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REVIEW

Acetyltransferases (HATs) as Targets for Neurological Therapeutics

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Abstract The acetylation of histone and non-histone proteins controls a great deal of cellular functions, thereby affecting the entire organism, including the brain. Acetylation modifications are mediated through histone acetyltransferases (HAT) and deacetylases (HDAC), and the balance of these enzymes regulates neuronal homeostasis, maintaining the pre-existing acetyl marks responsible for the global chromatin structure, as well as regulating specific dynamic acetyl marks that respond to changes and facilitate neurons to encode and strengthen long-term events in the brain circuitry (e.g., memory formation). Unfortunately, the dysfunction of these finely-tuned regulations might lead to pathological conditions, and the deregulation of the HAT/HDAC balance has been implicated in neurological disorders. During the last decade, research has focused on HDAC inhibitors that induce a histone hyperacetylated state to compensate acetylation deficits. The use of these inhibitors as a therapeutic option was efficient in several animal models of neurological disorders. The elaboration of new cell-permeant HAT activators opens a new era of research on acetylation regulation. Although pathological animal models have not been tested yet, HAT activator molecules have already proven to be beneficial in ameliorating brain functions associated with learning and memory, and adult neurogenesis in wild-type animals. Thus, HAT activator molecules contribute to an exciting area of research.

Keywords HAT activator molecule · Lysine acetylation · CREB-binding protein · Learning and memory · Adult neurogenesis · Neurodegenerative diseases

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Introduction

DNA is packed in the nucleus of mammalian cells in association with histones, non-histone proteins, and RNA in a highly organized structure known as chromatin. A nucleosome is a single unit of chromatin comprising 146 base pairs of DNA wrapped around histone octamers. The histone N-terminal tails are subjected to various post-translational modifications, including acetylation, methylation, phosphorylation, ubiquitination, and sumoylation [1, 2]. Histone acetyltransferase (HAT) catalyzes the acetylation of core histones through the addition of an acetyl group from the pseudo-substrate acetyl coenzyme A (acetyl-CoA) to the lysine residue on the ε-amino group on the N-terminal of histones. Apart from histone, HATs also have many non-histone protein substrates, suggesting a new nomenclature, KAT for lysine (K) acetyl transferase, replacing the term HAT [3]. However, in the following sections, we will use HAT to avoid possible confusion. Another class of enzymes, histone deacetylases (HDACs), catalyzes deacetylation through the hydrolysis of an acetyl moiety from the lysine residue.

Although the functional implications of each of these modifications have not been fully elucidated, studies have shown that it is difficult to identify the dynamic acetyl mark(s) that specifically respond to a pathway from the overall pre-existing marks that maintain the global chromatin structure. In terms of function, lysine acetylation initiates molecular processes leading to two biochemical consequences: 1) the recruitment of

coactivator complexes through conserved domains, such as bromodomains; and 2) the participation of co-repressor complexes through HDACs. Together, these changes will affect chromatin structure, leading to further functional consequences. Indeed, strict regulation of the dynamic balance between acetylation and deacetylation is critical for various cellular physiological phenomena, such as proliferation, differentiation, cell growth and gene expression. Most recently, the acetylation balance has been implicated in intracellular pH regulation [4].

Alterations in the acetylation balance have been shown in neurologic disorders and neurodegenerative diseases [5–7]. Despite decoding chromatin language in pathological conditions or cognitively deficient states, HDAC inhibitors (HDACi) might represent a good therapeutic option, as these compounds induce a histone hyperacetylated state that might compensate for acetylation deficits. HDACi-based therapeutic strategies were first applied to models of polyglutamine (polyQ) diseases, such as Huntington's [8, 9] and Kennedy's [10], and then subsequently revealed to be successful to some extent in several other animal models of neurodegenerative disease [5, 6, 11, 12]. Importantly, this strategy has also been successfully applied in animals subjected to experimental brain damage [13, 14] and recently shown to improve memory functions in aged mice [15]. HDACi are the only molecules used for increasing cellular acetylation, and two of these molecules have been approved for clinical use in cutaneous T cell lymphoma [16]. However, caveats remain as to the specificity and the molecular and cellular mechanisms underlying the activity of these inhibitors in neurons, whereby long-term application might be detrimental.

In this review, we will briefly describe different HAT families and the regulation, function, and important role of these molecules in the cell fate specification of neural stem cells. As enzymes, HATs are druggable, and few HAT activator molecules have been developed. We will also discuss the mechanisms for HAT regulation and impairment in neurodegenerative diseases and neuronal plasticity to understand the benefits of therapeutic strategies based on reactivating acetylation using HAT activators versus HDAC inhibitors. Moreover, we will describe two interesting studies concerning HAT activator molecules.

Although lysine acetylation is best characterized in the context of nuclear histones, combinatorial approaches and proteomic analyses have revealed almost 2,000 acetylated proteins in the cell that are involved in a broad range of cellular functions [17, 18]. Thus, the potential effect of HAT activation or impairment on nonhistone targets will also be reviewed.

HATs

Families of HATs

HATs catalyze the acetylation of lysine residues, which has been accepted as an important epigenetic marker. Acetylation occurs on both histone and nonhistone proteins, with an estimated 2,000–4,000 acetylated proteins and 15,000 acetylation sites in animal tissues [19]. The majority of the functional attributes of acetylation have been revealed as a result of several decades of research on histone acetylation, with recent evidence of nonhistone protein acetylation. In the context of chromatin, histones undergo acetylation to yield a more relaxed chromatin conformation resulting from hydrophobicity, a net change in the overall charge, and reduced electrostatic interactions. Acetylated histones recruit bromodomain-containing proteins, which are primarily transcription factors and cofactors, further enhancing gene expression [20]. HATs are highly conserved from yeasts to humans. Figure 1 summarizes the different HAT and HDAC families. These enzymes are broadly classified into cytoplasmic type A and nuclear type B HATs. Nuclear HATs are subclassified into 5 major families: 1) Gcn5-related N-acetyltransferases (GNAT), 2) p300/cyclic adenosine monophosphate response element-binding protein (CREB) binding protein (CBP), 3) MOZ, yeast YBF2, SAS2, and TIP60 (MYST), 4) transcription factor-related HATs, and 5) nuclear receptor-associated HATs. GCN5, a member of the GNAT family was the first identified acetyltransferase. The major members of the GNAT family are general control of amino acid synthesis 5 (Gcn5); elongation protein 3 (ELP3); p300/CBP-associated factor (PCAF); chromodomain on chromosome Y protein; establishment of cohesion 1; establishment of cohesion 1 homolog 1; establishment of cohesion 1 homolog 2 (a paralog of establishment of cohesion 1 homolog 1); ADA-two-A containing 2; and mechanosensory abnormal 17 [21]. GNATs comprise a conserved acetyltransferase domain, a bromodomain that recognizes acetylated lysine residues, and a transcription coactivator ADA2-binding domain. The 2 paralogs of p300/CBP family are transcriptional coactivators p300 and CBP. The 5 principal protein interaction domains of p300 and CBP are the nuclear receptor interaction domain; the CREB and myeloblastosis (MYB)-interaction domain; the kinase inducible binding domain (KIX), which binds to the Ser-133-phosphorylated kinase inducible domain region of CREB; the cysteine/histidine regions (CH1 and CH3); and the interferon response-binding domain, which is also the steroid receptor coactivator 1 interacting domain of CBP [22]. p300/CBP also possesses an acetyltransferase domain, bromodomain, and a plant homeodomain-type zinc finger motif. The members of the MYST family of acetyltransferases, including TAT interacting proteins 60 (Tip60), monocytic leukaemia zinc-finger protein (MOZ), males absent on the first (MOF), monocytic leukaemia zinc-finger protein related factor (MORF) and human acetylase binding to ORC1 (HBO1), have a 240 amino acid-long MYST region with a canonical acetyl-CoA-binding site and a C2HC-type zinc finger motif. Most of the MYST family acetyltransferases are characterized by the presence of a chromodomain,

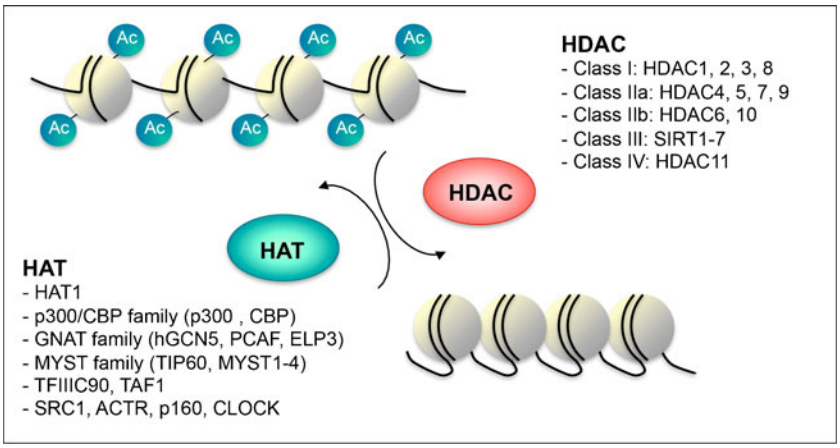

Fig. 1 Histone acetyletransferase (HAT) and histone deacetylase (HDAC) families. Illustration of chromatin conformation according to the HAT/HDAC balance. The acetylation levels of nucleosome histone tails, at lysine residues, are determined through the interplay between acetylation and deacetylation mechanisms engaged respectively through HATs and HDACs enzymes. The different families and classes of enzymes are noted. Ac = Acetyl; CBP = cyclic adenomonophosphate response element-binding (CREB) binding protein; GNAT = Gcn5-related N-acetyltransferases; hGCN5 = human general control of amino acid synthesis protein 5-like 2; PCAF = p300/CBP-associated factor; ELP3 = elongation protein 3; MYST = MOZ/YBF2/SAS2/TIP60; TIP60 = TAT interacting proteins 60; TFIIIC90 = transcription factor IIIC 90kDa; TAF1 = TATA Box Binding Protein-Associated Factor, SRC1 = steroid receptor coactivator 1; ACTR = SRC-3, steroid receptor coactivator/AIB-1, Activated In Breast cancer-1/TRAM-1, thyroid hormone receptor activator molecule 1/ NCOA3, nuclear receptor coactivator 3

involved in protein–protein interactions. Structural alignments suggest these chromodomains to be slightly different than the canonical polycomb associated chromodomains [23].

HAT activities have been identified in several proteins associated with transcription activation through hormonal signals. This family of HATs is classified as nuclear receptor coactivators, which include steroid receptor coactivator-1, SRC-3, steroid receptor coactivator/AIB-1, Activated In Breast cancer-1/ TRAM-1, thyroid hormone receptor activator molecule 1/ NCOA3, nuclear receptor coactivator 3 (ACTR), and transcriptional intermediary factor 2 (reviewed in [24]). These enzymes are evolutionarily related to HATs, which interact with p300. The transcription factor-related HATs include TATA box binding protein (TBP)-associated factor TAFII250 and TFIIIC. TAFII250 is a subunit of the general transcription factor transcription initiation factor II D (TFIID). The general function of TFIIIC involves the initiation of the transcription promoter complex through DNA binding and the recruitment of TBP-containing TFIIIB and RNA polymerase III [25]. At least three subunits of TFIIIC (TFIIIC110 and TFIIIC90) harbor HAT activity *in vitro* [26]. However, this classification should be reconsidered, as several nuclear HATs exhibit nuclear cytoplasmic shuttling, and cytoplasmic lysine acetylation has been associated with important physiological outcomes [27].

HAT Function and Regulations

Acetylation plays a central role in numerous biological processes, including gene expression [28, 29], chromatin dynamics, cell-cycle progression [30–33], DNA repair [34], and apoptosis. HATs are regulated through various mechanisms, including auto-acetylation, signaling pathways-induced modifications, and cellular metabolites.

Auto-acetylation

Auto-acetylation involves the regulation of enzyme activity through the acetylation lysine residues, typically resulting in increased catalytic activity. The first reported acetyltransferase to undergo auto-acetylation is Tip60. Lysine 327 in the active site of the MYST domain is conserved amongst all the MYST proteins and acts as a key regulatory marker for enzyme activity upon acetylation. The intra- or intermolecular auto-acetylation of p300/CBP-associated factor (PCAF) specifically targets 5 lysine residues in the nuclear localization signal. Auto-acetylated PCAF localizes to the nucleus and activates gene transcription. Deacetylated PCAF is located primarily in the cytoplasm of apoptotic cells, suggesting a role for PCAF auto-acetylation in the regulation of cellular processes [35]. Similarly, p300 and CBP activity is also regulated through auto-acetylation [36]. The auto-acetylation of p300 induces a structural conformational change, leading to the exposure of substrate-binding regions. p300 auto-acetylation results in the acetylation of approximately 12 lysine residues in the unique activation loop of p300. Thus, the acetylation status of this enzyme facilitates the compartmentalization and induction enzymatic activity [36]. To maintain acetylation homeostasis, the nicotinamide adenine dinucleotide (+)-dependent HDAC sirtuin 2 (SIRT2) regulates p300 auto-acetylation [37]. HDAC3 deacetylates PCAF [38] and SIRT1 deacetylates Tip60 [39].

HAT Function of CBP

The HAT function of CBP can be regulated by different signaling pathways affecting its phosphorylation status by nuclear calcium or cyclic adenosine monophosphate pathways [40, 41], or its arginine methylation level by the coactivator-associated arginine methyltransferase I [42, 43]. Such modifications affect the enzymatic activity.

Cellular Metabolites

Cellular metabolites, such as nicotinamide adenine dinucleotide (+) and acetate, also act as regulators of acetylation. These compounds modulate HDACs; however, the direct roles of cellular metabolites on HATs have not been thoroughly investigated [4, 44].

HATs During Neural Development

Among the HATs, CBP/p300 are crucial enzymes in development; mutations and deletions of either enzyme causes Rubinstein–Taybi syndrome, characterized by mental disability, among other features [45]. Several studies have described a role for CBP/p300 in neural development. In mice, the monoallelic abrogation or loss of the enzymatic activity of either enzyme results in embryonic lethality observed as early as E9.0 to E11.5 in a dominant fashion, consistent with the early stages of neural development, with impaired hematopoiesis, angiogenesis, heart, lung, and intestine organogenesis [46–49]. Interestingly, an analysis of the distribution of the p300 messenger RNA (mRNA) during mouse development showed the elevated expression in the neural tissue, suggesting the involvement of this enzyme in neural development. Consistently, knocking out CBP or p300 leads to an open neural tube, potentially reflecting defects in twist (without changes in twist expression) or other transcription factors, such as paired box 3 (PAX3) and activating enhancer binding protein 2 (AP2), thereby affecting neural development [49, 50]. Neural tube closure typically begins at E8.5 and spreads along neural folds; however, in CBP-null embryos, different types of neural tube closure defects are observed. Hemorrhaging in the telencephalon and mesencephalon, reflecting defective vasculature, has also been observed and hypothesized as the primary cause of embryonic death [50].

At the molecular level, HATs have been implicated in the cell fate specification of neuronal stem cells (NSC) (Fig. 2). p300 bridges signal transducers and activators of transcription 3 and mothers against decapentaplegic homolog 1 (Smad1), leading to synergistic astrocyte differentiation from neural progenitors [51]. CBP/p300 complexes with the transcription factor neurogenin 2 and the retinoic acid receptor to induce histone acetylation and transcriptionally active chromatin during motor neuron specification [52]. The closely related basic helix-loop-helix (bHLH) factor neurogenin 1 (Ngn1) represses gliogenesis through the sequestration of the CBP–Smad1 complex away from astrocyte differentiation genes, such as glial fibrillary acidic protein (GFAP), during neurogenesis [53]. CBP/p300 and Smad1, separately or together, subsequently associate with neurogenin at neural-specific promoters, such as NeuroD, thereby promoting neuronal differentiation [53]. The post-translational modifications of CBP and p300 also regulate the functions of these enzymes, and the phosphorylation of CBP through the atypical protein kinase C (aPKCζ) plays a critical role in controlling glial and neuronal differentiation [54].

Among the other families of HATs, the role of Gcn5 in neural development has also been documented, as the acetyltransferase activity and sufficient expression of this enzyme are required for neural tube closure in mice [55, 56]. Surprisingly, while p300 HAT mutants exhibit defects in multiple organ systems, the effects of mutating Gcn5 are restricted to the neural tissue, implicating the specificity of Gcn5 acetyltransferase activity, with potential redundancy with PCAF in other tissues [55]. Gcn5 also plays HAT-independent roles during development, and the complete loss of this protein leads to early embryonic lethality after gastrulation [57, 58]. Gcn5, as a member of the Spt-Ada-Gcn5-acetyltransferase (SAGA) complex, accelerates neural dysfunction characteristic of polyQ-Atxn7, which causes spinocerebellar ataxia type 7 [59]. At the transcriptional level, knocking out Gcn5 in NSCs leads to changes in gene expression in a pattern similar to the Myc knockout (KO). This functional overlap indicates that Gcn5/Myc coregulate transcriptional programs in NSCs, a process required for stem cell proliferation and normal brain growth [60]. Interestingly, the KO of both CBP/p300 and Gcn5 leads to neural tube closure defects, reminiscent of knocking out other transcriptional regulators, such as p53, suggesting the complex, but overlapping, functions of various factors in neural tube closure.

While the effects of knocking out other proteins of the Tip60/NuA4 complex have been studied previously, the function of the MYST family of HATs in neural development remains unknown. However, the role of the interaction between Tip60 and ATXN1 in spinocerebellar ataxia type 1 pathogenesis, involving cerebellar degeneration, implicates a role for these HATs in neural development [61].

Though the roles of different HATs in neural development have been well-studied or at least indicated, further extensive studies will be required to provide a more detailed picture of the role of histone acetylation in the regulation of transcriptional programs during neural development.

Because acetylation plays a significant role during neural development, it would be intuitively obvious that deacetylation through HDACs also plays a role in modulating cell differentiation during neural development. Particularly, HDAC1 and HDAC2 play a role in oligodendrocyte differentiation through crosstalk with the canonical Wnt signaling pathway, mediated

through transcription factor 7-like 2 (TCF7L2) [62] (Fig. 2). The inhibition of HDAC1 and HDAC2 causes the developmental plasticity of precursors, leading to differentiation into other cell types [63, 64].

Druggability of HAT Domains

An imbalance in acetylation homeostasis leads to a plethora of disease conditions; hence, the modulation of the activity of HATs could be an efficient method for therapeutics. Several domains of HAT, which play essential roles in the cell, can be targeted using small molecule modulators. These targets include 1) HAT domains, 2) auto-acetylation residues/regions, and 3) bromodomains, which recognize acetylation marks. These can be targeted and modulated using a small molecule or peptide approach. Several groups worldwide are designing synthetic or natural chemical probes that target epigenetic modifications. Small-molecule chemical probes have recently contributed to advances in the search for epigenetic drugs. The first reported HAT inhibitor, Lys-CoA, specifically inhibited p300 HAT activity [65]. Extracts from plants with medicinal value have served as therapeutics in the medieval world and present an excellent platform to develop new-generation therapeutics. The first reported HAT inhibitor from natural sources was obtained from *Garcinia indica*. Garcinol from *G. indica* nonspecifically inhibits p300 and PCAF HAT activity, but, recently, this inhibitor has shown great promise as a potent anticancer drug [66]. Owing to the specific focus of this article, we shall confine the review to HAT activators and their therapeutic potential.

Known HAT Activator Molecules (Structure and Their Possible Mechanism of Action)

The use of small molecules to modulate enzyme function is an emerging concept, and various molecules (synthetic and natural) have been identified with strong therapeutic potential against numerous diseases, including cancer, AIDS, diabetes, depression, and neurodegenerative conditions [7, 67, 68]. HAT activators are a class of small-molecule modulators that activate enzyme activity. The first reported and the most characterized HAT activator is N-(4-chloro-3-trifluoromethyl-phenyl)-2-ethoxy-6-pentadecyl-benza-mide (CTPB), derivatized using anacardic acid as a synthon [69, 70]. Anacardic acid

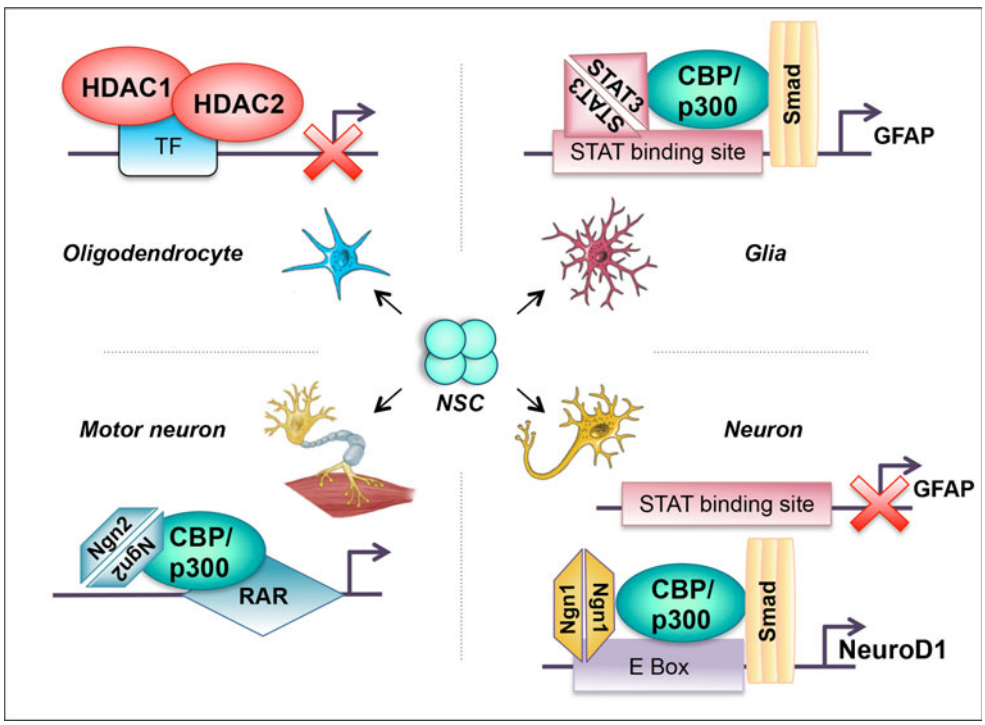

Fig. 2 Role of acetylation in different lineage determination. The neural stem cells (NSCs) exist in a niche, which can be differentially modulated to specific neuronal lineages. A differential recruitment of specific transcription factors (TF) to the same acetyltransferases determine specific neural cell fates from the NSCs. Cyclic adenomonophosphate response element-binding (CREB) binding protein (CBP)/p300 histone acetyletransferases (HATs) interact with STAT and SMAD activating glial fibrillary acidic protein (GFAP) expression, thus specifying the glial lineage. Increased expression of neurogenin (Ngn1) titrates this complex, thus leading to the release of STAT, blocking GFAP expression. The new Ngn1–CBP/p300–SMAD complex subsequently binds to the E box elements, which results in a neuron cell type due to the activation of NeuroD1 expression [53]. CBP/p300 when bound to retinoic acid receptor (RAR) and neurogenin 2 (Ngn2) leads to a differentiation of the motor neuron cells. The deacetylases histone deacetylases (HDACs) HDAC1 and HDAC2 act as a general repressor, blocking the transcription factor and thereby resulting in oligodendrocyte specification

can be isolated from cashew nut shell liquid, and this compound acts as an inhibitor of p300 and PCAF HAT activity. In contrast, CTPB can efficiently activate p300 HAT activity in a concentration-dependent manner, but does not alter PCAF HAT activity. *In vitro* CTPB induces the maximum activation of p300 HAT activity to ~4-fold at a 200–275 μM concentration. Interestingly, CTPB could also enhance p300 HAT-dependent transcription from a chromatin template *in vitro*. The mechanism of activation through CTPB and its derivative N-(4-chloro-3-trifluoromethyl-phenyl)-2-ethoxy-benzamide (CTB) was explored using surface-enhanced Raman spectroscopy, indicating a conformational change upon activator binding, which possibly recruits more acetyl-CoA and enhances auto-acetylation. Furthermore, the location of –CF3 and –Cl at the para position of the benzamide ring of CTPB and CTB is critical for HAT activation [71]. As CTPB and CTB are hydrophobic in nature, these compounds might form micelle-like structures in aqueous solution and directly bind to the hydrophobic pockets of p300. As most of the hydrophobic pockets of p300 are present in proximity to the HAT domain, the –CF3 and –Cl regions of these molecules could bind to the amide groups of the α-helix and β-sheets of p300 HAT domain and alter its conformation. In need of a more stable and potent activator of HATs, TTK21 was synthesized from salicylic acid. TTK21 enhances p300 and CBP acetylation *in vitro* and, upon conjugation with a carbon nanosphere (CSP), could enter the nucleus of the neural-derived cells, SHSY-5Y, and cross the blood–brain barrier (BBB), inducing histone H2B and H3 acetylation in specific regions of the mouse brain [72] (described in detail in the section 'Potential use of HAT Activator as Therapeutic Option').

Another small molecule with strong HAT activation ability towards p300/CBP is nemorosone, a derivative of benzophenone. Nemorosone is a polyisoprenylated benzophenone derivative that bears a C(1) acyl group and an adjacent C(8) quaternary center without any secondary cyclization. Thermodynamic studies using surface plasmon resonance indicated that nemorosone has high affinity towards p300 protein (0.25 μM), and this interaction is associated with a low kinetic dissociation constant (3.2×10^{-4} s^{-1}), suggesting a hardly dissociable complex with a stable tertiary structure. Furthermore, the major region of nemorosone, which interacts with p300, was identified as a hydroxylated enol involving C(2), C(3), and C(4) [73]. Efforts to isolate small-molecule activators using the basic backbone structure of anacardic acid are currently underway. In a recent study, pentadecylidenemalonate was prepared, which surprisingly showed mixed inhibitor/activator properties towards HATs, as this chemical inhibited p300/CBP HAT activity and activated PCAF HAT activity [74, 75]. Pentadecylidenemalonate/SPV106 could cross mammalian cell membranes and enhance histone H3 acetylation. Moreover, this chemical is also the only reported PCAF activator.

HAT Impairment in Neurodegenerative Disorders

Neurodegenerative diseases, such as Huntington's (HD), Parkinson's (PD), Alzheimer's (AD), or amyotrophic lateral sclerosis (ALS), are characterized by a progressive loss of neuronal structure and function that leads to neuronal death. In these diseases, impairments of HAT activity, histone, and nonhistone protein acetylation have been reported, associated with a decrease of cognitive functions and/or motor impairments. In this section, we will describe how HAT function is impaired in different pathologies (e.g., nuclear delocalization, enzymatic activity inhibition, etc.), how this dysregulation will contribute to the overall pathogenic process, and how maintaining adequate HAT/HDAC homeostasis in the cell is particularly important for neuronal survival [76–78], and how HATs might constitute targets for new therapeutic strategies. Table 1 summarizes the substrates of HATs and their potential links to neurological disorders.

HD

HD is a rare and fatal inheritable genetic disorder characterized by a loss of coordination (chorea), cognitive dysfunction, and psychiatric symptoms. At the cellular level, HD is characterized by intraneuronal inclusions, alterations in synaptic function and widespread neuronal death at the late stage of the disease, the striatum being the most affected region. Other brain regions, such as the cortex and the cerebellum, are also affected [79]. HD reflects an abnormally high number of unstable CAG repeats within the 5'-end of the coding region of the gene encoding the Huntingtin (Htt) protein. The number of repeats affects the severity and the onset of the disease, generally initiated at mid-life. The polyQ expansions alter the Htt protein functions and confer self-aggregation properties [80].

An initial study demonstrated that CBP is found in polyQ aggregates [81]. Indeed, CAG expansions bind and sequester transcriptional regulators, including CBP and PCAF in animal models [8, 9]. The resulting depletion of CBP from the nucleus induced a loss in its activity and a decrease in CBP-activated gene expression [9, 82, 83]. Interestingly, the soluble form of mutant Htt also promoted the degradation of CBP [84]. In addition, CBP sequestration into ubiquitin-positive nuclear inclusions and decreased CBP-mediated activation of gene expression [e.g., *brain-derived neurotrophic factor* (*Bdnf*)] were shown in a newly generated mouse model displaying HD-like-2, consistent with observations in HD patient brains [85]. In *Drosophila* models, reduced PCAF levels were associated with enhanced neurodegeneration. The CBP/p300 family also exhibited a strong influence over HD pathology, while the MYST family members had less of an effect [86].

HAT disruption in HD has several downstream consequences that might play a role in the pathophysiology of the disease. For instance, CBP alterations could directly affect

Table 1 Histone acetyltransferases (HATs), their substrates, and potential links to neurological diseases. Summary of the different HATs for which a potential relationship to pathological conditions or mechanisms has been documented. The associated modifications of histone and non-histone substrates induced through HAT impairments and potentially implicated in these diseases are also reported. The model (cellular, animal, or human) and the brain tissues in which modifications have been observed are indicated

HATs	Substrates		Models	Related pathologies or mechanisms
CBP	Histone	H3, H4	*In vitro*, cellular and *Drosophila* lines	HD [8]
		H3	HdhQ7/Q111 mice (hipp)	HD [88]
		H3, H4	Cellular and C57BL/6J mice (striatum, substantia nigra)	PD [111]
		H3	SOD1 G86R mice (spinal cord)	ALS [76, 126]
		H3	EID1 trangenic mice (hipp)	AD [157]
		H2A, H2B >> H3, H4	$Cbp^{+/-}$; cKO CBP mice (hipp)	LTM [199, 204]
		H2B >> H3, H4	Adenoviral CBP inhibition (hipp)	LTP and LTM [205]
	Non-Histone	p53	Cellular and R6/2 mice (striatum)	HD [9]
		UBF-1	Cellular	HD [92]
		Htt	Cellular, mice (cotex, striatum), *Caenorhabditis elegans* models, and human brain	HD [91]
		α-tubulin	Human brain	HD [94]
		p53	Cellular	Axon regeneration [137, 138]
		p53	EID1 transgenic mice (hipp)	AD [157]
		Tau	Cellular and human brain	AD [162]
P300	Histone	H3	EID1 transgenic mice (hipp)	AD [157]
	Non-histone	p65	Cellular, transgenic mice (substantia nigra)	PD [112]
		p53	EID1 transgenic mice (hipp)	AD [157]
		Tau	Cellular and human brain	AD [162]
ELP3	Non-histone	α-tubulin	Cellular	ALS [128]
		Bruchpilot (ELKS)	*Drosophila* lines	ALS [132]
PCAF	Histone	H3, H4	*In vitro*, cellular, and *Drosophila* lines	HD [8]
	/	/	*Drosophila* lines	HD [86]

CBP=cyclic adenomonophosphate response element-binding (CREB) binding protein; ELP3=elongation protein 3; PCAF=p300/CBP-associated factor; UBF-1=upstream binding factor-1; Htt=huntingtin; hipp=hippocampus; SOD1=superoxide dismutase 1, EID1=EP300-interacting inhibitor of differentiation 1; cKO=conditional knockout; HD=Huntington's disease; PD Parkinson's=disease; ALS=amyotrophic lateral sclerosis; AD=-Alzheimer's disease; LTM=long-term memory; LTP=long-term potentiation

striatal regulations, and thereby motor impairment, influencing the transcription dependent of its binding partner CREB, a key regulator of striatal vulnerability [87]. A decrease of histone H3ac, associated with decreased CBP/CREB-dependent gene expression, was observed in the hippocampus of the HdhQ7/Q111 transgenic mouse model, an event that might explain some cognitive deficits associated with HD [88]. A 30 % increase in *Hdac1* expression was also observed in the cortices and striata of HD R6/2 mice, but is unlikely to be a cause of a detectable decrease in global histone acetylation [89]. Alterations in the acetylation of CBP-target nonhistone proteins, such as p53 [9, 90, 91] or the upstream binding factor-1 [92] also play a role in the progression of the disease. The Htt protein is subjected to acetylation that targets mutant Htt to autophagosomes for degradation [91]. The turnover of mutant Htt is thus regulated through the balance between CBP and HDAC1, and the loss of CBP in HD might explain the accumulation of mutant Htt [91]. Moreover, the acetylation of tubulin (likely through cytoplasmic acetyltransferases) regulates anterograde and retrograde axonal transport through signaling the anchoring of molecular motors, such as Kinesin-1 to microtubules [93]. As a decrease of acetylated-tubulin has been observed in postmortem brain samples [94], one could predict that a disruption of intracellular trafficking could occur in HD patients, as observed in HD mice neuronal culture and leading to the alteration to the alteration of vesicular BDNF transport [95].

At the level of bulk chromatin, a genome-wide deacetylation of H3 histone (H3K9K14ac) was observed in the striatum of the R6/2 mouse model, but no association with a specific HAT was observed [96]. However, the authors observed that an H3ac association at specific gene loci strongly correlated with expressed genes in both wild-type and transgenic striata, suggesting that these changes in histone H3ac, although genome-wide, were not sufficient to trigger the transcriptional dysfunctions associated with HD [96].

Several studies of HD using *in vitro* and *in vivo* models have confirmed CBP involvement in HD physiopathology;

thus, the use of a molecule to activate HAT function would be of prime interest. The partial rescue of neuronal loss was described after CBP overexpression, whereas the genetic depletion of CBP worsened the phenotype of HD mice [83, 97, 98]. However, the overexpression of PCAF was not sufficient to ameliorate the HD phenotype in transgenic flies, suggesting that therapeutic strategies aimed at increasing PCAF protein levels are likely ineffective in ameliorating HD pathology; notably, increasing the HAT activity of PCAF has not been tested, and other trials targeting PCAF activity are needed [86]. Increasing the acetylation of histones and non-histone proteins via the use of HDAC inhibitors also counteracts neurodegeneration [8, 88, 99–101]. Intriguingly, McFarlan et al. [96] also demonstrated that HDAC inhibition re-established altered transcriptional levels in the striatum of the R6/2 mouse model, but only slightly improved H3ac binding to specific promoter, emphasizing the idea that the overall chromatin environment surrounding a gene would be more adapted to therapeutic targeting than simply increasing the acetylation of the histones.

PD

PD is a late-onset neurodegenerative disorder characterized by progressive motor dysfunctions (loss of muscle rigidity, tremor, and bradykinesia), the selective loss of nigrostriatal dopaminergic neurons and the presence of intraneuronal protein inclusions, called Lewy bodies (LBs), in the patient's brain. PD has been associated with both environmental and genetic factors, with most of the cases (90 %) being sporadic. However, gene mutations or variations in the number of transcript copies lead to the appearance of hereditary PD forms. These genes include *PARK2* (implicated in the targeting to proteasomal complex), *PINK1* (involved in mitochondrial response to stress), and *α-synuclein* (which forms, when misfolded, the large intracellular aggregates termed LBs) [102, 103].

Several leads for PD pathophysiology have recently emerged. First, according to the range of mutated genes described in this disorder, defective proteasomal machinery or mitochondrial dysfunctions could intervene in the pathological mechanism. More recently, the involvement of deficient epigenetic regulations has also been described, despite the fact that no particular HAT has been implicated in PD. Indeed, in *Drosophila*, toxic nuclear aggregates of α-synuclein interact with histone H3 and promote its deacetylation, possibly through a histone-"masking" mechanism [104]. Consistent with this result, several studies targeting HDAC members through sodium butyrate or valproic acid have shown an increase in histone acetylation, associated with prosurvival and anti-inflammatory effects, and decreased neurotoxicity markers [105–110].

Surprisingly, other studies have associated increased HAT activity with PD. The exposure to Dieldrin, a neurotoxic pesticide associated with PD etiopathogenesis, was shown to induce histone H3 and H4 hyperacetylation via the time-dependent CBP accumulation in dopaminergic neurons [111]. Alternatively, wild-type α-synuclein reduces p300 expression level and HAT activity. As a consequence, the reduced acetylation of the p65 subunit of NFκB was observed, eventually leading to a decrease in the transactivation of the pro-apoptotic gene *PKCδ*. Native α-synuclein exhibits a neuroprotective effect through the inhibition of p300 HAT activity [112]; however, the interaction between mutant α-synuclein and p300 remains elusive.

ALS

ALS is a fatal adult-onset neuromuscular disorder, affecting upper and lower motor neurons, and leading to progressive muscle wasting, paralysis, and, eventually, death [113]. Motor neuron degeneration is associated primarily with the pathological aggregation of ubiquitin, fused in sarcoma protein, and the transactive response DNA binding protein (TAR) DNA-binding protein of 43-kDa in the cytoplasm of motor neuron cell bodies [114, 115]. In addition, ALS has also been associated with an important impairment of energy metabolism [116]. Although most ALS cases occur sporadically, 10 % of all ALS cases are inherited, among which 10–20 % are caused by mutations in the gene encoding superoxide dismutase-1 (SOD1). These mutations confer an adverse pro-apoptotic activity to SOD1, which is associated with oxidative damage and mitochondrial function disturbance, leading to increased neuronal vulnerability. Most of the SOD1 mutant proteins are prone to aggregation, and cytoplasmic inclusions have been detected in human patients and model systems [113, 117]. Even if the premature death of motor neurons is determinant in the onset of this disorder, the molecular mechanism of neuronal degeneration are multi-factorial, and the cause of ALS pathogenicity remains a matter of debate [118, 119].

The study of a symptomatic ALS mice model (SOD1 G86R) identified the loss of CBP and decreased histone H3ac in the lumbar spinal cord cholinergic motor neurons [76]. A gene expression profile analysis performed on laser microdissected degenerating motor neurons from sporadic ALS patients revealed the down-regulation of the *cbp* gene [120]. A comparison of HDAC expression revealed a reduction of HDAC 11 mRNA and increased HDAC 2 levels in postmortem ALS brain and spinal cord specimens [121]. Mouse models bearing a *SOD1* mutation have been used to test therapeutic strategies with HDACi. Some studies have described an amelioration of motor performance and/or an increased survival of motor neurons in the G93A transgenic ALS mouse model, with phenylbutyrate [122] or valproate [123]. Sodium phenylbutyrate combined with an antioxidant [124] or riluzole [125] showed a beneficial effect. However, in the G86R mouse model, valproate restored histone acetylation in the spinal cord and CBP levels in motor neurons, but failed

to improve mice survival, as a major detrimental effect on the neuromuscular junction was observed [126].

Altered microtubule-dependent trafficking associated with the damaged transport of mitochondria was identified in ALS [127]. Microtubule trafficking is affected by the acetylation of α-tubulin through the HAT ELP3 [128], and allelic variants of ELP3 were associated with sporadic cases of ALS [129]. Recent evidence obtained from the SOD1 G93A mouse model showed that the deletion of HDAC6, a HDAC that deacetylates α-tubulin, did not affect disease onset, but significantly extended mice survival. This protective effect was associated with an increased level of α-tubulin acetylation that maintains motor axon integrity [130]. Recently, a controversial study showed that HDAC6 knockdown increased the formation of large aggresome-like inclusions of mutant SOD1. This phenotype was associated with an increase of α-tubulin acetylation and retrograde transport of mutated proteins. Mutant SOD1 oligomers and small aggregates sequester and inactivate HDAC6, favoring tubulin acetylation and leading to the formation of large pathologic inclusions [131]. Thus, if ELP3 represents a strong candidate to design new activator-based therapies, then much effort must be made to understand the precise outcomes of tubulin acetylation. Moreover, ELP3 has been recently described to acetylate Bruchpilot, a large cytoskeletal-like protein detected in the presynaptic active zones in *Drosophila*, thereby regulating synaptic vesicle capture and neurotransmitter release efficiency. ELP3 loss-of-function or decreased expression, as in ALS, could thus result in the alteration of active zones function and morphology [132].

The site-specific acetylation of p53 leads to selective response to various signals [133]. The abnormal regulation of p53 has been observed in ALS patients [134], and cellular and animal ALS models [135, 136]. Interestingly, p53 acetylation at K320 through p300/CBP and PCAF serves as a prosurvival signal, and promotes neurite outgrowth and neuronal maturation [137]. Activating HAT activity in ALS motor neurons might mediate p53 K320 acetylation and facilitate targeting toward pro-survival rather than pro-apoptotic functions. However, an increase of p53 acetylation on K382, a known substrate for p300/CBP and HDAC SIRT1, induced apoptotic functions [138]. Thus, the CBP loss [76, 126] and SIRT1 overexpression [139] observed in motor neurons might induce a neuroprotective effect.

Overall, it is difficult to predict the expected effect of acetylation modulators in complex neurodegenerative diseases that affect several non-neuronal cell types [119, 140]. In particular, the effect of HAT activation in the neuromuscular junction, which is tightly regulated through chromatin acetylation [141, 142], has not been documented; however, studies have shown the deleterious effect of valproate [126].

AD and Related Diseases

AD is an age-related neurodegenerative disorder characterized by a progressive loss of memory and a deterioration of cognitive functions [143]. From the histopathologic point of view, neurofibrillary tangles (aggregates of cytoskeletal hyperphosphorylated tau protein), extracellular amyloid plaques [formed by the pathologic proteolytic processing of amyloid β precursor protein (APP)], and massive neuronal death are observed in several brain regions (cortex, hippocampus, and amygdala) [144, 145]. One distinctive hallmark of AD is the progressive and irreversible loss of cholinergic neurons in the basal forebrain [146]. Most AD cases are late in onset and are likely influenced by both genetic and environmental factors. Familial (FAD) forms represent 0.1 % of AD cases and have an autosomal dominant transmission mode associated with mutations in three genes: the *APP* gene, and the *presinilins 1* and *2*. In addition, one genetic risk factor, the ε4 allele of apolipoprotein, has been firmly implicated in AD, but the identification of many new risk genes for late-onset disease are still being discovered [147].

Recent literature shows that epigenetic regulations could stand as a valuable therapeutic strategy for AD [148]. Particularly, several studies report acetylation dysregulations associated with pathological markers of this disease. We have previously shown that the activation of the APP-dependent signaling targeted CBP to a caspase-6 degradation in primary cortical neuron cultures [76]. Notably, caspase-6 activity was highlighted in neurofibrillary tangles of AD brain patients [149–151]. Thus, the caspase 6-dependent degradation of CBP in AD, leading to an acetyltransferase loss in diseased neurons, has been hypothesized, suggesting HAT activation as an interesting strategy in AD. In addition, the genes encoding presenilins PS1 and PS2 have also been associated with CBP dysfunctions in specific cortical regions; the deletion of these two genes leads to a reduction of CBP protein and mRNA levels in both the cytoplasm and nucleus of cortical cells, whereas the total and phosphorylated forms of CREB remain unchanged. As a consequence, the genes regulated through the CREB/CBP complex are partially repressed [152]. This study suggests a positive regulation of CBP expression through presenilins. Interestingly, these conditional $PS1^{-/-}$/$PS2^{-/-}$ mutants presented a decreased long-term potentiation (LTP), associated with long-term memory (LTM) deficits and hyperphosphorylated tau [152]. Thus, the effect of PS absence clearly alters the CBP-dependent pathway, and the effect of FAD-associated PS mutations remains unknown. Two studies conducted in cellular systems further reported that the overexpression of wild-type PS1 stimulated the transcriptional activity ability of CBP and of p300, while FAD-associated PS1 mutations did not produce this effect [153, 154]. However, Marambaud et al. [155] described a molecular pathway linking FAD-associated PS1 mutations with increased CBP function in cellular models. Briefly, the authors proposed that

FAD mutations inhibit the production of an intracellular peptide N-Cad/CTF2 originally cleaved through wild-type PS1, thereby preventing CBP degradation and resulting in up-regulated CREB-mediated transcription. Importantly, whether this mechanism exists *in vivo* remains unknown.

A convincing experiment reporting the beneficial effect of CBP overexpression in an AD pathological model was recently published, showing that the *in vivo* hippocampal administration of viral particles carrying CBP restored the learning and memory deficits of AD triple transgenic mice [156]. Thus, by directly modulating CBP levels, the authors re-established CREB activity and BDNF expression in the hippocampus. Therefore, increasing CBP activity might be an interesting therapeutic tool in this case. In addition, an endogenous inhibitor of p300/CBP (EP300-interacting inhibitor of differentiation 1 or EID1) was shown to translocate from the cytoplasm to the nucleus in the hippocampus of the brain of an AD patient [157]. Interestingly, the authors showed that the neuron-specific expression of human EID1 gene in a mouse model reduced hippocampal LTP and impaired spatial memory. This phenotype was associated with the hypo-acetylation of histone H3 and p53 [157]. This study also confirmed an association between CBP activity deregulation and human pathology.

The acetylation modulation could also affect the pathological marks of AD. A recent study has shown an interesting action of PCAF in an AD non-transgenic mice model, as intracerebroventricular injections of Aβ peptides failed to induce toxicity in PCAF KO mice; indeed, these peptides that had a deleterious effect in wild-type mice and did not worsen PCAF KO mice memory deficits [158]. Consistent with these observations, neprelysin, a peptidase promoting Aβ degradation, presented increased expression in PCAF KO, rendering these mice insensitive to amyloid toxicity [158]. Moreover, restoring brain levels of CBP, while improving memory function, did not modify Aβ levels, plaques, or Tau immunoreactivity in a model exhibiting both amyloid plaques and neurofibrillary tangles [156]. Restoring memory functions with the HDAC inhibitor 4-phenylbutyrate increased dendritic spine density in CA1 and the clearance of intraneuronal Aβ accumulation [159, 160], even when a similar treatment did not affect Aβ levels and plaques [161]. Further, HDAC inhibition promotes decreased tau phosphorylation through, at least, down-regulating GSK3β activity [161]. Nonetheless, the inhibition of p300 and likely CBP has been associated with decreased Tau acetylation and the elimination of hyperphosphorylated Tau species [162]. In addition, an aggregation of acetylated-tau was found in pathological brains of AD patients and, hence, was suggested to be a new AD pathological hallmark [163]. These investigators further demonstrated in cellular systems that tau itself had a MYST-like acetyltransferase activity that could account for its self-acetylation [164]. Therefore, activating these HATs could result in increased Tau deposits. Thus, it is essential to determine whether the effects of HAT activation affect the mechanisms underlying AD pathology development.

Few studies have examined the role of acetylation in memory disorders other than AD, and no studies have shown a role for HAT in these diseases. One exception is frontotemporal dementia, a neurologic disease involving behavioral and language problems, leading to memory deficits. Some familial cases reflect progranulin haploinsufficiency [165]. A recent study showed that the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) increased progranulin mRNA and protein expression in haploinsufficiency progranulin human cells [166], suggesting that increasing acetylation should be beneficial. Notably, increased HDAC6 levels have been reported in the temporal cortex of patients with frontotemporal lobar degeneration with TAR DNA-binding protein of 43-kDa inclusions [167], suggesting that hypoacetylation could be involved in the pathophysiology. HDAC6 concentration had also been shown in LBs in PD and dementia with LBs [168]. However, LBs might represent a cytoprotective response to sequester toxic proteins [169]; thus, the effect of HDAC6 accumulation in α-synuclein aggresomes remains unknown. Overall, these studies suggest an important role for nuclear and cytoplasmic acetylation regulation in these diseases.

HAT in Synaptic Plasticity and Memory

During the last decade, several studies described the involvement of epigenetic regulations in cognitive functions. These mechanisms facilitate the adaptation of neuronal gene expression patterns according to experience, broadening the functions of neuronal networks. Indeed, transcriptional regulations are required in LTM formation *in vivo* [170, 171], as in *ex vivo* models of synaptic plasticity (LTP) [172, 173], and are highly dependent of CREB and NFκB activities [174, 175]. Among these regulations, histone acetylation plays an important and well-characterized role, whereby both HATs and HDACs are key regulators of cognitive processes. Moreover, emerging evidence has also implicated non-histone protein acetylation in cognitive functions. Although we present seminal studies supporting the involvement of acetylation mechanisms in memory and plasticity, we will focus on newly published findings, as extensive and complete literature is available on this topic [11, 176–178].

Histone Acetylation in Synaptic Plasticity and Memory

The induction of H3 acetylation has been previously reported in hippocampal CA1 formation at 1 h after contextual fear conditioning (CxFC; a commonly used task for hippocampus-dependent associative learning) [179]. This rise in histone acetylation was associated with an activation of both N-methyl-D-aspartate receptors and the extracellular signal-

regulated kinase (ERK) signaling pathway, which are upstream factors for the stabilization and the formation of LTM. In 2010, Peleg et al. [15] revealed that CxFC causes an increase of several histones residues (H3K9K14, H4K5K8K12), as observed 1 h after exposure to the trial, in 3-month-old wild-type mice. Genome-wide analyses revealed that H4K12 acetylation was associated with transcriptional modifications after learning, and the differential expression of 2,229 genes was been identified through chromatin immunoprecipitation sequencing. The expression of the *formin 2* gene (an actin nucleator, important for synaptic plasticity and memory) was increased in a H4K12 acetylation-dependent manner [15]. The same year, we [180] also demonstrated that hippocampal-dependent spatial memory consolidation in the Morris Water Maze (MWM) increased H3K9K14 and H4K12 histone residues in the H2B N-terminus region. Interestingly, these hyperacetylations were associated with the increased expression and activity of several HATs, among which the proximal promoter of CBP was enriched in the acetylated forms of histones. The up-regulation of several memory-related genes (*cFos* and *Bdnf-IV*) was also identified in associated with increased CBP activity [180]. In addition, the BDNF neurotrophin plays an important role in synaptic plasticity and behavioral adaptations. Interestingly, H3K9K14 acetylation was increased after BDNF treatment, another HDAC activity-dependent mechanism [181]. Indeed, the use of trichostatin A (TSA) and SAHA on hippocampal slices treated with BDNF abolished the histone acetylation induction and BDNF-positive effect on dendritic spines. A recent study from our laboratory further assessed acetylation responses during early stages of spatial and fear memory learning before trace consolidation. In both cases, H2B N-terminal (K5K12K15K20), H3K9K14, and H4K12 acetylation was increased in the learning paradigm, whereas H3K9K14 acetylation was already activated in response to the experimental context (swimming, exploration…) [182]. Thus, it is likely that specific acetylation marks on H2B and H4 histones play a role during memory formation, while the acetylation of H3K9K14 could be more easily modified in response to the environment (i.e., processing of the context). It is suggested that the rapid acetylation of the chromatin at H3K9K14 occurs within 1 h of the processing of the context whether a memory is formed or not, which could relax the chromatin to facilitate gene promoter access or tag chromatin for further acetylation on H2B- and H4-specific marks. Notably, chromatin structure modifications, such as the acetylation of H3 and H4 at specific residues, also occur in response to an enrichment of the environment [14]. Thus, increasing HAT activity could thus be an interesting tool to restore hippocampus-dependent memory formation.

Several studies, inhibiting or activating HDACs, have also shown their implications in memory processes. Thus, HDAC2 overexpression has been associated with an impairment of hippocampus-dependent memory formation (cued, and CxFC and MWM) and working memory in mice, while HDAC2 KO presented enhanced memory formation. HDAC1 overexpression had no effect on these tasks [183]. Transgenic mice with focal homozygous deletions in Hdac3 in the CA1 region of the dorsal hippocampus demonstrated enhanced LTM for object location together with increased H4K8 acetylation and the transcription of both Nr4a2 and c-fos [184]. More recently, HDAC1 activity has been associated with fear memory extinction for the inhibition of excess fear. The overexpression of HDAC1 in the adult mouse hippocampus increased this specific form of learning [185]. Furthermore, the loss of HDAC4 (in 2-month-old mice) and HDAC5 (in 10- but not 2-month-old mice) impaired memory functions, with an alteration in the CxFC and the MWM tasks in both cases [186, 187].

Changes in histone acetylation have also been observed in other brain regions, such as the lateral amygdala. In rats, an amygdala-dependent auditory fear conditioning training stimulates H3 acetylation in an ERK signaling-dependent manner. Consistent with this result, the treatment of amygdala slices with TSA causes an enhancement of LTP [188]. Cued fear conditioning was also impaired after HDAC5 knockdown (in 10-month-old mice) or HDAC2 overexpression (in 4-month-old mice) [183, 186], confirming a link between histone acetylation and amygdala proper functioning.

Non-histone Protein Acetylation in Synaptic Plasticity and Memory

In addition to histones, the acetylation of non-histone proteins has also been associated with the processes of synaptic plasticity and memory formation. In 2007, Zhang and collaborators identified an F-actin binding protein, cortactin, as a new target for acetylation. Cortactin acetylation is regulated through different factors (PCAF, p300, HDAC6, and SIRT1), leading to the reduction of cortactin binding to F-actin and cell mobility [189, 190]. Recently, Cortactin acetylation was also shown to affect dendritic spine morphogenesis, promoting the dendritic clustering of PSD95 and Shank1, two post-synaptic proteins, in excitatory hippocampal synapses. Cortactin acetylation can be promoted through BDNF and glutamate stimulation [191].

Nuclear factor kappa B (NFκB) is another non-histone substrate for acetylation; its function in synaptic plasticity and several types of LTM has previously been established and reviewed elsewhere [192, 193]. Interestingly, in cultured cells, it was shown that CBP and p300 acetylate the NFκB p65 subunit in a stimulus-dependent manner, which, subsequently, could be deacetylated through HDAC3. p65 acetylation regulates NFκB nuclear function, and acetylation increases its DNA binding affinity (K221) and transcriptional activity (K301) [194]. In contrast, IκBα binds and sequesters the deacetylated form, switching NFκB function off [195].

Consistent with these *in cellulo* studies, visual fear conditioning induces NFκB activity in the rat amygdala through increased CBP activity and p65-CBP interactions, associated with an enhancement of p65 acetylation and DNA binding [196]. More recently, a function for NFκB acetylation has been described in depression. Treatment of the depressed Flinders Sensitive Line rats with L-acetylcarnitine (LAC; an endogenous acetylating agent) had a rapid (3 days) and long-lasting (2 weeks after drug withdrawal) antidepressant action. LAC rescued mGlu2 receptor mRNA and protein expression in the hippocampus of these rats via increased p65 K310 acetylation and the downstream activation of NFκB. Moreover, LAC re-establishes H3 K27 acetylation of both *grm2* (encoding the mGlu2 protein) and *bdnf* promoters, particularly in the depressed rats' prefrontal cortex [197]. Notably, epigenetic modifications are consistently implicated in the physiopathology of major depressive diseases and psychiatric-related disorders, such addiction, schizophrenia, or vulnerability to stress, as reviewed in [11]. The use of an HAT activator could thus represent an interesting therapeutic option in such disorders, particularly in depressive and schizophrenic behaviors, where an impairment of acetylation was reported.

Transgenic HAT Animal Models

The involvement of lysine acetylation in memory and synaptic plasticity has led to the generation of several transgenic models to study the functions and consequences of the loss of HATs in these processes.

To gain insights into the functions of CBPs, several mouse strains were generated, including hemizygous, conditional KO, transgenic and region-specific (viral induction)-depleted mice. These models are reviewed in [198], and have been analyzed at the molecular level in different learning and memory tasks. Studies examining the effect of a partial or total loss of CBP function show the involvement of its HAT activity in LTP and LTM, and suggest that CBP is not required for the formation of short-term memory (STM) [47, 199–202]. Nevertheless, another study using a conditional model with complete CBP inactivation in excitatory neurons of the forebrain showed an impairment of both memory types [203]. However, more recent studies confirm CBP involvement in LTM. The use of a conditional KO CBP model in forebrain neurons identified an alteration of LTM in an object recognition task, whereas the performances of CBP in the MWM or in a CxFC task were not altered [204]. However, CBP loss in the dorsal CA1 hippocampus, through adenovirus injections, induced alterations of histones H2B, H3, and H4 acetylations, and a loss of CBP-dependent transcriptional programs [205]. These mice exhibited deficits in LTP and in the formation of LTM during object recognition and CxFC tasks, confirming that CBP-dependent chromatin modifications are involved in the consolidation of certain forms of memory. Thus, CBP HAT function is clearly involved in the normal adult CNS functioning, particularly in synaptic plasticity mechanisms associated with learning and memory.

p300 conditional transgenic mice, expressing an inhibitory truncated form of p300, have LTM deficits in object recognition and CxFC tasks. These mice lack activation domains and the p300 C-terminal domain containing the HAT function, causing an overall decrease in acetylation of H3K9K14 residues in the forebrain [206]. Moreover, p300 conditional ablation in specific forebrain subregions, during the postnatal period, leads to long-term recognition and contextual fear memory deficits [207].

PCAF KO mice exhibit STM impairments at 2 months of age, while no LTM deficits were detected [208]. These alterations are associated with a strong response to stress (corticosterone increase). At 6 months, these mice show altered LTM, as shown with the MWM task, and this phenotypes remain, even after 12 months. This transgenic model is characterized by a complete PCAF inactivation, resulting in the altered expression or activation of different factors involved in STM processes (cFos and ERK1).

Potential use of HAT Activator as a Therapeutic Option

The impairment (e.g., deregulation, degradation, sequestration, etc.) of HAT(s) has been described in several neurodegenerative diseases ('HAT Impairment in Neurodegenerative Disorders' section) and neurodevelopmental disorders. Thus, the specific activation of HAT activity could be useful in pathological situations where a decrease in the levels of these enzymes has been described. One example is the case of the Rubinstein–Taybi syndrome that presents a haploinsufficiency in CBP and, in some cases, p300 [45, 209–211]. A therapeutic strategy based on CBP/p300 reactivation could be useful, even in the adult, for re-establishing at least some cognitive functions [198, 212], particularly for ALS, in which motor neurons present lower quantities of CBP owing to degradation [76]. In addition, HDACi are poorly efficient in this context, as these molecules were deleterious for the neuromuscular junction, despite a significant improvement of motor neuron survival [126]. A HAT activator could also be relevant for its use in AD and related diseases, as this molecule could improve both neuronal survival, neurogenesis, and memory-related alterations (see below). However, the efficacy of HAT activators in pathological animal models remains undocumented.

HAT Activation *vs* HDAC Inhibition as a Therapeutic Strategy

How HDACi efficiently affects pathological mechanisms is not well understood [5]. Notably, amongst the 14 HDAC

isoforms described so far, class I HDAC2 and HDAC3 (but not HDAC1) have been associated with the promoters of genes implicated in synaptic plasticity [183, 213], potentially explaining some of the HDACi beneficial effects on memory formation. HDAC2 was further increased in AD postmortem brains [214]. Interestingly, at least one wild-type allele of *cbp* was required to mediate the effects of HDAC inhibition on memory functions [215]. A supportive study demonstrated that HDACi were inefficient in a complete knock down of *cbp* [203]. Thus, simply inducing a histone hyperacetylated state with HDACi does not adequately replace HAT activation, at least in certain functions (i.e., memory formation), likely reflecting the other potential roles of HAT (e.g., CBP). The indirect (HDAC inhibitor-mediated) activation of p300/CBP HAT auto-acetylation, which stimulates HAT activity [36, 216], could also contribute to the beneficial effects of HDACi. Thus, it seems essential to envisage direct stimulation of the HAT function, as a new therapeutic tool in neurodegenerative diseases; by directly targeting the remaining HAT(s), one could re-activate the deficient enzymatic function, as well as all the other related functions that are not typically considered using an HDACi strategy. HATs are recruited at promoter loci through, in part, lysine acetylation recognition of conserved bromodomains [20]; together with the proper bound coactivator complexes, HATs acetylate nucleosomes at specific promoter sites (see 4, 5/ in Fig. 3). Following an HDACi treatment, the global levels of acetylation are indeed increased, but this activation will not necessarily occur at specific defective HAT-targeted sites.

In addition, Hazzalin and Mahadevan [217] showed that the turnover of histone acetylation is important to produce gene induction, as observed for the *fos* and *jun* genes. Indeed, HDACi rapidly enhanced histone acetylation at these genes, but inhibited their transcription; these results are in contrast to the predominant view that increased histone acetylation is characteristic of enhanced transcription [217]. Thus, on certain genes, HDACi directly inhibits gene induction, reminiscent of the low percentage of genes that are actually activated after HDACi treatment [218]. This result also suggests that both HAT and HDAC complexes have to be present and active to the specific acetylation mark to activate transcription, suggesting that a strategy aimed at activating the HAT function might be more efficient than inhibiting the HDAC to re-establish proper transcription in a given pathological context (see 6/ in Fig. 3).

Last, the effects of HDAC inhibition and HAT activation on nonhistone proteins (e.g., p53, NFkB, cortactin, tubulin, etc.), i.e., those not directly associated with transcription, should be further documented in pathological conditions.

In vivo Effect of HAT Activators on Brain Functions

Only a few HAT activators have been produced, and most of these molecules are cell impermeant [69, 70]. So far, only two

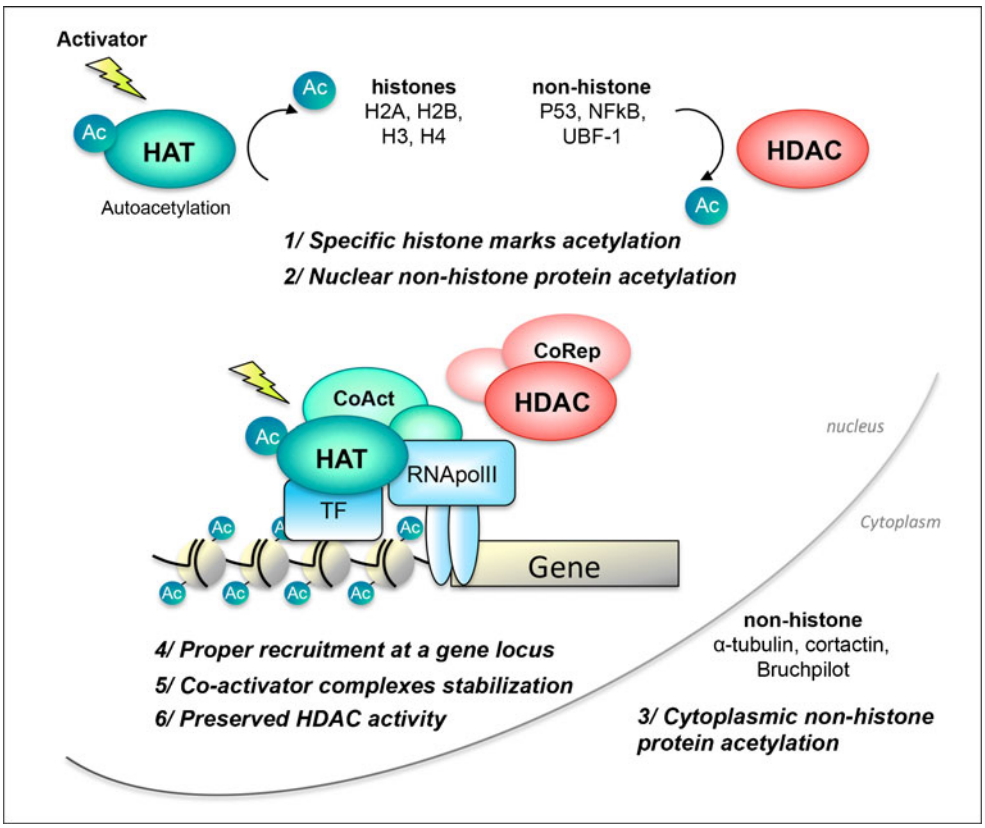

Fig. 3 Histone acetyltransferase (HAT) activation as a therapeutic strategy. Illustration of the beneficial effects of the use of a HAT activator at the cellular level (see 'HAT Activation *vs* HDAC Inhibition as a Therapeutic Strategy'). The activation of the HAT preserves the "acetylation code" of nuclear and cytoplasmic proteins (1–3), along with a proper positioning at gene loci (4) and recruitment of coactivators (5). Importantly, this strategy will preserve the histone deacetylase (HDAC) activity surrounding gene loci (6), otherwise impaired when following an HDAC inhibition strategy. Therefore, as both HAT and HDAC activities are present, a correct acetylation turn-over is possible, allowing transcriptional proceedings, see [217]. Ac=Acetyl; NFκB=nuclear factor kappa B; UBF-1=upstream binding factor-1; CoAct=coactivator; CoRep=co-repressor; TF=transcription factor; RNApolII=RNA polymerase II

HAT activator molecules, a PCAF activator, SPV106 [219], and a CBP/P300 activator, CSP-TTK21 [72], have been shown to cross the BBB, consistent with the use of these compounds to study brain functions *in vivo*. Both of these compounds were active after systemic administration in adult mice (Fig. 4).

Wei et al. [219] used SPV106 to demonstrate a role for PCAF in fear extinction. Fear conditioning and extinction are two distinct forms of learning that engage different molecular pathways. Fear extinction involves the gradual reduction in the fear response through the repeated presentation of a non-reinforced conditioned stimulus, which generates a new memory that competes with the original fear memory trace. As hippocampal acetylation or HATs such as CBP/P300 are essential to form contextual fear, fear extinction also involves epigenetic mechanisms [185, 220–222]. Notably, as discussed above, HDAC1 regulates extinction learning via a mechanism involving H3K9 deacetylation and the subsequent trimethylation of target genes [185]. Interestingly, HDAC1 was up-regulated in postmortem brain samples from schizophrenic patients [223, 224]. Using a pharmacological approach with the PCAF activator SPV106 and the PCAF inhibitor (H3-CoA-20-Tat), these authors demonstrated that PCAF activity facilitated the formation of fear extinction memory, but was not essential for fear acquisition [219]. These results suggest that PCAF regulation is an attractive target for the treatment of fear-related anxiety disorders.

Based on the small molecule HAT activator CTPB [69], we have synthesized several derivatives, from which TTK21 [N-(4-chloro-3-trifluoromethyl-phenyl)-2-n-propoxy-benzamide] was selected using a low-throughput enzyme assay, as this molecule efficiently activated the HAT activity of the CBP and

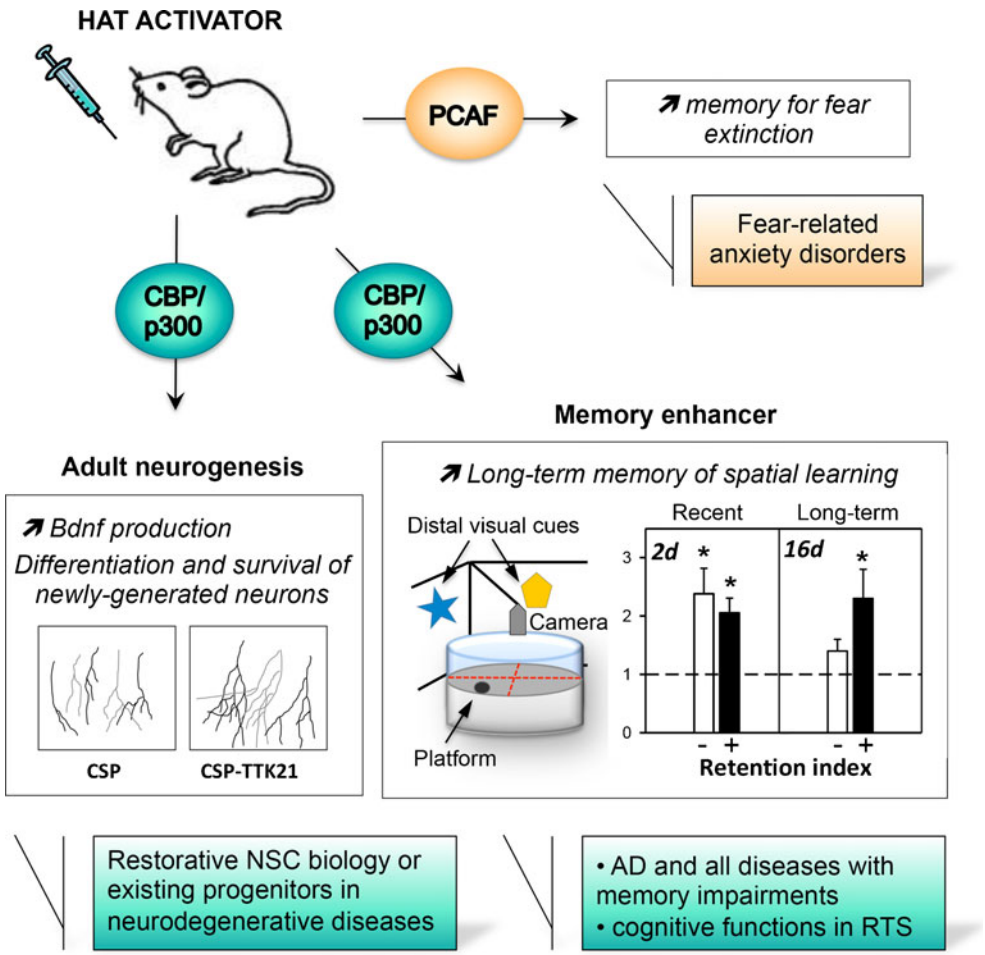

Fig. 4 Effects of histone acetyltransferase (HAT) activator molecules on brain functions and their potential therapeutic use in diseases. In rodent models, the described effects of different HAT activators [SPV106 for p300/cyclic adenomonophosphate response element-binding (CREB)-associated factor (PCAF) [219] or carbon nanosphere (CSP)-TTK21 for CREB-binding protein (CBP)/p300 [72] are depicted]. The drawings represent the effect of CSP-TTK21 on newly generated (doublecortin-positive) neurons with increased dendritic branching measured in the hippocampus of adult mice 3 days after CSP-TTK21 injection. For spatial memory, CSP (−)- or CSP-TTK21 (+)-injected mice were tested in the Morris water maze and retention was evaluated 2 days (recent, 2d) or 16 days (long-term, 16d) after a weak protocol of acquisition. The retention index indicates significant retention of the platform location in the CSP-TTK21 injected group at long delays without effect on recent memory (*$p<0.05$). For further details see [72]. The potential applications in diseases are summarized in the boxes (see text). NSC=neural stem cells; AD=Alzheimer's disease; RTS=Rubinstein Taybi syndrome

p300 HATs [72]. However, similar to the parent compound CTPB, TTK21 was poorly permeable to living cells, but when conjugated to a glucose-derived CSP, CSP-TTK21 was able to cross membranes and induce histone acetylation. Moreover, after systemic injection, we detected acetylated histones in the frontal cortex and dorsal hippocampus of adult C57BL6/J mice, showing that the new CSP-TTK21 compound passes the BBB and reaches different parts of the brain. The effect of this HAT activator was also tested on 2 important hippocampal functions: adult neurogenesis and spatial memory formation. Remarkably, CSP-TTK21 treatment promoted the formation of long and highly-branched doublecortin-positive neurons in the subgranular zone of the dentate gyrus, suggesting that CBP/p300 activation favors the maturation and differentiation of adult neuronal progenitors. At the molecular level, we observed that CSP-TTK21 induced mRNA levels of the neuroD1 differentiation marker and BDNF, a neurotrophin required for the terminal differentiation of newly generated neurons. The concomitant enrichment of acetylated-histone was measured on the proximal promoter of these two genes. Finally, we observed that CBP/p300 activation during spatial training, while not improving the retention of recent memory (2 days), resulted in a significant extension of memory duration over 16 days. Thus, by inducing adult neurogenesis and LTM formation, our data show that the direct stimulation of CBP/P300 HAT function could have important effects in terms of therapeutic options for brain diseases (Fig. 4).

Concluding Remarks

Taken together, the results obtained *in vivo* show that new HAT activator molecules represent an important scientific advance and provide new therapeutic options for brain diseases. Indeed, molecules that favor and promote the *in vivo* maturation and differentiation of newly generated neurons in the adult present an obvious advantage in several neurodegenerative diseases. For instance, the transplantation of neural stem cells (NSC) rescued dysfunctional neurons in 2 studies associated with PD [225] and spinal cord injury [226]. Beneficial results were also observed in a mutant SOD mouse model of ALS [227]. Thus, the transplantation of undifferentiated NSCs achieves functional effects in animal models of neurologic disorders [228, 229], and it is likely that restorative NSC biology could be assisted by HAT activator molecules, thereby promoting neurotrophin production and the maturation of progenitors on site ([72]; Figs. 2 and 4). Notably, impaired neurogenesis, and specifically the survival and differentiation of neuronal progenitors, have been reported in mouse models of AD [230, 231]. Thus, the activation of differentiation programs (*neuroD1*, *bdnf*) in pathological brains might be a promising strategy in AD.

Moreover, the positive effect of environmental enrichment (EE) is associated with increased histone-tail acetylation in young rodents [14, 232, 233]. EE promotes various plasticity mechanisms in the hippocampus, including *bdnf* gene up-regulation, enhanced dendritic branching, and the stimulation of adult neurogenesis [234–237], reminiscent of our observations that CSP-TTK21 activates CBP/p300 activity. Furthermore, CBP-deficient mice present no response to the beneficial effect of EE on the induction and enhancement of spatial navigation capabilities during neurogenesis, highlighting the contribution of CBP to EE effects [233]. However, EE efficiently restored brain functions in animal models of neurodegenerative diseases [14, 238]. Together, these data suggest that therapeutic approaches with HAT activator molecules could present regulations similar to those induced through EE. This approach might combat pathological signaling or improve successful aging, as the aging brain retains considerable functional plasticity.

Thus, HAT activator molecules provide a promising and exciting area of research, but improvement of drug design, specificity, and targeting to the brain is still required. Notably, HAT activator molecules need further testing in animal models of neurologic pathologies.

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Disclosures None.

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