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Review

Rubinstein-Taybi syndrome: molecular findings and therapeutic approaches to improve cognitive dysfunction

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Abstract. Rubinstein-Taybi syndrome (RTS) is a rare human genetic disorder characterized by mental retardation and physical abnormalities. Many RTS patients have a genetic mutation which has been mapped to chromosome 16p13.3, a genomic region encoding cyclic AMP (cAMP) response element binding protein (CREB) binding protein (CBP). CBP is a transcriptional co-activator that binds to CREB when the latter is phosphorylated and promotes gene transcription. CREB-dependent gene transcription has been shown to underlie long-term memory formation. In this review we will focus on recent findings regarding the biology of CBP and its role in memory formation and cognitive dysfunction in RTS. We will also review the role of CBP in other neurological disorders, including Alzheimer's disease, Huntington's disease and amyotrophic lateral sclerosis. Finally, we will discuss novel therapeutic approaches targeted to CBP/CREB function for treating the cognitive dysfunction of RTS and other neurological disorders.

Keywords. Rubinstein-Taybi Syndrome (RTS), cAMP-responsive element binding protein (CREB), CREB-binding protein (CBP), phosphodiesterase inhibitor 4 (PDE4), long-term memory, histone acetyltransferase (HAT), histone deacetylase inhibitor (HDAC).

Rubinstein-Taybi syndrome: What is it?

Rubinstein-Taybi syndrome (RTS) is a human genetic disorder characterized by mental retardation and physical abnormalities including broad thumbs, big and broad toes, short stature and craniofacial anomalies such as beaked nose, down-slanting palpebral fissures and hypoplastic maxilla [1–3]. RTS was first described by Rubinstein and Taybi in 1963. The first published case of RTS, however, was reported by Michail et al. (1957) from Athens, who described a 7-year-old boy with a disorder that retrospectively looks like RTS [4].

Compared with other genetic disorders with cognitive dysfunction (e.g. Down syndrome), RTS is a relatively rare syndrome. It occurs in about 1 in 125,000 to 1 in 720,000 births and accounts for as many as 1 in 300 cases of institutionalized mentally retarded patients. RTS affects males and females equally. The exact etiology of RTS is not established, and as of yet there is no indication for environmental causes, although they cannot be excluded [5]. The existing familial data indicating rare recurrence in siblings suggests that most mutations occur de novo. Such data are difficult to accumulate, however, because most RTS patients do not reproduce. In this regard, the recent report by Hennekam et al. of RTS in a mother and son provides important support for dominant inheritance of this disorder [5].

Although the exact molecular-genetic etiology of RTS is not clearly understood, several groups of researchers established that RTS is associated with breakpoints, mutations and microdeletions of chromosome 16p13.3 [6–13]. In 1995, Petrij et al. first reported that mutations in the

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gene encoding the cyclic AMP (cAMP)-response element binding protein (CREB) binding protein (CBP), which is located on chromosome 16p13.3, could be causative of RTS [10]. Furthermore, these authors showed that RTS results not only from gross chromosomal rearrangement(s) of chromosome 16p, but also from heterozygous point mutations in the CBP gene itself, suggesting that the loss of one functional copy of the CBP gene underlies the developmental abnormalities and mental retardation in RTS patients [10]. A follow-up study of 194 patients with clinical features of RTS showed that microdeletions and truncating mutations in CBP account for approximately 20% of the mutations in individuals with RTS [11]. However, subsequent DNA sequencing of the CBP gene revealed pathogenic mutations in 56% of patients with RTS, a higher rate than previously detected [12]. More recently, Roelfsema et al. sequenced the CBP and EP300 genes (the latter shares some functional and sequence homology with CBP) in 92 patients with RTS and found 3 patients with inactivating mutations in EP300 [13]. This is the first gene other than CBP which has been linked to RTS. Taken together these data support the concept that RTS is a genetically heterogeneous disorder which may be caused by mutations in CBP as well as mutations in other genes in up to 50% of the cases.

Although CBP loss of function is a common feature in RTS patients, they nonetheless display a wide variation in the severity of mental retardation and other clinical manifestations. The intelligence level of RTS patients is usually very low, with an average IQ of 34 by aged 25 [2]. However, some individuals have higher scores and less profound developmental defects. These differences could be due to the heterogeneity of mutations in the CBP gene observed in RTS patients or to heterogeneity in genetic background. To date, two models of how CBP mutations may result in RTS have been proposed: (i) haploinsufficiency and (ii) dominant negative effects. For haploinsufficiency, two functional copies of the gene are required to produce sufficient protein for normal development and function, while for a dominant-negative mechanism, abnormal product derived from the mutant allele inhibits the wild-type product. To date, evidence supporting both mechanisms has been reported. For example, the haploinsufficiency mechanism is supported by observations that both truncated mutants and null mutants can cause human RTS [11, 12]. Alternatively, the findings that microinjection of the CBP-CREB binding domain into fibroblasts blocks transcriptional activation of a CRE-*lacZ* reporter gene support the dominant negative inhibiting mechanism of RTS [14, 15]. Taken together with evidence from studies of genetically engineered mouse models of RTS (see below), it seems likely that both mechanisms of CBP dysfunction can play a role in the development of RTS phenotypes.

Biology of CBP and cognition

CBP was first described in 1993 by Chrivia et al. as a nuclear transcription coactivator that binds specifically to CREB when it is phosphorylated by protein kinase A (PKA) [16]. CBP is a large nuclear phosphoprotein consisting of 2442 amino acids with a molecular mass of approximately 250 kDa that comprises several different domains: three cysteine-histidine-rich domains, a bromodomain, a PKA phosphorylation site, two zinc finger motifs, an N-terminal nuclear receptor binding domain, a C-terminal TAD and a histone acetyltransferase (HAT) domain [9]. Having many identified protein-interacting domains, CBP can function as a link and a signal integrator between the basal transcription machinery and certain DNA-binding factors, namely CREB, Jun, Fos and NF-kB (for reviews see [17–20]). As a binding partner, CBP is a focal point for many molecular pathways. As such, CBP plays an important role in the complex biological processes that affect cell growth, transformation, development and neuronal plasticity (for reviews see [17, 19, 21–24]).

What are the biological mechanisms whereby dysfunction in CBP could cause the cognitive deficits in RTS? Biologically, this can be accomplished through disruption of either of the two main functions of CBP. First, CBP acts as a nuclear transcriptional co-activator that binds to the activated form of the CREB protein [16, 25, 26], and second, CBP acts as a HAT [19, 20, 27–30] (Fig. 1). In neurons, CBP can be activated by several kinases including (PKA), calcium/calmodulin-dependent kinase IV (CaMKIV) and mitogen-activated protein kinases (MAPK), suggesting that it is an important target of multiple signaling pathways [31–36]. Importantly, these signaling pathways (PKA, MAPK and CaMKIV) play a dominant role in activation of CREB in various physiological processes, including learning and memory [37–49]. CREB phosphorylation enables its interaction with CBP and links kinase pathways driven by neuronal activity to transcription of genes that are important for learning and memory. Consequently, acting as a co-activator, CBP enhances the ability of phosphorylated CREB to activate transcription of cAMP-responsive genes. CREB and CRE-dependent genes have been established to underlie long-term memory formation in several invertebrate and vertebrate species [39, 50–60], raising the possibility that cognitive deficits in RTS patients may derive from impaired CBP function during long-term memory formation [61, 62].

Another important function of CBP is its HAT activity [27, 28]. Histone acetylation relates to the transcriptional availability of chromatin [63]. Specifically, hyperacetylated histones accumulate within transcriptionally active regions of the chromatin, and hypoacetylated histones accumulate within transcriptionally silent regions. His-

tone acetylation disrupts repressive chromatin structure and allows for transcription apparently via three mechanisms: (i) it promotes transcription factor access to the DNA; (ii) it weakens inter-nucleasomal interactions, destabilizing higher-order chromatin structure; and (iii) it promotes the progression of RNA polymerase during transcription. In essence, when histones are acetylated, the DNA becomes 'unwound' from the histones and facilitates the binding of transcription complexes to DNA [63] (Fig. 1).

The HAT domain of CBP resides in the central region of the protein, and both the N- and the C-terminal regions can activate transcription. This modular organization allows CBP to provide a physical bridge for assembly of transcription co-activator complexes. Taken together, it is plausible that CBP plays a dual role in transcription activation: (i) as a bridging protein interacting directly with CREB and other transcription factors; and (ii) as a HAT that contributes to transcription by acetylating histones, thereby disrupting repressive chromatin structure [19] (Fig. 1). Hence, it is likely that CBP dysfunction in RTS may interfere with the transcriptional machinery and activation of downstream genes by reducing the functional availability of CREB and/or by disrupting HAT-induced chromatin remodeling.

While considering the role of CBP in the cognitive dysfunction of RTS, it is important to emphasize its critical role in development. Evolutionary CBP is a highly conserved protein sharing about 95% similarity between human and mouse. CBP orthologs have been found in a number of different organisms, including *Drosophila melanogaster*, *Caenorhabditis elegans* and *Arabidopsis thaliana*. Numerous studies have documented the involvement of CBP in embryogenesis and developmental processes, particularly in model systems such as *Drosophila* and mouse (for excellent reviews, see [21, 22]). At almost every stage of development CBP takes on different binding partners and expression patterns that affect cellular patterning and differentiation. During development many molecular pathways in vertebrates and invertebrates interact directly with CBP/CREB and/or are regulated by CBP/CREB. Thus far, however, it has been difficult to clearly link a specific defect in CBP during development to mental retardation observed in adult RTS patients. To date, we can only speculate that some of the developmental defects in CBP function con-

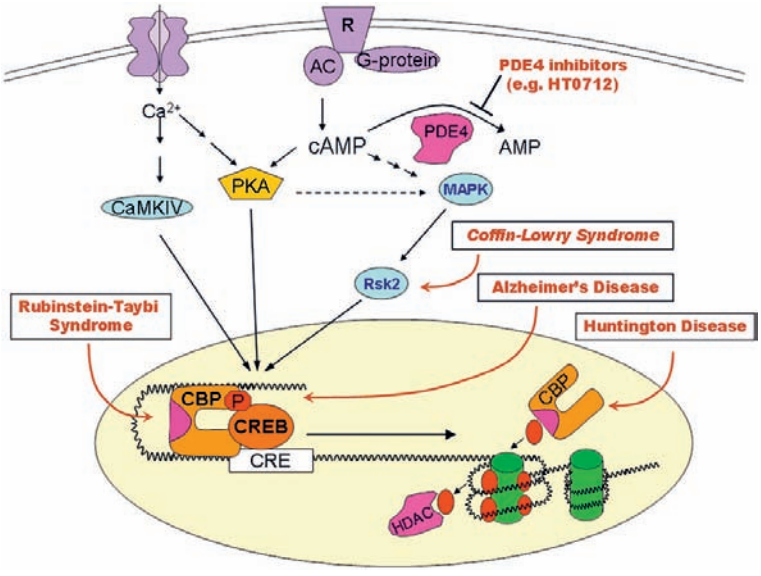

Figure 1. Biology of CBP and heritable forms of cognitive disorders. Molecular genetic mutations have been identified for various forms of heritable cognitive disorders. Interestingly, most of these mutations correspond to biochemical components of memory formation. Memory formation begins with the influx of Ca^{2+} through NMDA receptors and/or the activation of adenylyl cyclase via neuromodulators (e.g. dopamine). In turn, this causes a rise in cAMP levels that activates PKA and other kinases (e.g. MAPK and CaMKIV). The cAMP-signaling cascade reaches the nucleus, where its components (e.g. PKA, RSK2) phosphorylate transcription factors such as CREB. When CREB is phosphorylated, CBP binds to it, thereby promoting changes in gene expression important for long-term memory formation. Newly synthesized proteins result in long-term changes in cell function, such as growth and maturation of synaptic connections. To date, several molecular mutations have been identified for various inherited cognitive disorders, including Rubinstein-Taybi syndrome, Coffin-Lowry syndrome, Huntington's disease and Alzheimer's disease, all of which are consistent with disruptions of the biochemistry of brain plasticity and memory formation (also see, Weeber and Sweatt, 2002; Tully et al., 2003) [58, 62]. Recent evidence suggests that pharmacological treatments that enhance signaling in the CREB/CBP pathway (e.g. PDE4 inhibitors) can rescue memory deficits in animal models of RTS and AD [59, 72, 113]. (AC, adenylyl cyclase; AMP, adenosine monophosphate; CaMKIV, calcium-calmodulin-dependent protein kinase IV; CBP, cAMP-response-element-binding protein (CREB)-binding protein; HDAC, histone deacetylase; MAPK, mitogen-activated protein kinase; NMDA, N-methyl-D-aspartate; PDE4, phosphodiesterase 4; PKA, protein kinase A; RSK2, ribosomal S6 kinase).

tribute to the mental retardation in RTS patients (for our hypothesis see below).

Animal models of RTS: rescuing long-term memory deficits

The evidence that RTS is a consequence of reduced levels of CBP is based on RTS cases resulting from heterozygous defects of CBP. Indeed, many RTS patients are heterozygous for CBP mutations which yield truncations of the CBP C-terminus, suggesting that a dominant-negative mechanism may contribute to the clinical symptoms. As we described above, CBP is a transcriptional co-activator that binds to CREB when the latter is phosphorylated and facilitates gene transcription. Truncated CBP would bind to phospho-CREB but would not be able to activate transcription. CREB-dependent gene expression has been shown to underlie long-term memory formation in multiple species, leading to the intriguing speculation that the mental retardation in RTS patients may derive from reduced CBP function during long-term memory formation [61]. To this end, Oike et al. [15] generated a C-terminal truncation mutation in mouse CBP, which appears to act in a dominant-negative fashion to recapitulate many of the clinical features observed in RTS patients. Homozygous $CBP^{-/-}$ mutants are embryonic lethal, while heterozygous $CBP^{+/-}$ mice show reduced viability and growth retardation. In their initial study, Oike and colleagues showed that $CBP^{+/-}$ mice have normal learning and short-term memory but defective long-term memory for two passive avoidance tasks. These findings provided the first behavioral evidence of cognitive dysfunction in a mouse model of RTS, substantiating the notion that normal CBP function is required for memory formation.

We extended the observations of Oike et al. to a novel object recognition task, an ethologically relevant and nonaversive task that relies on a mouse's natural exploratory behavior [59]. Normal mice can remember having explored an object and show a preference for exploring novel objects. During training for this task, mice are presented with two identical objects, which they explore for some time by orienting toward, sniffing and crawling over. To test for memory of this experience, mice are presented at a later time with two different objects, one of which was previously explored and thus is 'familiar', and the other of which is novel. If the mouse remembers the familiar object, it will spend more time exploring the novel object.

We found that $CBP^{+/-}$ mutant mice have impaired long-term memory, but normal short-term memory for novel object recognition (Fig. 2a). These findings corroborate the observations of Oike et al. and establish that mutations in CBP can yield specific defects in long-term memory formation [15, 59].

Because CBP/CREB function was reduced but not eliminated in these mice, the possibility existed to improve long-term memory formation by enhancing upstream signaling onto CBP/CREB. To this end, we examined two phosphodiesterase 4 (PDE4) inhibitors, the prototypical PDE4 inhibitor rolipram and a novel one, HT0712, for their ability to abolish memory deficits in $CBP^{+/-}$ mice [59]. Indeed, as predicted, we found that a single dose of either rolipram or HT0712 delivered shortly before training was able to restore long-term memory to normal levels in $CBP^{+/-}$ mice (Fig. 2b). To address whether the drug's effects were specific to the molecular lesion in CBP, we reduced the duration of training so that wild-type mice showed almost no memory. We then gave increasing doses of the HT0712 until we achieved maximal long-term memory. We reasoned that because $CBP^{+/-}$ mice had less functional CBP than wild-type mice, they would require higher concentrations of the drug to respond comparably to wild-type mice. Indeed, we discovered that $CBP^{+/-}$ mice had a rightward shift in the dose response curve compared with wild-type mice. These findings provide strong support for the molecular specificity of the drug action [59] (Fig. 3).

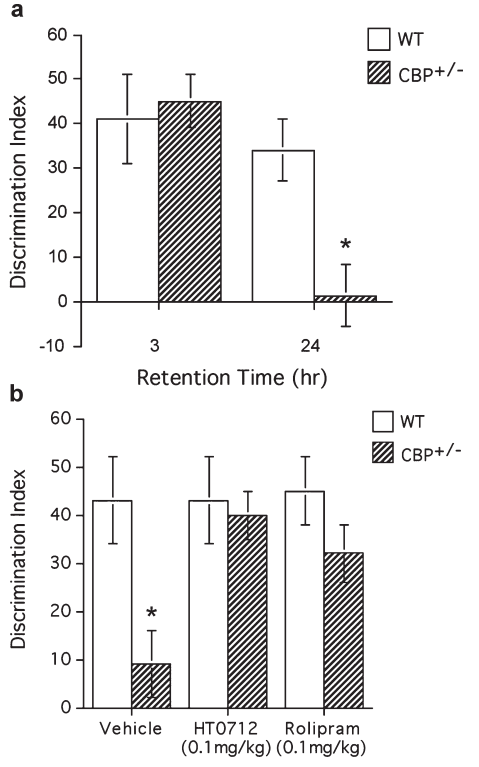

Figure 2. Object recognition in a mouse model of RTS. (*a*) Long-term (24 h) but not short-term (3 h) memory is impaired in $CBP^{+/-}$ mutant mice. (*b*) PDE4 inhibitors (HT-0712 and rolipram) ameliorate the long-term memory defect of $CBP^{+/-}$ mutant mice (* = $p < 0.05$ $CBP^{+/-}$ vs. wild-type mice) (adapted from [59]).

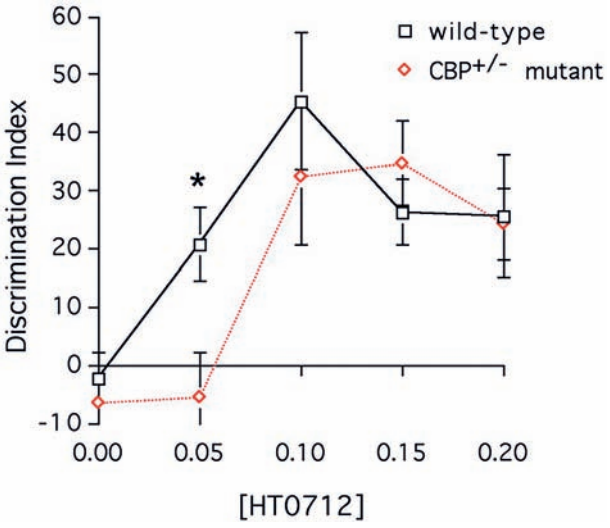

Figure 3. Pharmacological rescue of long-term memory deficit in $CBP^{+/-}$ mutants is dose-dependent. HT0712 dose sensitivity is decreased in $CBP^{+/-}$ mutant mice (* = $p < 0.05$ $CBP^{+/-}$ mice vs. wild-type controls) (adapted from [59]).

Our findings provided the first demonstration that the memory impairments of $CBP^{+/-}$ mutants can be ameliorated by inhibitors of PDE4. These PDE inhibitors likely enhance signaling to CREB during memory formation by increasing the magnitude and/or duration of cAMP levels in response to experience-dependent changes in neural activity [43, 64–68]. This effect is specific molecularly, because $CBP^{+/-}$ mutants require a higher dose of HT0712 than wild-type mice to produce an equivalent amount of enhanced memory. This result was expected since the genetic lesion of $CBP^{+/-}$ mice likely reduces the levels CBP/CREB available for functional activation via cAMP signaling. Hence, greater upstream enhancement is required for a comparable effect on downstream targets [59]. Given that CBP interacts with several transcription factors [17–20, 69, 70], our results strongly suggest CBP/CREB to be the relevant interaction for long-term memory formation. Because of the observed molecular and pathological similarities between these $CBP^{+/-}$ mice and patients with Rubinstein-Taybi syndrome, we hypothesize that the mental retardation of RTS patients likely results, at least in part, from functional defects in long-term memory formation. Further, PDE4 inhibitors may ameliorate this biochemical block on memory formation, thereby rendering RTS patient capable of benefiting from training and experience.

Another model for RTS, a null allele mouse modeling the haploinsufficiency mechanism of RTS, was generated by Tanaka and colleagues [71]. Similar to the mice we studied, homozygous CBP mutants are embryonic lethal. Unlike our mice, however, fewer of those mutants (7 out of 21 mice studied) exhibit phenotypes resembling the clinical features of RTS [71], making these heterozygous mice overall a less favorable model for RTS. In their original study Tanaka and colleagues did not perform behavioral analysis of these $CBP^{+/-}$ mutant mice. However, recently Alarcon and colleagues tested these mice in the similar fear based and object recognition tasks as we and Oike et al. did previously [59, 72]. In agreement with our findings, Alarcon et al. found that $CBP^{+/-}$ mutant mice have normal short-term memory but deficient long-term memory in the object recognition and contextual memory tasks. In addition to their behavioral findings, Alarcon et al. also showed that long-term potentiation (LTP), a form of synaptic plasticity that is thought to underlie the storage of some types of memory in the hippocampus, was deficient in $CBP^{+/-}$ mutant mice. This deficiency in LTP was abolished with the PDE4 inhibitor rolipram or by overexpressing a constitutively-active form of CREB [72]. These findings confirmed and strengthen our original hypothesis that PDE4 inhibitors would improve long-term memory formation by enhancing upstream signaling onto CBP/CREB.

Alarcon and colleagues also found reduced HAT activity in their mutant mice which raised the possibility that such molecular mechanism may also contribute to the observed memory deficits in these mice. To determine whether this was really the case, they treated animals with histone deacetylase (HDAC) inhibitor SAHA prior to training in contextual fear conditioning. The HDAC inhibitor reversed the memory deficit observed in contextual conditioning [72]. These findings showed that enhancing CREB function and/or increasing the HAT activity of CBP may be efficacious for treating RTS.

More recently, two additional groups of researchers generated mouse models of RTS in which the CBP trangene expression was restricted to the forebrain [73, 74]. The molecular techniques used by these authors allow for a mutation to be spatially restricted to neurons within the hippocampus, striatum, amygdala and cortex, as well as for a transgene to be temporally expressed postnatally. Both groups reported that CBP mutations restricted to the forebrain disrupt formation of long-term memory. These studies confirmed our and Alarcon's et al. findings and provide further support for the role of CBP in hippocampal dependent memory formation in the adult organism.

In summary, the present findings demonstrate that CBP/CREB likely function together as a molecular switch during long-term memory formation, and mutations in CBP can be detrimental to this process. The current evidence indicates that it is possible to overcome the deficits in long-term memory by enhancing CREB/CBP signaling with PDE4 inhibitors or with HDAC inhibitors. These findings suggest that PDE4 and HDAC inhibitors may prove to be novel therapeutics for treating cognitive dysfunction in RTS patients.

CBP in neurological diseases

In the past few years considerable progress has been made in revealing the role of CBP/CREB function not only in RTS, but also in the molecular etiology of other human neurological disorders, such as Huntington's disease, Alzheimer's disease and amyotrophic lateral sclerosis.

Polyglutamine diseases

Huntington's disease (HD) belongs to a family of neurodegenerative diseases including (i) spinal bulbar muscular atrophy (SBMA), (ii) (iii) dentatorubral and pallidoluysian atrophy (DRPLA) and (iv) spino-cerebellar ataxia (SCA) that are characterized by expanding CAG repeats coding for polyglutamine (polyQ) (for reviews see [75, 76]). Although there is no unambiguous single protein-protein interaction that is responsible for the pathology of these diseases, there are two common factors connecting them. First, all are characterized by selective neuronal degeneration in specific regions of the CNS. Second, all these diseases contain expanding CAG repeats encoding for multiple copies of glutamine (polyglutamine [polyQ]) in the genome. Converging evidence from *Drosophila* [77–84], mice [85–87] and humans [87] suggests that polyQ aggregates cause neurotoxicity depending on where the polyQ is expressed. Here we focus on HD as a representative model on how polyQ can lead to CBP/CREB dysfunction and neuronal death.

HD is an autosomal-dominant neurodegenerative disease caused by CAG trinucleotide repeats in exon 1 of the huntingtin (*htt*) gene. Normally, the htt protein is found predominately in the cytoplasm. In the mutant, however, htt is localized mainly in the nucleus where it forms aggregates of the mutant protein. These polyQ aggregates have been shown to bind to a number of transcription factors and co-factors, resulting in their functional impairment (reviewed in [88]). In particular, much of the attention has been on the functional disruption of CBP by the binding of polyQ to the HAT domain [82, 89, 90]. This decreases soluble levels of CBP [91]. The loss of accessible CBP leads to a transcriptional dysfunction of CBP/CREB-mediated gene expression [87, 88, 92–96] and a subsequent decline in neuronal survival [90]. In addition, the binding of polyQ to CBP results in a decrease in histone acetylation, which further restricts CBP/CREB transcription. Combined, these effects result in a lack of pro-survival signals, leading to neuronal death [87, 91, 94, 95, 97].

Converging evidence from recent studies suggests that biochemical interventions which facilitate CBP/CREB function can ameliorate the effects of mutant htt protein. For example, Nucifora et al. demonstrated that CBP was depleted from its normal nuclear location and was present in polyQ aggregates in a neuronal cell culture model of HD, a transgenic mouse model of HD and Huntington's disease in humans [87]. Expanded polyQ repeats interfere with CBP-activated gene transcription. Importantly, Nucifora et al. found that by overexpressing CBP they could rescue CBP reporter gene expression and ameliorate polyQ-mediated toxicity [87]. In a second study, Wyttenbach et al. demonstrated a decrease in CRE-mediated transcription in polyQ transfected cells. By amplifying CREB/CBP signaling with cAMP or forskolin (which constitutively activates adenylyl cyclase to produce cAMP), they could partially rescue the CRE-mediated transcription [94]. Finally, Sugars et al. reported that overexpression of a transcriptionally active form of CREB rescued CRE-mediated transcription, reduced polyQ aggregation and protected against polyQ-induced cell death [95]. Additional evidence supporting CBP dysfunction comes from the correlation of hypoacetylation with neuronal degeneration in polyQ diseases [82, 84, 98]. For example, reversal of hypoacetylation by either CBP overexpression or HDAC inhibition rescues cell loss [82, 84] and extends animal survival in a dose-dependent manner *in vivo* [98, 99]. Taken together these findings indicate that modifying CBP/CREB function may provide a potential therapeutic approach for treating polyQ diseases such as HD.

CBP in Alzheimer's

Alzheimer's disease (AD) is an age-associated neurodegenerative disease characterized by mild cognitive impairment at its onset. During the later stages, the disease progresses to severe deficits in multiple memory systems accompanied by changes in personality and cognitive decline. Current evidence suggests that AD begins as a disorder of synaptic function and plasticity (for reviews [100–103]). Over time AD progresses to mass neuronal cell death and irreversible brain damage. The initial synaptic dysfunction is associated with the deposition of the amyloid β-peptide (Aβ), particularly its 42-aa form (Aβ_{1-42}) [104–110]. Aβ_{1-42} can disrupt synaptic function [107] and CREB transcription at very low (non-toxic) concentrations [111]. Aβ is a protein fragment cleaved from a larger protein called amyloid precursor protein (APP) during metabolism and is implicated in CBP/CREB dysfunction. The final step in the generation of Aβ from APP is proteolysis by gamma-secretase. The most common cause of familial early onset AD is the result of mutations in the genes encoding APP and presenilins 1 and 2 (PS-1 and -2), the latter of which alters gamma-secretase activity to increase Aβ production. Although the precise mechanisms by which APP and PS mutations increase Aβ deposition and contribute to the pathology of the disease remain to be determined, recent studies have demonstrated that mutations in APP and PS1 affect CREB/CBP function [66, 110–114].

Although there is eventual synaptic loss in mouse models of AD, the deficits in memory formation and LTP precede

synaptic depletion [106]. This suggests that biochemical changes occur before synapse and neuronal loss. Recently Vitolo and colleagues described an important link between Aβ deposition and CREB dysfunction in cultured hippocampal neurons [66]. They observed a significant decrease in PKA activity in hippocampal neurons following $A\beta_{1-42}$ administration. They also found that pretreatment with $A\beta_{1-42}$ blocked the increase in CREB activation following glutamate stimulation. This $A\beta_{1-42}$-induced decrease in PKA/CREB signaling also coincides with a decrease in LTP. Importantly, Vitolo and colleagues were able to rescue CREB activity in hippocampal cultures and LTP in hippocampal slices with the administration of the PDE4 inhibitor rolipram [66].

In addition to evidence of CREB/CBP dysfunction *in vitro*, recent studies on APP and PS1 double-transgenic mice also have pointed to dysfunction of CREB/CBP *in vivo* [113, 114]. APP and PS1 double-transgenic mice display progressive memory loss and Aβ deposition [115–118]. Recently, Gong et al. used rolipram to magnify cAMP/CREB signaling in their double transgenic animals [113]. They found that rolipram ameliorated both LTP and memory deficits in this mouse model of AD [113]. Importantly, this effect was long-lasting: the transgenic mice treated with rolipram at 3 months of age had normal contextual memory and normal levels of CREB at 7–8 months of age, while vehicle-treated mice did not [113]. In another study, Saura et al. evaluated PS1/2 conditional knockout mice in which PS1/2 is selectively eliminated in excitatory neurons in the forebrain [114]. The conditional knockout mice had LTP and memory deficits that were amplified with age. These mice had decreased levels of CBP leading to reduced transcription of CBP/CREB genes, such as c-fos and BDNF [114]. Taken together, these studies implicate CREB/CBP in AD and suggest the potential for therapeutic strategies targeted to CBP/CREB in age-related memory impairment.

CBP in amyotrophic lateral sclerosis

ALS, also called Lou Gherig's disease, is a neurodegenerative disease that is characterized by progressive degeneration of motor neurons in the brain and spinal cord. The loss of motor neurons results in muscle weakening and eventually paralysis and death. ALS has both sporadic and familial forms. Familial ALS is linked with a genetic mutation in the Cu^{2+}/Zn^{2+} superoxide dismutase (SOD-1) gene and accounts for approximately 5–10% of all ALS cases (for reviews [119, 120]). The symptoms, pathology and progression of familial ALS are similar to the sporadic form, which suggests similar mechanisms of neurodegeneration. Several mouse strains with mutations in the SOD-1 gene have been generated as a mouse model of ALS (reviewed in [121]). These mouse models of ALS display motor neuron degeneration which is accompanied by motor deficits and eventual death. The progression of the disease in the mouse model closely follows that of the human disease [122]. Recently, Rouaux et al. found reduced CBP levels in protein extracts prepared from lumbar spinal cord of transgenic SOD-1G86R mice [123]. In addition, histone acetylation was decreased in motor neuron nuclei in the spinal cord of SOD-1G86R mice compared with wild-type littermates [123]. Together, these studies provide support that CBP/CREB signaling is an important component of neuronal function and survival in ALS [24, 123].

Summary

Rubinstein-Taybi syndrome, Huntington's disease, Alzheimer's disease and amyotrophic lateral sclerosis all share impaired CBP/CREB function. Taken together, a pattern emerges that suggests that CBP/CREB dysfunction may be an important factor in multiple neuronal diseases. It is still unknown whether impaired CBP/CREB function is the cause of these neuronal diseases or a convergent downstream effector of the initiating diseases. However, because multiple signaling mechanisms converge onto the CREB/CBP molecular switch, the upstream components of these signaling pathways are emerging as therapeutic targets for drug intervention. Further research on molecular lesions associated with neuronal disorders will elucidate the molecular mechanisms of their pathologies. Such work promises to yield important new insights not only into the neurobiology of brain function but also to novel therapeutics for treating patients.

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