

Activation and repression in the nervous system

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The mechanisms underlying transcriptional activation and repression have become much clearer. Recent evidence suggests that transcription factors that do not bind DNA directly, the co-activators and co-repressors, mediate a large number of cell signaling events. Their association with histone acetylases, to mediate activation, or deacetylases, to mediate repression, provide a model for explaining how gene expression is regulated.

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Abbreviations

CBP	CREB-binding protein
CRE	cAMP-response element
CREB	CRE-binding protein
HDA	histone deacetylase
N-CoR	nuclear receptor co-repressor
NMR	nuclear magnetic resonance

Introduction

The elaboration of a neuronal phenotype involves both positive and negative modes of transcriptional regulation. One of the best studied gene activation pathways in neurons involves the transcription factor CREB (cAMP-response element binding protein). Originally identified as a mediator of cAMP signals, CREB is activated by calcium and growth factor pathways as well [1,2]. CREB interacts with a genetic element termed the CRE (cAMP-response element), which was identified initially in neuropeptide genes. The presence of CRE sequences in multiple genes may allow their coordinate activation.

Coordinate repression of genes also has an important role in neuronal physiology. Indeed, in vertebrates, the initial decision to become a neural cell (neural induction) is attributable, in part, to a repressor pathway that blocks 'neuralness' in non-neural tissues [3,4]. One factor that blocks expression of neural genes in non-neural cells is the transcriptional repressor REST (also called NRSE; [5,6]). REST, which is expressed exclusively in non-neuronal cells, binds to a DNA element (RE1/NRSE) present in many neurally expressed genes and prevents their inappropriate transcription (reviewed in [7]). The

precise mechanism of REST action is unknown, but a mechanism identified recently for other repressors may provide important clues. This review summarizes the emerging picture of how gene repression and activation are mediated. These two processes have become linked mechanistically in a conceptually pleasing way.

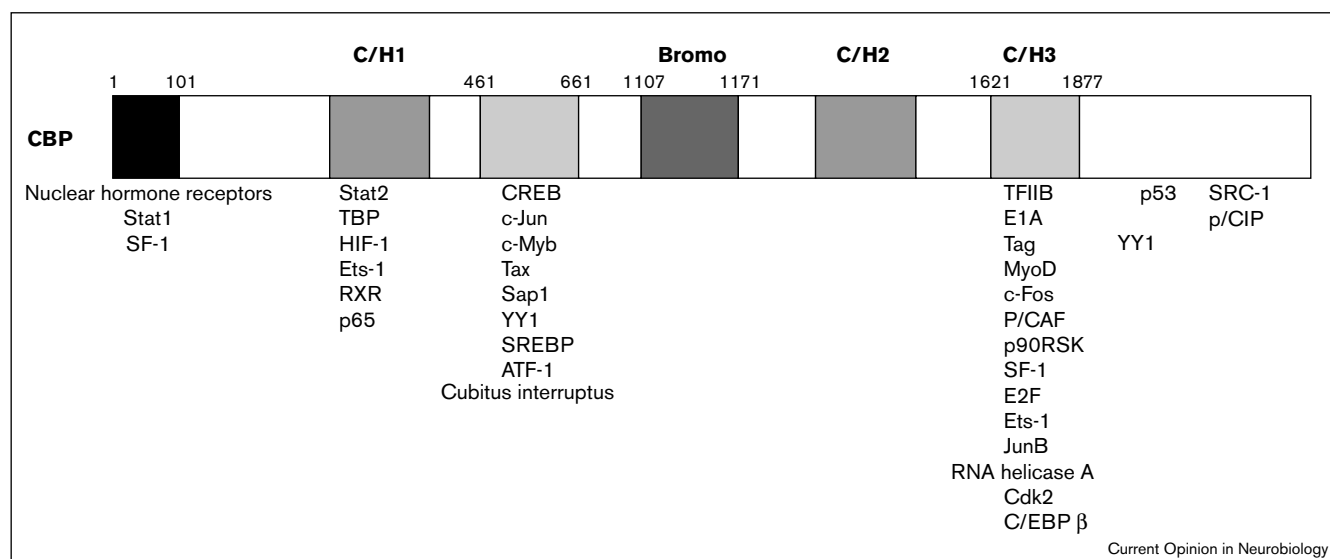
Co-activators – new components of the transcriptional machinery

The major function of DNA-binding transcriptional activators is to stabilize the association of basal transcription factors with the promoter [6]. In the past few years, a new class of co-activator proteins has been identified that do not bind DNA directly. These co-activators have multiple functions — they modify the chromatin factors that repress gene expression, link DNA binding transcriptional activators to the basal transcriptional apparatus, and possibly alter components of the transcriptional machinery through covalent modifications.

The best characterized co-activator in neurobiological systems is the CREB-binding protein, CBP [8]. CREB is activated by phosphorylation of a particular serine residue (Ser133) within a region designated as the 'kinase inducible domain (KID)'. Phosphorylation of CREB promotes association with CBP (or its homolog p300), a step that appears to be essential for gene activation [9,10]. The affinity of this interaction is relatively low, approximately 300 nM, which may explain why CBP was not detected in standard biochemical protein isolation procedures. Mutagenesis studies suggested that hydrophobic residues flanking Ser133 are important for CREB-stimulated gene expression. The basis for this finding may now be understood, at least in part, from nuclear magnetic resonance (NMR) studies of the phosphoCREB–CBP interaction domain [11••]. The CREB sequences in the complex were found to take a 90° turn after binding to CBP, thereby resurrecting the hypothesis that phosphorylation may unmask cryptic CREB activation domains.

Is the structural basis of the phosphoCREB–CBP interaction now completely understood? Probably not, for two reasons. First, Lundblad *et al.* [12], as well as Parker *et al.* [13], have reported that the CBP fragment used in the NMR study does not actually bind very well to phosphorylated CREB. (In the former study, no binding of phosphorylated CREB to this CBP fragment was detected; in the latter, binding was significantly diminished.) It is possible, therefore, that regions of CBP critical for the specificity of phosphoCREB binding are missing from the NMR study. Thus, it is not certain at this point whether there is a distinct phosphoserine-binding motif in CBP that recognizes phosphorylated transcription factors.

Figure 1



Proteins that interact with CBP. C/H, putative zinc-finger motifs; Bromo, bromodomain, a motif in several other co-activators of transcription.

What about the hypothesis that the binding to CBP un-masks a cryptic CREB activation domain? Unfortunately, the region of CREB examined in the NMR study did not include the glutamine-rich portion of CREB proposed to mediate transcriptional induction [14]. Thus, the allosteric model of CREB activation remains uncertain.

Co-activators as integrators

Although identified originally as a co-activator for CREB, CBP is now thought to interact with a wide variety of transcription factors (Figure 1). Most factors appear to bind through one of three interaction domains in CBP—the amino-terminus, the CREB-binding domain (also designated the kinase interaction site, or KIX, although several non-phosphorylated transcription factors bind to this region as well), and the third zinc-finger domain (the binding site for transcription factors, effectors, and modulators of CBP action such as P/CAF [15], RNA helicase A [16•] and p90RSK [17]). In many cases, transcription factors require activation (either by associating with ligand or through phosphorylation) before they can bind to CBP. In other instances, an activation step does not appear to be required. Recent studies suggest that some factors interact with multiple portions of CBP [18].

It is important, however, to recognize that, aside from CREB, few of the CBP interactions with other proteins have been described in much detail. As mentioned previously, the affinity of phosphoCREB for CBP is relatively low. It is possible, therefore, that some interactions, especially those identified in overexpression experiments, could be spurious. Antibody microinjection experiments [19] have been useful in determining which interactions are biologically significant, as have gene

ablation approaches. For example, Akimaru *et al.* [20•] used genetic approaches to show that CBP mediates the activity of the *Drosophila* transcription factor cubitus interruptus, a component of the hedgehog signaling pathway.

Competition for limiting amounts of CBP could explain how signaling via STATs (signal transducers and activators of transcription) dampens retinoic acid receptor-mediated gene regulation or how glucocorticoid receptor actions are antagonized by the AP-1 transcription factor [21,22]. Recently, Mink *et al.* [23] suggested that the transcription factors c-Myb and C/EBP synergize by binding to different portions of p300; and Merika *et al.* [24] have proposed that CBP/p300 is required for synergistic signaling through the interferon-β enhanceosome (the complex of transcription factors that forms on the enhancer). It is not entirely clear that multiple transcription factors can interact with CBP simultaneously, however. Determining whether CBP actually integrates different transcriptional pathways in intact animals remains an important, and unresolved, issue.

The mechanism of co-activator function

Two models have been proposed to explain how CBP/p300 activates gene expression. First, it may directly contact components of the general transcriptional machinery. Several potential targets for CBP/p300 have been suggested, including the general transcription factors TFIIB and TFIID, and RNA helicase A; the helicase is proposed to bridge CBP and the RNA polymerase II holoenzyme [16•]. The 125 E1A transforming protein of adenovirus may compete for the RNA helicase A binding site on CBP, thereby preventing CBP from interacting with RNA polymerase II.

The second model proposes that CBP remodels chromatin to allow binding of general transcription factors to the promoter [25••]. This chromatin-remodeling activity is believed to involve histone acetyltransferase (HAT) activities that are both intrinsic to CBP/p300 [26] and provided by associated proteins such as P/CAF, SRC-1 [27] and p/CIP [28]. P/CAF (p300/CBP-associated factor) is a homolog of the yeast transcription factor GCN5. SRC-1 (steroid receptor co-activator-1) was originally identified as a co-activator for the progesterone receptor, and p/CIP is a related factor. Several studies have suggested that distinct histone acetyltransferase activities mediate different gene activation pathways [19,29]. How the acetylation of histone proteins changes chromatin structure is not entirely clear, however. A long-favored model, that acetylation decreases the association of the positively charged histones with negatively charged DNA, is not completely supported by recent crystallographic studies [30]. It is possible that histone acetylation affects other aspects of chromatin condensation.

Recent evidence indicates that histones may not be the only targets of the CBP/p300 acetyltransferase activity. Gu and Roeder have reported that the carboxy terminus of the tumor suppressor p53 may become acetylated by CBP/p300 as well [31••]. This is an intriguing finding because the DNA-binding ability of p53 is blocked by a repression domain located in the carboxy terminus. Acetylation of this domain was shown to promote the binding of p53 to target DNA sequences, presumably by unmasking the DNA-binding domain. The general transcription factors TFIIE and TFIIIF, and the co-activator PC4 can apparently be acetylated by CBP/p300 as well, but the functional consequences of these modifications are unknown [32].

Transcriptional repression – the mirror image of activation?

Transcriptional repression can antagonize activation through several routes (reviewed in [33]). For example, some repressor proteins block the binding of basal transcription factors to the promoter while others block the binding or function of activator proteins. Co-repressors can bridge repressor proteins to components of the basal transcriptional apparatus or allow DNA-binding repressors to alter aspects of chromatin. This latter mechanism was revealed in recent work showing that repression mediated by the nuclear hormone receptors (retinoic acid and thyroid hormone receptors), by the Mad/Max family of transcription factors, and by the retinoblastoma protein share molecular components, suggesting that the ultimate mechanism of repression is basically the same.

Not surprisingly, knowledge of vertebrate repression mechanisms has received a fillip from experiments performed in yeast. It had been known for some time that a molecule termed Sin3p was a negative regulator of transcription in yeast [34]. Later work indicated that

the yeast transcriptional repressor Rpd3 was likely to be in the same pathway as Sin3p because the two proteins regulated a common set of genes and mutations in the two genes led to the same phenotype [35,36]. The Rpd3 protein was shown to be a component of a yeast histone deacetylase (HDA) complex, suggesting a chromatin target. Mammalian homologs of yeast Sin3p (mSin3) and Rpd3 (HDAC1 and HDAC2) were identified and an explosion of papers linked repressor–Sin3 and Sin3–HDAC interactions. Mouse Sin3 was shown to function as a transcriptional co-repressor for the Mad/Max and Mxi/Max heterodimers that control cell transformation and growth through direct protein–protein interactions [37••,38]. Furthermore, the repressor function of mSin3 was shown to depend upon associated HDA activity mediated by interactions with HDAC proteins [39••,40••]. Concurrently, investigators studying the repression mediated by the unliganded thyroid and retinoic acid receptors identified a new family of mammalian co-repressors termed N-CoR (nuclear receptor co-repressor) and SMRT. These proteins were found to utilize the same mechanism as described above [41••–43••]. Nuclear hormone and Mad/Max repression both required a complex of mSin3 and histone deacetylase. These data taken together generated a new model for repression involving the restructuring of chromatin through histone deacetylase activity with Sin3 as the linchpin.

Are the hook-ups to Sin3 always the same? Probably not. The sites on Mad and Mxi that interact with mSin3 are not present in N-CoR and SMRT, and the mSin3-interaction domains in N-CoR are distinct from those in SMRT [37••,41••–43••]. On the Sin3 side, there are also distinct interaction domains for the different co-repressors. The predicted structure of mSin3 contains four amphipathic helices termed PAH1–PAH4. Mad interacts with the PAH2 domain in Sin3 whereas N-CoR and SMRT interact with PAH1.

Is mSin3 the only co-repressor that associates with a histone deacetylase? Recent work on the retinoblastoma protein indicates that it too can interact with HDAC1 to cause repression of its target protein, E2F [44••,45••]. The repressor function in this case negatively regulates the cell cycle during mitosis. The involvement of histone deacetylases thus provides the perfect balance for the gene activation/histone acetylase pathway discussed above. However, it should be noted that other studies indicate that not all repressor mechanisms involve HDAC activity, suggesting that important factors are yet to be discovered (for example, see [46•]).

Does a specific repressor mechanism ensure that neural genes are expressed only in the nervous system? It is still too early to know. As mentioned earlier, many genes expressed exclusively in vertebrate neurons are repressed in non-neural cells by a mechanism involving the transcriptional repressor protein REST/NRSF. Re-

removal of the REST/NRSF binding site leads to ectopic expression of transgenes *in vivo* [47,48], although the precise pattern of expression is dependent on the presence of other DNA elements [49]. A distinct repressor protein mediates neural-specific expression of the GAP-43 gene [50], and novel repressor proteins that block expression of neural-specific genes in *Caenorhabditis elegans* have been identified [51]. Co-repressors specific for neural genes have not been identified, although domains in REST are likely to interact with such factors [52]. The NAB1 and NAB2 co-repressor proteins have been shown to be required for repression of the immediate early genes *NGFI-A* and *Krox20*, but whether these complexes are tethered to mSin3 and associated with histone deacetylase activity is not known.

Conclusions

Many questions remain about both gene activation and repression in the nervous system. It is important to remember that most studies on the mechanism of repression utilize transient transcription assays. Does a distinct set of factors serve to maintain repression throughout the lifetime of the animal? Clearly, it would be problematic if liver cells, for example, suddenly expressed neuronal genes and became electrically excitable. It is also not known precisely how acetylation and deacetylation actually affect chromatin structure. Hopefully, answers to these questions will be forthcoming.

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