et al. 1997, Yin et al. 1994, Lamprecht *et al*. 1997, Kogan *et al*. 2000, Pittenger *et al*. 2002, Graves *et al*. 2002). Further, using the CREB alpha/delta knockout mice as a platform, Han et al., (2007) showed that viral-mediated CREB delivery to the lateral amygdala completely rescued auditory fear memory impairment (Han *et al*. 2007). Interestingly, these authors further found that the relative level of CREB activity at the time of learning is a key factor in determining whether a neuron was recruited into the memory trace. A caveat to some of these studies was the finding that the disruption CREB alpha and delta isoforms led to a compensatory upregulation of CREB beta expression (Blendy et al. 1996), as well as CREM (Hummler et al. 1994). However, other approaches which employed CREB antisense oligonucleotide-based infusion approaches, and transgenic approaches in which endogenous CREB is repressed via the expression of a dominant negative form of CREB (i.e., CREB-S133A and A-CREB) have reported similar deficits in plasticity and learning to those reported using the CREB alpha/delta knockout mice (Guzowski & McGaugh 1997, Kida et al. 2002, Jancic *et al*. 2009). As further support for CREB in neuronal plasticity and memory, mice that express a constitutively active form of CREB, VP16-CREB mice, show a lower threshold for the late-phase long-term potentiation (L-LTP) induction in the Schaffer collateral pathway and an enhanced consolidation of context and cued fear memory (Barco *et al*. 2002, Viosca *et al*. 2009). Further, within the hippocampus, the dephosphorylation of CREB at Ser 133 is associated with the induction of long-term depression (LTD) (Mauna *et al*., Thiels *et al*. 1998). These data, along with work by Impey et al. (1998) showing that a CRE-mediated reporter is activated by stimuli that induce learning and memory reveal a key role for CREB in mammalian memory formation.

Finally, it should be noted that the literature is not completely consistent on the role of CREB in synaptic plasticity and memory formation. Along these lines, work by Balschun et

al. (2003) reported that the conditional disruption of all isoforms of CREB had only limited effects on hippocampal-dependent cognitive tasks, and no effect on LTP and LTD formation (Balschun *et al*. 2003). Additionally, it should also be noted that effects observed in one brain region might not necessarily extend to other brain regions. Along these lines, in cerebellar purkinje neurons, CREB-mediated transcription has been implicated in the induction of the late phase of long-term depression (LTD) (Ahn *et al*. 1999), a result that appears to be inconsistent with the role of CREB in the hippocampus. Although the precise reasons for these disparate physiological effects are not known, the key underlying function of CREB (converting short-term changes in neuronal activity into long-term changes in cellular function) is likely conserved throughout the CNS. Hence, whether CREB-mediated transcription initiates a new baseline state of cellular plasticity that either decreases or enhances synaptic efficacy likely depends on the underlying synaptic circuitry and cellular phenotypes.

CREB in neuronal development and cell survival

CREB has a critical role in nervous system development, and in the neuroprotective response to pathophysiological effectors. Initial work indicating a role for CREB in development came from studies in which all CREB isoforms (i.e., alpha, beta, delta) were inactivated. CREB null mice died immediately after birth and exhibited marked central nervous system developmental defects including a reduction in the axon projections comprising the corpus callosum and the anterior commissures (Rudolph *et al*. 1998). However, no obvious increases in cell death were detected in the CNS (Lonze *et al*. 2002). This limited phenotypic effect may in part result from a compensatory upregulation in the expression of CREM in the CNS (Rudolph *et al*. 1998). In support of this interpretation, the deletion of both *Creb1* (all isoforms) and *Crem* resulted in marked apoptosis, causing a severe reduction of neuronal and glial precursors during CNS development (Mantamadiotis *et al*. 2002). Interestingly, in the developing peripheral nervous system, CREB null (i.e., alpha, beta, delta) mice show enhanced apoptosis and impaired growth of sensory neuron axons (Lonze *et al*. 2002). At a mechanistic level, this effect appears to be mediated by an inability of NGF to stimulate CREB-dependent pro-survival and axonal growth developmental programs (Riccio *et al*. 1999).

Within the mature CNS, CREB-mediated transcription is required for neuronal survival. For example, over-expression of a dominant negative CREB (CREB S133A) in the cingulate cortex of adult mice results in significant apoptosis and cortical neurodegeneration (Ao *et al*. 2006). In addition, Mantamadiotis *et al*., (2002) showed that the postnatal deletion of both CREB and CREM led to hippocampal neurodegeneration in CA1 pyramidal cell layer, as well as a thinning of the dentate gyrus. Likewise, marked neuronal cell loss was detected in the dorsal striatum. This finding indicates that CREB has critical roles not only in neuronal differentiation and development but also in viability of postmitotic neurons (Mantamadiotis et al. 2002).

A substantial effort has been dedicated to unraveling the molecular mechanisms by which CREB regulates neuronal survival. Much of this work has centered on the both the transcription of neurotrophins, such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-I), pituitary adenylate cyclase-activating polypeptide (PACAP), and leptin, all of which have been shown to affect neuronal survival and development (Tabuchi *et al*. 2002, Kingsbury *et al*. 2003, Lambert *et al*. 2001, Fukuchi *et al*. 2005, Maymo *et al*., Zhang & Chen 2008), and neurotrophin-regulation of CREB-mediated transcription. For example, within the peripheral nervous system, NGF and BDNF regulate sympathetic neuronal survival via CREB-mediated expression of the antiapoptotic gene B Cell Lymphoma-2 (Bcl-2) (Riccio *et al*. 1999). Another CREB-regulated antiapoptotic gene,

myeloid cell leukemia sequence 1 (Mcl-1), regulates apoptosis during CNS development and DNA damage-induced cell death (Wang *et al.* 1999, Arbour *et al.* 2008).

Given the essential role that CREB plays in nervous system physiology, it might be reasonable to assume that tonic upregulation of CREB signaling would have beneficial effects. However, recent work has revealed deleterious consequences to sustained CREB activation. Indeed, using a tetracycline-inducible constitutively active VP16-CREB transgenic mouse model, Lopez de Armentia et al., (2007) showed that chronic activation of CRE-mediated gene expression (2-3 weeks) led to epileptic seizures and a marked loss of hippocampal neurons. Interestingly, neuronal degeneration resulting from CREB inhibition and CREB activation appears to occur through distinct mechanistic processes. While inhibition of CREB triggers neuronal cell death via a pro-apoptotic process (Ao et al. 2006), chronic CREB activation triggers cell death via an excitotoxic mechanism (Valor *et al.*, Lopez de Armentia *et al.* 2007). Gene profiling indicated that chronic CREB activation stimulates the induction of cell stress and inflammatory genes, which likely actuate or contribute to the excitotoxic cell loss (Lopez de Armentia et al. 2007). These data provide important considerations for the development of therapeutic strategies designed to augment CREB-dependent transcription.

CREB regulation under physiological and pathophysiological conditions

The examination of CREB phosphorylation at Ser 133 has provided useful insights into how physiological and pathophysiological levels of neuronal activity regulate CRE-mediated transcription. Central to this body of work is the idea that there are ‘permissive’ levels of neuronal activity, which allow robust CREB phosphorylation (and in turn CRE-mediated transcription), and that there are pathophysiological levels of neuronal activity that trigger CREB dephosphorylation, which in turn blocks neuroprotective CRE-mediated signaling. As a seminal work in this literature, Hardingham *et al.* (2002) showed that there are functionally distinct synaptic (neuroprotective) and extrasynaptic (excitotoxic) NMDA receptor complexes with oppositional effects on CREB phosphorylation, anti-apoptotic gene expression and cell viability (Hardingham *et al.* 2002). Paralleling this, Lee et al. (2005) showed that excitotoxic levels of glutamate receptor activity selectively stimulate the phosphatase calcineurin, which leads to rapid CREB Ser 133 dephosphorylation (via PP1), and a blockade of CRE-mediated transcription. Interestingly, calcineurin inhibition attenuates glutamate toxicity and converts the transient glutamate-evoked increase in CREB phosphorylation into a long-lasting elevation (~3 hrs). Taken to a whole-animal context, these studies would suggest that in response to excitotoxic challenges, neurons within an excitotoxic foci (i.e., the ‘core’ region) would exhibit limited CREB phosphorylation, whereas cells in ‘penumbral’ regions would exhibit elevated CREB phosphorylation, which would reflect a potentially neuroprotective response (Lee *et al.* 2005a). Indeed, in a 3-nitropropionic acid (3-NP) model of Huntington’s disease (HD), CREB phosphorylation was potently repressed prior to cell death within the neurotoxic striatal core region, whereas robust CREB phosphorylation (as well as Bcl-2 expression) was detected in the penumbral region (Choi *et al.* 2009). Likewise, in a cerebral ischemia model, both CREB phosphorylation and CRE-mediated gene expression were limited to penumbral regions (Irving *et al.* 2000, Sugiura *et al.* 2004). In something of a parallel to these studies, Walton & Dragunow (2000) used a hypoxic-ischemia model to show that CREB Ser 133 is selectively phosphorylated in dentate granule cells, a hippocampal cell layer which showed marked resistance to cell death (Walton & Dragunow 2000).

Although CREB phosphorylation at Ser 133 is a useful marker of cell viability, there are many other phosphorylation sites on CREB (described above) that regulate CREB-dependent transcription. Along these lines, it is worth restating that in response to genotoxic

stress, CREB is phosphorylated at Ser 121 and Ser 271 by ATM and HIPK2, respectively (Dodson & Tibbetts 2006, Sakamoto *et al.*). Ser 121 phosphorylation inhibits CREB dependent transcription, while Serine 271 phosphorylation activates it. Of note, Ser 271 phosphorylation-dependent transcription is independent of Ser 133 phosphorylation (Hailemariam *et al.*). Collectively, these data suggest that there is a myriad of complex, context specific, kinase signaling events that regulate CREB transactivation, and, in turn cell survival.

CREB and oxidative stress

In addition to the ability of CREB to regulate neuroprotection via the upregulation of neurotrophins and anti-apoptotic genes, recent studies indicate that CREB also protects neurons via the regulation of reactive oxygen species (ROS) detoxification. Along these lines CREB has also been shown to stimulate the expression of antioxidant genes including heme oxygenase 1 (HO-1) (Gong *et al.* 2002, Kronke *et al.* 2003) and manganese superoxide dismutase (MnSOD) (Kim et al., 1999). CREB also regulates a broad class of antioxidant genes via the inducible expression of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) (Herzig *et al.* 2001). St. Pierre et al. (2006) showed that CREB binds to the PGC-1α enhancer region and that hydrogen peroxide-induced PGC-1α expression is repressed by either mutating the CRE site or disruption of CREB binding.

The work of St. Pierre et al. was nicely supported in an *in vivo* investigation that employed an A-CREB transgenic mouse line. In this study, Lee et al. (2009) showed that the attenuation of CRE-mediated gene expression led to a marked increase in seizure-induced ROS production. Paralleling this, there was a reduction in both basal and inducible PGC-1α and HO-1 expression. Importantly, seizure-induced cell death was significantly increased in A-CREB mice, relative to non-transgenic controls. Finally, in neuronal culture, disruption of CREB-mediated transcription significantly increased vulnerability to ROS-induced cell toxicity (Lee *et al.* 2009). These data suggest that CREB functions as an essential upstream effector of neuroprotective signaling against ROS-mediated cell toxicity.

CREB and pre-conditioning-evoked neuroprotection

The ability of CREB to drive neuroprotective signaling in an activity-dependent manner raised the interesting prospect that CREB plays a key role in the well-characterized preconditioning response that attenuates the effects of subsequent toxic stimuli. Support for this idea has come from studies showing that CRE-mediated transcription is activated by ischemic preconditioning stimuli (Mabuchi *et al.* 2001). Further, the disruptions of CRE-mediated gene expression, via the *in vivo* infusion of a CRE decoy oligonucleotide markedly diminished the effectiveness of a preconditioning stimulus (Hara *et al.* 2003). Similarly, Lee et al., (2009) showed that the efficacy of a BDNF ‘preconditioning’ microinjection against seizure-induced cell death was inhibited by the repression of CREB-mediated transcription (Lee et al. 2009). Together, these data clearly indicate that the CREB/CRE transcriptional pathway is an underlying mechanism by which preconditioning exerts its neuroprotective effects.

CREB and disorders of the CNS

CREB dysregulation has been implicated in a number of congenital as well as acquired disorders of the CNS, including Alzheimer’s disease, Parkinson’s disease, Huntington’s disease (HD), Rubinstein-Taybi syndrome, ischemia, alcoholism, schizophrenia, addiction, and depression (Chalovich *et al.* 2006, Ma *et al.* 2007, Nucifora *et al.* 2001, Roelfsema & Peters 2007, Walton & Dragunow 2000, Wand 2005, Sawamura *et al.* 2008, Carlezon *et al.* 2005).

Among these disorders, the relevance of CREB to the pathogenesis of HD has been most intensively investigated. HD is an autosomal dominant heritable disease that is characterized by anemia and uncontrolled body movements, which are associated with the degeneration of striatal medium spiny neurons. The causative gene, Huntingtin (Htt), normally has less than 35 CAG triplet sequence repeats on the 5' region of its first exon and is transcribed as a long N terminal glutamine tail. However mutant Htt has over 35 CAG repeats, thus making an abnormally long glutamine tail. At a mechanistic level, inhibition of CREB-dependent transcription appears to be a principal mechanism by which mutant Htt leads to HD (Gil & Rego 2008, Semaka *et al.* 2006). Mutant Htt has been shown to interact with CBP and, in turn, repress CREB-dependent transcription (Nucifora et al. 2001). In an interesting parallel, genetic disruption of CREB leads to a pattern of striatal degeneration similar to that seen in HD (Mantamadiotis et al. 2002). Of note, another line of work has shown that CRE-mediated gene expression is enhanced in early stages of disease progression (Obrietan & Hoyt 2004), thus suggesting that mild striatal pathology leads to a protective program of CREB-dependent transcription, and that only during the later stages of the disease (ostensibly when CBP is sufficiently complexed) is CREB-dependent transcription repressed, thus accelerating disease progression.

Conclusion

Collectively, these studies indicate that CREB is a key component of diverse physiological processes, including nervous system development, cell survival, plasticity, as well as learning and memory. Importantly, dysregulation of the CREB transcriptional cascade following an array of neurodegenerative disorders will likely lead to profound effects on cell viability and cognitive function: two processes that, to date, have limited or no prospect of treatment. Indeed, these studies raise the possibility that carefully calibrated and targeted therapeutic strategies focusing on augmentation of CREB-mediated transcription may prove beneficial both for the enhancement of synaptic plasticity and the promotion of neuroprotection following CNS injury and various neuropathologies.

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Abbreviations

CREB	cAMP-responsive element binding protein
CRE	cAMP response element
b-zip domain	basic leucine zipper domain
ATF1	activation transcription factor 1
CREM	cAMP responsive element modulator
Q1 and Q2	glutamine rich domains 1 and 2
KID	kinase-inducible domain
TAF	TATA binding protein-associated factor
CaMKII and IV	Ca2+/CaM-dependent kinase II and IV
PKA	protein kinase A
MSK	mitogen/stress-activated kinas
RSK	ribosomal S6 kinase
PKC	protein kinase C

MK2	MAPKAP kinase2
CBP	CREB binding protein
ATM	ataxia telangiectasia mutated
CK	casein kinase
GSK3beta	Glycogen Synthase Kinase-3beta
HIPK2	homeodomain-interacting protein 2
PP1 and PP2A	serine/threonine-specific protein phosphatases type 1 and 2A
TORC	transducers of CREB regulatory activity
NGF	nerve growth factor
ChIP	chromatin immunoprecipitation
SACO	serial analysis of chromatin occupancy
SAGE	serial analysis of gene expression
LTP	long-term potentiation
LTD	long-term depression
BDNF	brain-derived neurotrophic factor
Bcl-2	B Cell Lymphoma-2
Mcl-1	myeloid cell leukemia sequence 1
TrkB	tyrosine receptor kinase B
IGF-1	Insulin-like growth factor 1
PACAP	pituitary adenylate cyclase-activating polypeptide
3-NP	3-nitropropionic acid
HD	Huntington’s disease
ROS	reactive oxygen species
HO-1	heme oxygenase 1
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator-1α
AD	Alzheimer’s disease
PD	Parkinson’s disease
Htt	Huntingtin