



Editorial

Modulating Epigenetic HAT Activity: A Promising Therapeutic Option for Neurological Disease?

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The epigenome (epi- derived from Greek for 'over' or 'above') with its rich cache of highly regulated structural modifications to the DNA, histone residues and histone variants, defines the three-dimensional structure of chromatin, the genetic material within the eukaryotic cell nucleus, and serves as the molecular bridge between transcriptional gene control and our environment [1]. Only a few years ago, such epigenetic gene control mechanisms were primarily viewed in the context of cell division and fate specification as they were thought to function primarily in maintaining "cell memory" as the cell steers through elaborate pathways during early development and differentiation, and seemed to bear little relevance to adult brain function, as the mature brain is primarily composed of post-mitotic and already highly differentiated neuronal cells committed to specialized functions that collectively determine neuronal responses to external stimuli. However, recent explorations of the brain epigenome are providing unprecedented insights into the importance of specific epigenetic modification patterns in controlling gene expression not only in early brain development, but in adult brain function as well, calling into place a 'reprogramming process' that allows for plasticity at many levels of the neural circuitry in response to environmental cues [2]. One issue to consider with reference to the mature brain and cognitive disorders is how the course of normal maturation as well as aging affects the brain epigenome. Indeed, an increasing body of evidence indicates that substantial reorganization of the brain epigenome occurs during aging and such age related epigenetic drift could further exacerbate an individual's vulnerability to neurodegenerative diseases. However, unlike age related accumulation of somatic mutations and structural changes to the DNA that are likely irreversible, most if not all of the epigenetic modification marks studied to date are in fact reversible, making targeting of the neural epigenome a promising strategy for neuroprotection and/or neuroregeneration both early in development as well as during the aging process [1].

Cognitive decline, particularly in memory capacity, is a normal part of aging and has been associated with aberrant changes in gene expression in the brain's hippocampus and frontal lobe [3]. Of the epigenetic modifications identified so far in the nervous system, histone acetylation, mediated by the counteractive effects of histone acetyltransferases (HATs) and histone deacetylases (HDACs) have been unequivocally associated with the transcriptional control

of genes that facilitate learning and memory [4,5]. An emerging hypothesis is that age related accumulation of aberrant epigenetic marks in chromatin in the adult brain cause gene misregulation that drives cognitive decline and memory impairment. Over the past decade, several studies have also reported reduced histone acetylation in animal models of neurodegeneration that exhibit cognitive decline, including models for Alzheimer's disease (AD) [6]. Accordingly, pharmacological treatments using non-selective HDAC inhibitors like valproic acid, trichostatin A and Sodium Butyrate have been demonstrated to have promising effects in reversing such cognitive deficits in some of these models likely by increasing "global" acetylation levels and potentially HDAC inhibitor dependent genetic programs [7]. Similarly, restoring acetylation status through HDAC inhibition has been shown to ameliorate disease progression in models of Parkinson's and Huntington's disease [8-11]. These studies in turn have ignited enormous interest in the therapeutic potential of HDAC inhibitors for various neurodegenerative conditions. However, there is also widespread speculation about the target specificity of HDAC inhibitors as HDACs function as classes of proteins with individual members being able to compensate for each other's functions [12]. Thus, the current use of pan-HDAC inhibitors that act by increasing global acetylation levels can also disrupt cellular acetylation homeostasis with subsequent negative consequences. Moreover, targeting a particular class of HDACs or individual members is currently an arduous task as the causative agents of memory impairing histone acetylation changes and hence, the best targets for pharmacological strategies, remain unknown [6]. Additionally, class-specific modulation of HDAC activity may lead to very different and potentially opposing clinical implications. For example, activation and/or overexpression of class I HDACs 2 and 3 is associated with neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and neural cell toxicity [13,14], while inhibition of another member of this class, HDAC 1 has been found to lead to neurodegeneration [15,16]. Another issue to consider in terms of HDAC based therapeutic efficacy is that although HDAC inhibitors are generally considered to promote neuronal growth and differentiation, they also exhibit toxicity in various cell types of the central nervous system. For instance, there is evidence that they could have potentially detrimental effects on the orderly maturation of astrocytes and oligodendrocytes [17-19]. Moreover, like their counterparts, the HATs—class I, II and III of HDACs also regulate lysine acetylation of non-histone proteins that exert neuroprotective effects [20,21] adding a further layer of complexity to the interpretation of therapeutic potentials of currently available broad spectrum or even class specific HDAC inhibitors for neurodegenerative diseases. Thus, the specificity and side-effect profiles of inhibitors of HDACs require additional investigation to fully gauge their neuroprotective abilities. Further exploration of isoform-selective HDAC inhibitors that are also region-specific may provide a therapeutic advantage in targeting specific cell and tissue functions under pathological conditions.

Rapidly emerging literature on specific HATs and their respective roles in memory formation and neuronal function and survival are beginning to open new doors in terms of exploring the efficacy of directly activating specific HAT function as a new and more selective epigenetic based therapy for cognitive disorders [12]. Indeed, it has become increasingly clear that chromatin acetylation status can be

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impaired during the lifetime of neurons through loss of function of specific HATs with negative consequences on neuronal function [12]. Once the acetylation balance is disturbed by the loss of HAT dose, the HAT:HDAC ratio tilts in favor of HDAC in terms of availability and enzymatic functionality, a fact highlighted by amelioration of several neurodegenerative conditions by various HDAC inhibitors [22]. In fact, a clue to explaining the net deacetylation observed during neurodegeneration came with the finding that dying neurons exhibit progressive loss of HAT activity and/or expression, particularly that of the HAT CREB binding protein (CBP) and to a lesser extent the HAT p300. Notably, overexpression of CBP under apoptotic conditions delays neuronal cell death, an event that was dependent on the HAT function of CBP [23,24]. CBP overexpression has also been shown to protect neurons from polyglutamine induced toxicity in Huntington's disease [25-27]. We have also reported a similar effect for Tip60, a multifunctional HAT that forms a transcriptionally active complex with the AD associated amyloid precursor protein (APP) intracellular domain (AICD). Neuronal specific loss of Tip60 HAT activity under APP induced neurodegenerative conditions enhances apoptotic neuronal cell death in a *Drosophila* AD model, an effect predominantly mediated through transcriptional dysregulation of pro-apoptotic and essential genes. Remarkably, overexpression of the HAT competent Tip60 leads to a marked decrease in APP induced apoptosis highlighting a neuroprotective role for Tip60 HAT function in AD associated pathogenesis [28].

Specific HATs are emerging as regulators that gate access to genes regulating specific neuronal processes that are essential for maintaining neuronal health and for mediating higher order brain functions. Expression of such gene profiles are negatively affected in neurodegenerative conditions with detrimental consequences, which likely explains at least in part, the neuroprotective function of certain HATs such as CBP and Tip60 under neurodegenerative conditions. For instance, CBP has been shown to mediate genes involved in specific forms of hippocampal long term potentiation, a form of synaptic plasticity thought to underlie memory storage [29]. In contrast, the HAT p300 has been shown to constrain synaptic plasticity in the prefrontal cortex and reduced function of this HAT is required for formation of fear extinction memory [30]. Importantly, overexpression of p300 but not HDAC inhibition has been shown to promote axonal regeneration in mature retinal ganglion cells following optic nerve injury, an effect mediated by p300 induced hyperacetylation of histone H3 and p53 that consequently leads to increased expression of selected pro-axonal outgrowth genes [31]. Overexpression of Tip60 under APP induced neurodegenerative conditions also induces intrinsic axonal arborization of the *Drosophila* small ventrolateral neurons, a well characterized model system for studying axonal growth [32]. It is important to note that modulation of specific HAT levels and/or activity may alter the expression of many genes or "cassettes" of specific genes that act together produce a neuroprotective effect. In fact, in the case of the HAT to Tip60, overexpression of wild type Tip60 but not the HAT defective mutant increases survival in a *Drosophila* AD model, an effect that is mediated *via* enhanced repression of a "cassette" of pro-apoptotic genes and induction of pro-survival factors like Bcl-2. These results indicate that Tip60 HAT activity exerts a neuroprotective effect by tipping the cell fate control balance in favor of cell survival [28]. Similar mechanisms may underlie the neuroprotective effects observed with other HATs like CBP and p300. In addition to regulation of gene expression, the HAT E1p3, known to acetylate microtubules, has been shown to be involved in the regulation of

synaptic bouton expansion during neurogenesis [33] and recent studies suggest that regulation of microtubule acetylation by the ELP3 might be commonly affected in neurological diseases making it a potential target for acetylation modulator based therapies (reviewed in [34]). Tip60 has also been recently shown to play a causative role in synaptic growth partly through acetylation of microtubules [35]. Together, these studies support the concept that modulation of expression levels and/or activity of specific HATs such as Tip60 could be an alternative therapeutic option for neurological conditions not only by reprogramming neuroprotective gene programs suited for cell survival, but also by directly modulating the function of downstream proteins involved in promoting neuronal growth and/or regeneration.

Importantly, targeting HATs can also be beneficial because unlike HDACs, HATs have non-redundant functions under physiological conditions and thus the presence of specific modulators can have more direct effects. In a study by [36], it was reported that the total protein amount and activity of various HDACs is not altered by mutant huntington protein expression in primary cortical neurons, while the HAT activity of CBP is in fact reduced. Thus, the neurodegeneration associated tilt in HAT:HDAC does not appear to include augmentation of HDAC protein level. Therefore, activation of specific HATs may not only restore general acetylation balance but in addition, also activate specific gene expression programs that consequently have neuroprotective effects. In support of this concept, a number of recent studies conclude that HDAC inhibitor induced hyperacetylation alone may not be sufficient to produce beneficial effects. In a study by [37], it was reported that HDAC inhibition mediated enhancement of synaptic plasticity and hippocampus dependent memory formation requires the presence of at least one wild type allele of *cbp* highlighting the requirement of HATs like CBP for site specific histone acetylation and the recruitment of the basal transcriptional machinery. Of note, increasing neuronal dosage of specific HATs to reinstate acetylation homeostasis calls for the same concern as does the utilization of HDAC inhibitors. Non-specific enhancement of HAT levels and/or activity may lead to further complications by skewing the acetylation balance in the neighboring cell population towards hyperacetylation. Therefore, in order to reap the full potential of specific HAT activators, it is essential to characterize specific HAT function in particular cellular processes as well as quantify HAT-HDAC dose in specific cell populations that are vulnerable to different degenerative etiology [22].

A major challenge with utilization of modifiers of cellular acetylation levels is the identification of *bona fide* targets of HATs and HDACs and the integration of histone and transcription factor acetylation into a broader context of neuronal, and importantly, cellular homeostasis [38]. Although still in its infancy, the neuroprotective effects displayed by HATs like CBP, p300 and Tip60 and specificity of these effects for particular neuronal processes appears more promising than currently available non-selective HDAC inhibitors. However, determining the genes or "cassettes" of genes that are regulated by such HATs and characterizing the survival or degenerative effects such genes have would subsequently facilitate the development of novel drugs and specific therapeutic strategies with lower adverse side effects than those currently available.

References

1. Jakovcevski M, Akbarian S (2012) Epigenetic mechanisms in neurological disease. *Nat Med* 18: 1194-1204.


2. Borrelli E, Nestler EJ, Allis CD, Sassone-Corsi P (2008) Decoding the epigenetic language of neuronal plasticity. *Neuron* 60: 961-974.
3. Sweatt JD (2010) Neuroscience. Epigenetics and cognitive aging. *Science* 328: 701-702.
4. Levenson JM, O'Riordan KJ, Brown KD, Trinh MA, Molfese DL, et al. (2004) Regulation of histone acetylation during memory formation in the hippocampus. *J Biol Chem* 279: 40545-40559.
5. Peixoto L, Abel T (2012) The Role of Histone Acetylation in Memory Formation and Cognitive Impairments. *Neuropsychopharmacology*.
6. Graff J, Rei D, Guan JS, Wang WY, Seo J, et al. (2012) An epigenetic blockade of cognitive functions in the neurodegenerating brain. *Nature* 483: 222-226.
7. Kazantsev AG, Thompson LM (2008) Therapeutic application of histone deacetylase inhibitors for central nervous system disorders. *Nat Rev Drug Discov* 7: 854-868.
8. Hockly E, Richon VM, Woodman B, Smith DL, Zhou X, et al. (2003) Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. *Proc Natl Acad Sci U S A* 100: 2041-2046.
9. Gardian G, Browne SE, Choi DK, Klivenyi P, Gregorio J, et al. (2005) Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington's disease. *J Biol Chem* 280: 556-563.
10. Outeiro TF, Kontopoulos E, Altmann SM, Kufareva I, Strathearn KE, et al. (2007) Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson's disease. *Science* 317: 516-519.
11. Monti B, Gatta V, Piretti F, Raffaelli SS, Virgili M, et al. (2010) Valproic acid is neuroprotective in the rotenone rat model of Parkinson's disease: involvement of alpha-synuclein. *Neurotox Res* 17: 130-141.
12. Selvi BR, Cassel JC, Kundu TK, Bouillier AL (2010) Tuning acetylation levels with HAT activators: therapeutic strategy in neurodegenerative diseases. *Biochim Biophys Acta* 1799: 840-853.
13. Janssen C, Schmalbach S, Boeselt S, Sarlette A, Dengler R, et al. (2010) Differential histone deacetylase mRNA expression patterns in amyotrophic lateral sclerosis. *J Neuropathol Exp Neurol* 69: 573-581.
14. Bardai FH, D'Mello SR (2011) Selective toxicity by HDAC3 in neurons: regulation by Akt and GSK3beta. *J Neurosci* 31: 1746-1751.
15. Bates EA, Victor M, Jones AK, Shi Y, Hart AC (2006) Differential contributions of *Caenorhabditis elegans* histone deacetylases to huntingtin polyglutamine toxicity. *J Neurosci* 26: 2830-2838.
16. Kim D, Frank CL, Dobbin MM, Tsunemoto RK, Tu W, et al. (2008) Deregulation of HDAC1 by p25/Cdk5 in neurotoxicity. *Neuron* 60: 803-817.
17. Hsieh J, Nakashima K, Kuwabara T, Mejia E, Gage FH (2004) Histone deacetylase inhibition-mediated neuronal differentiation of multipotent adult neural progenitor cells. *Proc Natl Acad Sci U S A* 101: 16659-16664.
18. Liu J, Casaccia P (2010) Epigenetic regulation of oligodendrocyte identity. *Trends Neurosci* 33: 193-201.
19. Pedre X, Mastronardi F, Bruck W, Lopez-Rodas G, Kuhlmann T, et al. (2011) Changed histone acetylation patterns in normal-appearing white matter and early multiple sclerosis lesions. *J Neurosci* 31: 3435-3445.
20. Dokmanovic M, Marks PA (2005) Prospects: histone deacetylase inhibitors. *J Cell Biochem* 96: 293-304.
21. Zhao W, Kruse JP, Tang Y, Jung SY, Qin J, et al. (2008) Negative regulation of the deacetylase SIRT1 by DBC1. *Nature* 451: 587-590.
22. Saha RN, Pahan K (2006) HATs and HDACs in neurodegeneration: a tale of disconcerted acetylation homeostasis. *Cell Death Differ* 13: 539-550.
23. Rouaux C, Jokic N, Mbeki C, Bouillier S, Loeffler JP, et al. (2003) Critical loss of CBP/p300 histone acetylase activity by caspase-6 during neurodegeneration. *EMBO J* 22: 6537-6549.
24. Anne-Laurence B, Caroline R, Irina P, Jean-Philippe L (2007) Chromatin acetylation status in the manifestation of neurodegenerative diseases: HDAC inhibitors as therapeutic tools. *Subcell Biochem* 41: 263-293.
25. Jiang H, Nucifora FC Jr, Ross CA, DeFranco DB (2003) Cell death triggered by polyglutamine-expanded huntingtin in a neuronal cell line is associated with degradation of CREB-binding protein. *Hum Mol Genet* 12: 1-12.
26. Jiang YM, Yamamoto M, Kobayashi Y, Yoshihara T, Liang Y, et al. (2005) Gene expression profile of spinal motor neurons in sporadic amyotrophic lateral sclerosis. *Ann Neurol* 57: 236-251.
27. Jiang H, Poirier MA, Liang Y, Pei Z, Weiskittel CE, et al. (2006) Depletion of CBP is directly linked with cellular toxicity caused by mutant huntingtin. *Neurobiol Dis* 23: 543-551.
28. Pirooznia SK, Sarthi J, Johnson AA, Toth MS, Chiu K, et al. (2012) Tip60 HAT Activity Mediates APP Induced Lethality and Apoptotic Cell Death in the CNS of a *Drosophila* Alzheimer's Disease Model. *PLoS One* 7: e41776.
29. Wood MA, Kaplan MP, Park A, Blanchard EJ, Oliveira AM, et al. (2005) Transgenic mice expressing a truncated form of CREB-binding protein (CBP) exhibit deficits in hippocampal synaptic plasticity and memory storage. *Learn Mem* 12: 111-119.
30. Marek R, Coelho CM, Sullivan RK, Baker-Andresen D, Li X, et al. (2011) Paradoxical enhancement of fear extinction memory and synaptic plasticity by inhibition of the histone acetyltransferase p300. *J Neurosci* 31: 7486-7491.
31. Gaub P, Joshi Y, Wuttke A, Naumann U, Schnichels S, et al. (2011) The histone acetyltransferase p300 promotes intrinsic axonal regeneration. *Brain* 134: 2134-2148.
32. Pirooznia SK, Chiu K, Chan MT, Zimmerman JE, Elefant F (2012) Epigenetic Regulation of Axonal Growth of *Drosophila* Pacemaker Cells by Histone Acetyltransferase Tip60 Controls Sleep. *Genetics*.
33. Singh N, Lorbeck MT, Zervos A, Zimmerman J, Elefant F (2010) The histone acetyltransferase Elp3 plays in active role in the control of synaptic bouton expansion and sleep in *Drosophila*. *J Neurochem* 115: 493-504.
34. Nguyen L, Humbert S, Saudou F, Chariot A (2010) Elongator - an emerging role in neurological disorders. *Trends Mol Med* 16: 1-6.
35. Sarthi J, Elefant F (2011) dTip60 HAT activity controls synaptic bouton expansion at the *Drosophila* neuromuscular junction. *PLoS One* 6: e26202.
36. Hoshino M, Tagawa K, Okuda T, Murata M, Oyanagi K, et al. (2003) Histone deacetylase activity is retained in primary neurons expressing mutant huntingtin protein. *J Neurochem* 87: 257-267.
37. Vecsey CG, Hawk JD, Lattal KM, Stein JM, Fabian SA, et al. (2007) Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB:CBP-dependent transcriptional activation. *J Neurosci* 27: 6128-6140.
38. Langley B, Gensert JM, Beal MF, Ratan RR (2005) Remodeling chromatin and stress resistance in the central nervous system: histone deacetylase inhibitors as novel and broadly effective neuroprotective agents. *Curr Drug Targets CNS Neurol Disord* 4: 41-50.

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