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Targeting CREB-binding protein (CBP) loss of function as a therapeutic strategy in neurological disorders

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Abstract

Histone acetylation/deacetylation is a master regulation of gene expression. Among the enzymes involved in this process, the CREB-binding protein (CBP) displays important functions during central nervous system development. Increasing evidence shows that CBP function is altered during neurodegenerative processes. CBP loss of function has now been reported in several diseases characterized by neurological disorders such as the Rubinstein–Taybi syndrome or polyglutamine-related pathologies (Huntington's disease). Our recent work suggests that CBP loss of function could also be involved in Alzheimer's disease and amyotrophic lateral sclerosis. In a simplified apoptotic model of primary neurons, we described CBP as a substrate of apoptotic caspases, an alternative to its classical proteasomal degradation. In these neuronal death contexts, histone acetylation levels were decreased as well. Altogether, these data point to a central role of CBP loss of function during neurodegeneration. In order to restore proper acetylation levels, a proposed therapeutic strategy relies on HDAC inhibition. Nevertheless, this approach lacks of specificity. Therefore new drugs targeted at counteracting CBP loss of function could stand as a valid therapeutic approach in neurodegenerative disorders. The challenge will be to respect the fine-tuning between cellular HAT/HDAC activities.

Keywords: CBP; Histone acetylation; Neurodegenerative diseases; Apoptosis; Caspase-6; HDAC inhibitors

1. Apoptosis and neurodegenerative diseases

Apoptosis is a physiological programmed cell death that allows the control of cellular homeostasis during development. In the adult, apoptosis guides the fate of individual cells or organs. Nevertheless, it can also be activated under pathological conditions, notably in the central nervous system. Indeed, post-mortem analyses of human brains and in vivo animal models gave evidence of programmed cell death in different neurodegenerative diseases, reviewed in Ref. [1]. Apoptotic hallmarks were found in Alzheimer's disease [2,3], Parkinson's disease [4], Huntington's disease [5] and amyotrophic lateral sclerosis [6,7].

Neuronal apoptosis can be modeled in vitro with primary neuronal cultures. For example, this active form of cell death is induced by K^+-starvation of cerebellar granule neurons (CGN) from 7-day-old mice [8–10]. This model presents classical morphological and biochemical hallmarks of apoptosis such as cell shrinkage, chromatin condensation and nuclear fragmentation [9,11], accompanied with internucleosomal DNA fragmentation and caspases activation that are responsible for the degradation of neuroprotective proteins [12,13]. Cytochrome *c* release from mitochondria [14] and up-regulation of pro-apototic factors [15,16] were also described in this model.

2. Transcriptional modifications during neuronal apoptosis

As an active cell death, apoptosis occurs with transcriptional modifications leading to activation of pro-apototic

Abbreviations: CBP, CREB-binding protein; CREB, cyclic AMP-responsive element-binding protein; HAT, histone acetyltransferase; HDAC, histone deacetylase; CGN, cerebellar granule neurons; RTS, Rubinstein–Taybi syndrome; AD, Alzheimer's disease; APP, amyloid precursor protein; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; htt, Huntingtin; SBMA, spinal and bulbar muscular atrophy; TSA, trichostatin A; SAHA, suberoylanilide hydroxamic acid; NaBu, sodium butyrate

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genes and repression of neuroprotective genes [16–18]. Indeed, transcription/translation inhibitors prevent or delay apoptosis in response to a wide range of insults [11,19]. However, the fine mechanisms of transcriptional regulation implicated in apoptosis are still obscure, particularly because the deep changes occurring on chromatin during this process, i.e. global nuclear condensation, should lead to a broad transcriptional repression. Indeed, the nucleosomal structure participates in transcriptional regulations, through post-translational modifications such as acetylations, methylations or phosphorylations of the chromatin [20] and these mechanisms could participate to transcriptional regulation during apoptosis. Histone acetylations, performed by histone acetyltransferases (HATs) [21], occur on conserved lysine residues of the amino-terminal tails of core histones, and induce a chromatin opening by perturbing higher-order chromatin folding. The deacetylation process is performed by histone deacetylases (HDACs) [22]. Therefore, by affecting the chromatin folding, HATs and HDACs control both DNA accessibility and transcriptional regulation [23]. It should be noted that these enzymes are also able to acetylate/deacetylate non-histone proteins such as transcription factors, thus adding another level of regulation to transcription [21,22].

Several publications report a role for histone acetylation modifications during apoptosis [24–26]. For example, artificial histone hyperacetylation using HDAC inhibitors can induce neuronal apoptosis [27,28], while several diseases such as neurological disorders are associated with an imbalance in acetylation levels [29,30]. It seems thus that neuronal survival is the result of a balance between HAT and HDAC activities.

Among HATs, CREB-binding protein (CBP) [31–33] is of particular interest, because of its ability to regulate the transcription factor CREB, that displays neuroprotective functions [34,35]. However, CBP not only acts as a transcriptional co-activator on CREB, but also on a plethora of transcription factors [36].

3. CBP loss of function in neurological disorders

Interestingly, CBP loss of function has been linked to several neuropathologies. The earliest described was the Rubinstein–Taybi syndrome (RTS), an autosomal dominant syndrome characterized by mental retardation and skeletal malformations [37,38]. Alterations in *cbp* gene were reported to be the cause of RTS [39]. Recent studies suggest that mutations affecting *cbp* gene in RTS patients would mainly target the HAT domain, leading to abolition of CBP HAT activity as well as its ability to transactivate CREB [40,41]. We have recently shown that specific CBP loss occurs during neuronal death in models relevant to neurodegenerative diseases, such as Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS) [26]. When cortical neurons were committed to die through the use of an antibody directed against the extracellular fragment of the amyloid precursor protein (APP) [42], they displayed not only CBP loss but also histone deacetylation [26], thus suggesting the possible implication of CBP loss of function in AD. Interestingly, this was also observed in dying motorneurons of a mouse model of ALS [43].

CBP loss of function was also described in other models of neurodegenerative diseases such as polyglutamine (polyQ) diseases [44,45]: spinocerebellar ataxia type 7 (SCA7) [46], spinal and bulbar muscular atrophy (SBMA) [47] and Huntington's disease (HD) [48].

Altogether, CBP loss of function appears relevant in different neuropathological contexts, defining CBP as a potential neuroprotective protein.

4. Mechanisms leading to CBP loss of function

Several mechanisms account for the observed CBP loss of function. *cbp* haploinsufficiency responsible for RTS leads to an insufficient amount of produced functional CBP [39]. *cbp* heterozygous-deficient mice present abnormal skeletal patterning [49] and deficiencies in long-term memory [50], whereas *cbp* diploinsufficiency induces embryonic death [49,51]. These observations suggest a role of CBP during development and during CNS formation in particular. Besides genetic alterations, CBP loss of function can also be achieved by sequestration as shown in some cases of polyQ diseases [44,45]. In that case, several reports evidenced the direct interaction between CBP and the mutated form of huntingtin protein (htt) that constitutes polyQ aggregates in HD. This was demonstrated in vitro in cell culture, as well as in vivo in striatal neurons from HD transgenic mice and in human HD post-mortem brains [48,52,53]. Interestingly, htt interacts with the HAT domain of CBP, thus inhibiting its HAT activity and leading to global histone deacetylation and cell death [54–56]. Alternatively, Jiang et al. also found that CBP recruitment by the mutated form of htt enhances its processing by the ubiquitin-proteasome pathway [57]. It is postulated that CBP sequestration leads to a decrease in CBP enzymatic activity responsible for neuronal function alterations.

We recently described another mechanism that accounts for CBP loss of function during neurodegeneration [26]. In normal conditions, CBP turnover is controlled by its degradation through the proteasome pathway [58]. Interestingly, we showed a specific CBP/p300 degradation in CGN undergoing apoptosis, without affecting other HAT family members as PCAF (p300/CBP associated factor) or TAFIIp250 (TATA box-binding protein associated factor p250) (Fig. 1) [26]. Our in vitro studies showed that CBP could be cleaved by an executioner protease of apoptotis: caspase-6, yielding two cleavage fragments that can be further processed by calpains (Fig. 1). This caspase-induced CBP degradation triggers a decrease in histone acetylation. CBP degradation and histone deacetylation

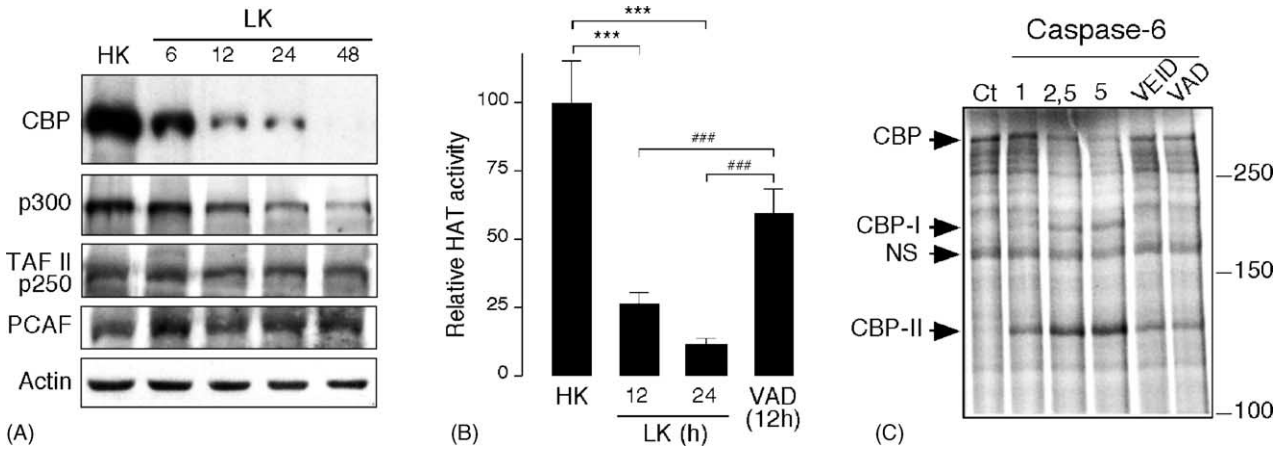

Fig. 1. Caspase-6 induced CBP degradation during neuronal apoptosis (adapted from [26]) (A) CBP, p300, TAFIIp250 and PCAF levels were monitored on K^+-deprived CGN (LK) for 6–48 h or not (HK). Actin: internal loading control. Results shown are representative of four independent experiments. (B) HAT activities were determined on extracts from CGN treated or not with LK (12 and 24 h), or LK/z-VAD-fmk (12 h, 50 μM), a broad caspase inhibitor, after HAT immunoprecipitation with antibodies recognizing CBP and p300. Data from three independent experiments performed in duplicate represents means ± SEM (arbitrary units relative to HK set as 100). $P < 0.001$, *** vs. HK; ### vs. LK. (C) [^{35}SMet]CBP recombinant protein was produced in vitro [26] and tested in a cleavage assay with recombinant capsase-6. Capsase-6 cleaves CBP in a dose-dependent manner (1, 2.5 and 5 units). Two cleavage fragments (CBP-I and CBP-II) can be detected with apparent molecular weights of 175 and 130 kDa, respectively (NS: non-specific); this cleavage can be reversed by z-VEID-fmk (50 μM), a caspase-6 inhibitor, and Ac-VAD-CHO (50 μM), a broad caspase inhibitor.

occur prior to nuclear condensation, thus suggesting that it is an early event of neuronal apoptosis. To our knowledge, this is the first description of a CBP degradation, through an alternative degradation pathway than the proteasome pathway. Such degradation observed during neuronal apoptosis confirms the implication of this HAT in neuronal homeostasis. It is noteworthy that the caspase-6 proenzyme, as well as the active caspase-6 fragment have been evidenced in pathological adult human AD brain tissue [59] suggesting that caspase-6 activation could be involved in Alzheimer's disease. Motorneuronal death occurring in the mouse model of ALS has also been described to be caspase-dependent [60,61], even if caspase-6 has not been studied in ALS models up to now.

CBP seems thus to be involved in a variety of neurological disorders, such as polyQ diseases, AD, ALS as well as in neuronal apoptosis, despite the diversity of affected neuronal populations and etiologies (Fig. 2). Given the diversity of these diseases, we postulate that CBP loss of function and subsequent histone deacetylation are common traits of neurodegeneration.

5. HDAC inhibition as a therapeutic strategy

As protein acetylation levels result from a balance of HAT and HDAC activities, several laboratories have investigated the possibility of compensating for decreased acetylation levels observed during neurodegeneration by pharmacological inhibition of the HDAC function (Fig. 3). A variety of HDAC inhibitors have been tested, such as trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA) or sodium butyrate (NaBu). TSA and SAHA were shown to reduce neuronal loss in an in vitro model of SBMA [55]. In a transgenic Drosophila model of HD, NaBu and SAHA induced a significant decrease in neurodegeneration development, and a decrease in early adult lethality [54]. Moreover, SAHA, that was shown to cross the blood–brain barrier, increases histone acetylation in the brain and dramatically improve the motor impairment in a mouse model of HD [62]. Therefore, pharmacological modification of HDAC activity seems to be an interesting strategy. Nevertheless, HDAC inhibitors (TSA, NaBu) are also potent neuronal apoptosis inducers. Six years ago, Salminen et al. described hallmarks of apoptosis in primary rat CGN and in mouse neuroblastoma Neuro-2a cells treated with TSA and NaBu [27]. We also described that the HDAC inhibitors TSA or NaBu were able to efficiently induce histone hyperacetylation as well as cell death in a dose-dependent manner [28]. TSA-induced cell death resulted from the execution of an apoptotic program, characterized by nuclear condensation, DNA laddering and caspase-3 activation, that are classical hallmarks of programmed cell death [28]. Interestingly, we showed that TSA signaled cell death through activation of the pro-apoptotic E2F-1 transcription factor [28]. It is thus conceivable that administration of broad-spectrum HDAC inhibitors could induce activation of genes that should otherwise stay silent, such as E2F-1 and its target genes, therefore displaying toxic effects. Caution should thus be taken when envisaging HDAC inhibition as a potential therapeutic strategy. Moreover, at the cellular level, such drugs are not efficient neuroprotector: when tested in a neuronal model of primary culture, neither TSA nor NaBu at each dose tested were able to counteract induced apoptosis (Fig. 4). In fact, they rather increased neuronal death at doses that efficiently reversed LK-induced histone deacetylation (Fig. 4). Consequently, these results invalidate

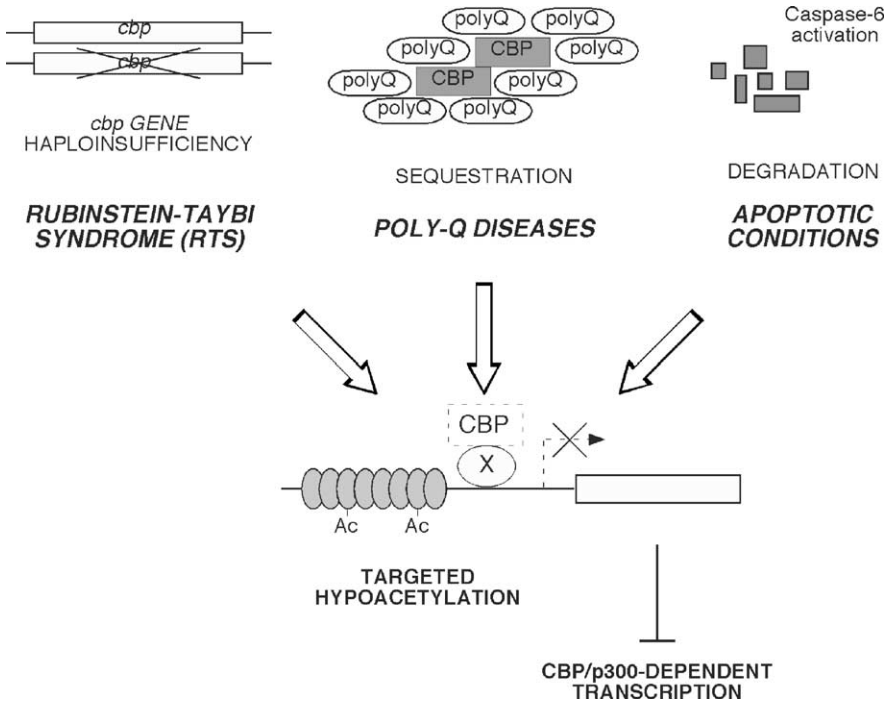

Fig. 2. Mechanisms leading to CBP loss of function. CBP loss of function has been observed in different contexts of neurological disorders. First, RTS outcomes from a mutation on an allele of the *cbp* gene that results in decreased amounts of functional CBP protein. Second, in several cases of polyQ diseases, decrease in the amount of available CBP can be achieved by sequestration of the protein by mutated polyQ proteins, forming aggregates in the cytoplasm or the nucleus. Third, CBP loss of function can result from a degradation of the CBP protein performed by caspase-6 activated during apoptosis.

the use of TSA or NaBu as therapeutic agents, despite the protection they displayed when administrated in animal models of neuropathologies [54]. It remains uncertain how potent these compounds are on a long-term basis.

It is noteworthy that all the compounds tested so far are general HDAC inhibitors. It is thus unlikely that they specifically reverse the histone acetylation pattern due to CBP loss. We postulate that a better therapeutic strategy

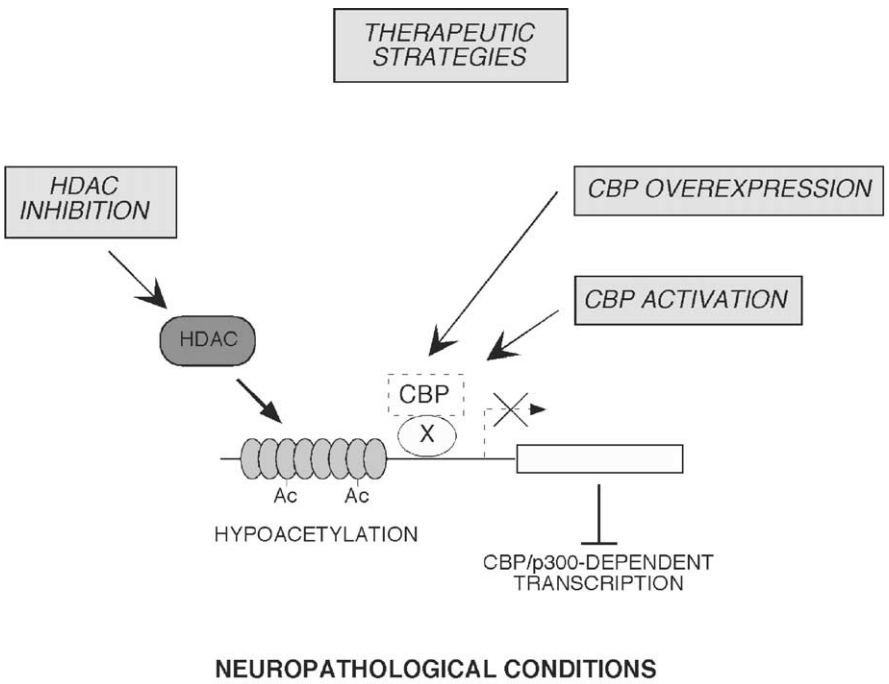

Fig. 3. Therapeutic strategies to counteract CBP loss of function. CBP loss of function leads to a decrease in histone acetylation levels as well as a decrease in CBP-dependent transcription. Two main approaches can be tested to reverse CBP loss of function consequences: either HDAC inhibition or CBP/HAT activation. Whereas both strategies would increase histone acetylation levels, HDAC inhibition would act on a broad range of genes, while CBP activation (over-expression or by a pharmacological approach) would specifically target both CBP-dependent histone acetylation and transcription.

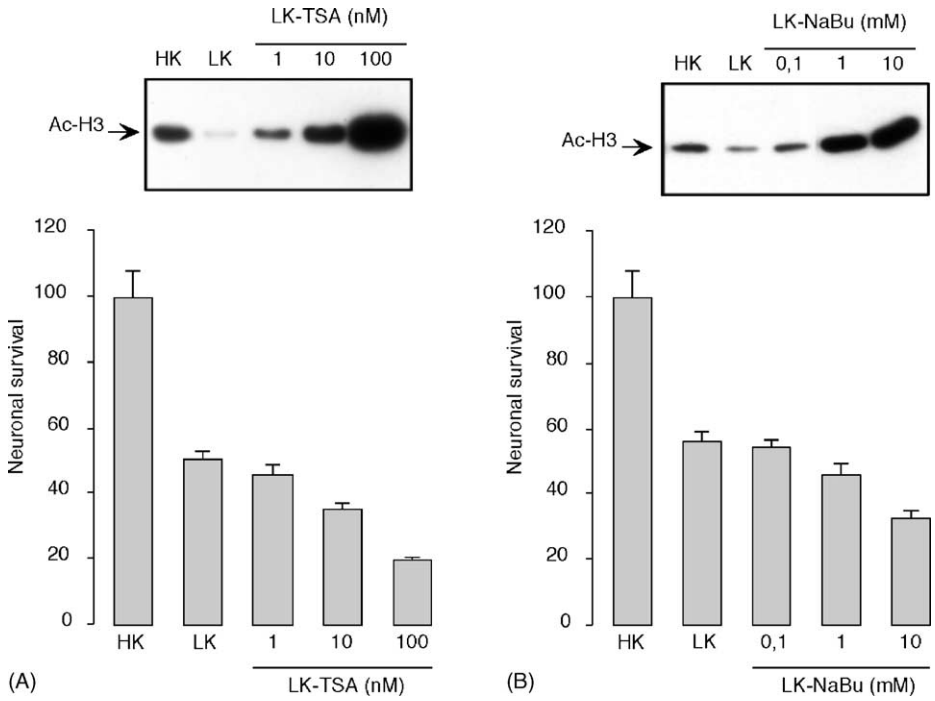

Fig. 4. HDAC inhibitors induce neurotoxicity at the cellular level. CGN were maintained in neuroprotective conditions (HK) or K^+-deprived (LK) to induce apoptosis, and treated with or without increasing doses of HDAC inhibitors as noted, trichostatin A (TSA) and sodium butyrate (NaBu) for 48 h. Following the treatment, acetylated histone H3 levels were monitored by Western blot, and survival measurements were performed using the colorimetric mitochondrial activity assay [63]. Results shown are representative of six independent experiments performed in duplicate. For materials and technical procedures, see Ref. [26].

would be to target CBP-linked histone deacetylations only. Moreover, it is possible that the CBP co-activator function is also required as well as its HAT activity in neuroprotection signalings. A specific CBP loss would not only mean that CBP-dependent acetylations are lost, but also its ability to exert the bridging function to transcription factors or to the basal transcriptional machinery. For example, the transcription factor CREB, a primary target of CBP, has been shown to participate in neuroprotection in many apoptotic contexts [35,63] as well as in HD [64–66] or RTS [41]. Thus, a simple acetylation status reversion with the use of HDAC inhibitor would not be sufficient to reverse CBP-dependent transcription default (see Fig. 3).

6. CBP over-expression

One means of counteracting CBP loss of function, preserving both HAT and co-activator functions, would be to over-express the protein (Fig. 3). This approach has already been investigated in a polyQ disease model such as transgenic Drosophila over-expressing htt, in which CBP up-regulation could not only restore the histone acetylation levels and the transcriptional regulation, but could also reduce both polyQ-induced aggregation and neurodegeneration [56]. In an SBMA model, CBP over-expression was able to block neuronal death [47,55], while it reversed toxicity in two cellular models of HD [53], demonstrating a role for CBP disruption in the disease process.

Our recent work has also shown that in K^+-deprived CGN, CBP over-expression could significantly reverse neuronal apoptosis [26]. We further demonstrated that the protective effects of CBP over-expression were dependent on its HAT activity [26], which indicates that neuroprotection likely relies on CBP-targeted acetylation rather than on broad acetylations. However, it is noteworthy that CBP over-expression is toxic in survival conditions, when tested in the same experimental conditions in which it displayed a beneficial effect on neurons undergoing apoptosis and this toxic effect is dependent on CBP's HAT activity [26]. This points to the fact that CBP-induced hyperacetylation can alter cellular viability as does broad acetylation achieved by HDAC inhibition (Fig. 5). Marambaud et al. also described the toxic effect of forced CBP up-regulation by lack of degradation, in pathological conditions related to AD [67]. Although the consequences of this pathological CBP up-regulation on acetylation levels have not been investigated, it is likely that this phenomenon is also accompanied with histone hyperacetylation, as it was shown for CBP over-expression [56,57].

Altogether, these results demonstrate the important role that fine-tuning of histone acetylation levels plays in neuronal homeostasis (Fig. 5), and more precisely, they pinpoint CBP-driven acetylation levels as crucial players to ensuring neuroprotection. Taking into account that a specific CBP loss of function is found in several neurodegenerative diseases, a therapeutic approach based on HDAC inhibition might not be the most suitable approach. Indeed,

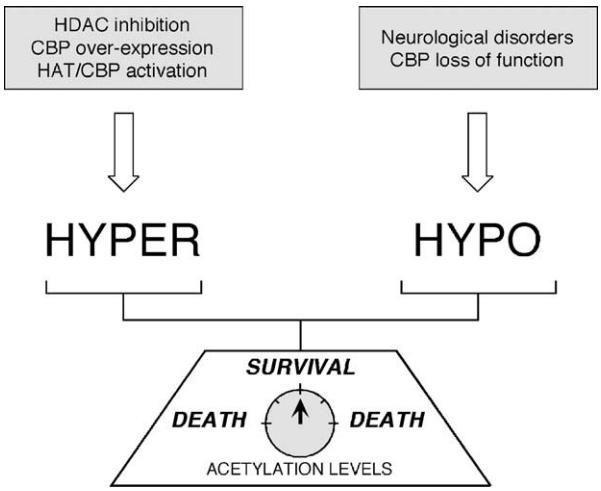

Fig. 5. Neuroprotection relies on a fine-tuning of HAT/HDAC activities. Neuronal death can be triggered by two means depending on the balance between HAT and HDAC activities. On one hand, acetylation levels can be harmed because of CBP loss of function, as in different neuropathologies. On the other hand, at a certain threshold, hyperacetylation ultimately leads to neuronal death. Thus, adopting a therapeutic approach aimed at restoring proper acetylation levels, either by inducing HDAC inhibition, CBP over-expression or HAT/CBP activation, could have dramatic effects on neurons, because of increased transcription of unwanted genes and/or chromatin status alterations. These cellular activities must remain finely tuned for neuronal survival.

HDAC inhibition will not only reverse CBP-dependent loss of acetylation, but will ultimately contribute to an overall increase in acetylation levels at non-specific promoters. In that respect, a finer strategy could be based on the elaboration of more selective HDAC inhibitors specifically targeting CBP-dependent acetylations. However, we suggest that a therapeutic approach that would focus on maintaining proper CBP levels with respect to the physiological HAT/HDAC equilibrium should be improved in the future. In particular, the design of new CBP activators [68] could reveal as potent neuroprotective drugs. Defining the mechanism of CBP loss of function associated with each disease becomes also important in order to help for the development of drugs that increase CBP stabilization. Finally, it is likely that characterization of the CBP targets implicated in neuroprotection, such as what has already been described for CREB [34,35], will also be of particular interest.

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