Chapter 7  
CREB-Dependent Transcription and Synaptic Plasticity

Angel Barco, Dragana Jancic, and Eric R. Kandel

Abstract The CREB family of transcription factors are involved in controlling the transcriptional responses to a wide range of extracellular signals in neurons. In this chapter we discuss the role of the CREB pathway in synaptic plasticity. We first describe how learning-related stimuli, of different nature and intensity, can activate signaling pathways that converge on the induction of CRE-driven gene expression and how the nuclear response orchestrated by CREB can alter future synaptic activity. Second, we will discuss how CREB’s control of synaptic plasticity contributes to learning, memory and other complex brain function. Finally, we will briefly outline how dysfunction of this activation pathway can lead to psychiatric and neurological disorders.

7.1 The CREB Family of Transcription Factors

The CREB family of transcription factors refers to a group of highly homologous proteins encoded by the genes creb, crem and atf-1. This family is characterized by a highly conserved basic region/leucine zipper (bZIP) domain that bind to a specific DNA sequence called cAMP-responsive-element (CRE) found in one or several copies in the promoters of many genes (Fig. 1). Although both, the CRE sequence and CREB, the prototypic member of this family of regulatory molecules, were first identified through studies investigating the regulation of the expression of the hormone somatostatin (Montminy and Bilezikjian, 1987), it was later found that CRE sites were present in the promoter of many other genes and that CREB contributed to the regulation of a variety of cellular responses (Habener et al., 1995; Johannessen et al., 2004; Mayr and Montminy, 2001). In particular, CREB has been involved in many aspects of nervous system function (Carlezon et al., 2003; Lonze and Ginty, 2002), from activity-dependent synaptic plasticity during development (Pham et al., 1999) and in the adult brain (Barco et al., 2003; Dash et al., 1991; Pittenger and Kandel, 1998), to neuronal survival (Dawson and Ginty, 2002; Walton and Dragunow, 2000).

ATF1, CREB and CREM are not the only transcription factors that bind to CRE sites. The term ATF/CREB family of transcription factors is used to refer to a broader group of bZIP transcription factors, including ATF2, ATF3 and ATF4, that
Fig. 1 CREB structure and relevant residues. CREB has a highly conserved leucine zipper and adjacent basic region responsible for DNA-binding, a regulatory kinase inducible domain (KID), and two glutamine-rich regions (Q1 and Q2). CREB is substrate of various enzymatic activities that affect its capability to bind CRE sites and activate transcription. Different symbols indicate the location of those residues relevant for CREB function discussed in the text (See Color Plate 5).

shares structural features with the CREB family and can also bind to CRE sites. Different ATF/CREB proteins can form selective heterodimers with each other and with other transcription factors such as AP-1 and C/EBP that do not belong to this family but share a bZIP DNA-binding domain.

Although homology in the bZIP domain is the main structural feature used to classify transcription factors belonging to the ATF/CREB family of transcription factors, other structural features are common to the several family members (Mayr and Montminy, 2001). Transcription activation in the CREB family is mediated by two types of transactivation domains: (a) The central kinase-inducible domain (KID), that contains several sites recognized by protein kinases and whose phosphorylation state determines the binding of the transcriptional co-activator CBP and that triggers the inducible transcriptional activity of CREB; and (b) the glutamine-rich domains that contribute to basal transactivation activity by interacting with the transcription machinery and stabilizing the interaction with CRE sites. In the case of CREB two glutamine-rich domains, designated Q1 and Q2, flank the KID domain (Fig. 1).

Whereas the atf-1 gene encodes only one major protein product, the creb and crem genes have a complex structure, with multiple exons and introns (Habener