The promise and perils of HDAC inhibitors in neurodegeneration

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Introduction
Histone deacetylases (HDACs) are enzymes that catalyze the removal of acetyl groups from lysine residues of proteins. Initially studied for their ability to deacetylate histones and influence chromatin, HDACs also remove acetyl groups from non-histone substrates thus playing a broader role in cell biology.¹,² In recent years, HDACs have received increasing attention in the context of neurological disease not only because protein acetylation has been implicated in neuropathology in myriad ways but also because HDACs are druggable targets. In this review, we present an overview of the HDAC superfamily, describe the role of HDACs in a few emblematic neurological disorders, and then move on to discuss the potential neurological side effects of modulating HDAC functions, particularly as we learn more about the functions of HDACs in the nervous system.

The HDAC Superfamily
HDACs belong to an evolutionary conserved family divided into four classes.³ Classes I, II, and IV are similar in that they all require Zn²⁺ as a cofactor.⁴ Class III, on the other hand, requires nicotinamide adenine dinucleotide (NAD⁺).⁵

Each of these classes, with the exception of class IV, is composed of more than one member. In addition, the metazoan HDACs are also often described by their homology to yeast HDACs, the first enzymes of that category to be characterized. Thus, the Class I family of HDACs – homologous to the yeast HDAC reduced potassium dependency 3 (RPD3) – includes HDAC1, 2, 3, and 8. These HDACs, with the exception of muscle-specific HDAC8, are expressed widely in the brain.⁶,⁷ Class I HDACs interact with key proteins as part of large multunit complexes. The complexes they form vary. Thus, HDAC1 and 2 share a high level of structural and functional similarity and participate in the formation of large transcriptional repressor complexes defined by the proteins SIN3A, nucleosome remodeling deacetylase (NuRD), and Co-REST; HDAC3 on the other hand interacts with another set of corepressors defined by the proteins silencing mediator for retinoid or thyroid-hormone receptor (SMRT) and nuclear receptor corepressor (NCoR).⁹

Abstract
Histone deacetylases (HDACs) represent emerging therapeutic targets in the context of neurodegeneration. Indeed, pharmacologic inhibition of HDACs activity in the nervous system has shown beneficial effects in several preclinical models of neurological disorders. However, the translation of such therapeutic approach to clinics has been only marginally successful, mainly due to our still limited knowledge about HDACs physiological role particularly in neurons. Here, we review the potential benefits along with the risks of targeting HDACs in light of what we currently know about HDAC activity in the brain.
HDACs 1 and 2 are strictly observed in the nucleus. Hence, it should not be surprising that their substrates are nuclear – these include the transcription factors p53, MyoD, E2F, yin yang 1 (YY1), retinoblastoma protein (pRb), and the estrogen receptor (ER),\textsuperscript{10–15} HDAC3 shuttles between the nucleus and the cytoplasm and deacetylates substrates in either compartment. The nuclear substrates include the transcription factors myocyte enhancer factor-2 (MEF2), sex-determining region Y (SRY) and P300/CBP-associated factor (PCAF); the cytosolic substrates include p65 and signal transducers and activators of transcription (STAT) proteins 1 and 3.\textsuperscript{16–21} The Class II family of HDACs – homologous to the yeast Histone Deacetylase 1 (HDA1) – is further divided based on structural parameters into two subclasses: class IIA includes HDACs 4, 5, 7, and 9; while class IIB includes HDAC6 and HDAC10. Members of both subclasses display tissue- and cell-specific expression, but importantly they are all expressed in the brain.\textsuperscript{22} At a subcellular level, HDAC6 is present predominantly in the cytosol functioning as a potent deacetylase of \(\alpha\)-tubulin,\textsuperscript{23,24} although recently other substrates of HDAC6 have been identified. These include the chaperone heat shock protein 90 (HSP90), the actin-binding protein cortactin, and \(\beta\)-catenin.\textsuperscript{25–27} The other class II HDACs shuttle between the nucleus and cytosol. Their cytoplasmic retention is dependent on phosphorylation and interactions with 14-3-3 proteins.\textsuperscript{28} Non-histone nuclear substrates include the transcription factors p53 and runt-related transcription factor 2 (RUNX2) in the case of HDAC4; GATA1 in the case of HDAC5; H1F1\(\alpha\) in the case of HDAC7; structural maintenance of chromosomes 3 (SMC3) in the case of HDAC8; paired box 3 (Pax3) and KRAB-associated protein-1 (KAP1) in the case of HDAC10.\textsuperscript{29–34} Their cytoplasmic substrates include myeloproliferative leukemia oncogene (MPL) and DNAJ8 – both deacetylated by HDAC4, tripartite motif-containing protein 29 (TRIM29) and heat shock protein 70 (HSP70), substrates of HDAC9 and HDAC10, respectively.\textsuperscript{34–37}

The Class III NAD\(^+\)-dependent HDACs – called sirtuins, because of their homology to the yeast ortholog silent information regulator 2 (SIR2)\textsuperscript{38} – comprise seven mammalian sirtuins, all expressed in the brain.\textsuperscript{39} SIRT 1, 2, 6, 7, and 7 are found in both the cytoplasm and nucleus, while SIRT 3, 4, and 5 are found localized to the mitochondria.\textsuperscript{40,41}

Aside from histones, SIRT1 deacetylates transcription factors such as TBP-associated factor 68 (TAF68), p53, p300, and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1\(\alpha\)).\textsuperscript{42–45} SIRT2 deacetylates cytosolic transcription factor p65, a subunit of nuclear factor \(\kappa\)B (NF-\(\kappa\)B), thus indirectly regulating the expression of NF-\(\kappa\)B-dependent genes.\textsuperscript{46} Interestingly, SIRT2 overlaps with HDAC6 in its ability to deacetylate \(\alpha\)-tubulin.\textsuperscript{47}

SIRT 3, 4, and 5 determine the global lysine-acetylation level, especially in mitochondria.\textsuperscript{6} SIRT3, possibly the predominant member of this subgroup, plays a major role in regulating energy metabolism through its effects on removing the acetyl group from acetyl-coenzyme A synthase 2 (ACS2), glutamate dehydrogenase (GLDH), isocitrate dehydrogenase 2 (IDH2), and the electron transport complex I.\textsuperscript{48–50} SIRT3 also regulates apoptosis by deacetylating nicotinamide phosphoribosyltransferase (NAMPT) and mitochondrial ribosomal protein L10 (MRPL10) in mitochondria and Ku70 in the nucleus.\textsuperscript{51–53} SIRT4 has recently been shown to regulate lipid metabolism by deacetylating malonyl CoA decarboxylase (MCD).\textsuperscript{54} SIRT5 on the other hand regulates the urea cycle by deacetylating carbamoyl phosphate synthetase 1 (CPS1).\textsuperscript{55} SIRT6 deacetylates the C-terminal-binding protein (CtBP) interacting protein and the acetyl transferase general control nonrepressible 5 (GCN5).\textsuperscript{56,57} SIRT7 increases cellular resistance to cytotoxic and oxidative stress through p53 deacetylation.\textsuperscript{58}

The Class IV HDAC family consists solely of HDAC11.\textsuperscript{59} Mainly found in the nucleus, little is known about its substrates except that it is expressed across development in the mammalian central nervous system (CNS) and possibly regulates inflammation through its inhibitory effect on interleukin 10 (IL-10) expression.\textsuperscript{60,61}

A comprehensive overview of HDAC superfamily is shown in Table 1.

## HDACs and Neurodegeneration

### Histone substrates and the translational role of HDACs

Histone acetylation occurs on the N-terminal tails of histones, reducing the basic charge of histones to promote an open, transcription-promoting conformation of chromatin. In addition, the residues themselves provide docking sites for transcription factors/activators including ATP-dependent chromatin modulators.\textsuperscript{52} By keeping histones deacetylated, HDACs repress gene expression.\textsuperscript{8} In this sense, they work against histone acetyl transferases (HATs) that acetylate histones and activate gene expression. Histone acetylation, to be sure, is only one of several histones and DNA covalent modifications that modulate chromatin topology – the so called “epigenome.” Since these modifications are highly synchronized, HATs and HDACs play important roles in mediating these changes.

There are two ways by which histone modulation via HDACs plays a role in neurodegeneration. In the first, a disease is caused by an HDAC-dependent transcriptional...
| Class | Cofactors | Members | Size (human) | Predominant subcellular localization | Predominant brain distribution (based on 202–204) | Nonhistone substrates (see the text for references) |
|-------|-----------|---------|--------------|-------------------------------------|--------------------------------------------------|--------------------------------------------------|
| I     | Zn^{2+}   | HDAC1   | 482 amino acids | Nucleus                            | Cortex, amigdala, hippocampus                     | p53, MyoD, E2F, yin yang 1 (YY1), retinoblastoma protein (pRb), estrogen receptor (ER) |
|       |           | HDAC2   | 488 amino acids | Nucleus                            | Cortex, amigdala, hippocampus, locus coeruleus    | p53, MyoD, E2F, yin yang 1 (YY1), retinoblastoma protein (pRb), estrogen receptor (ER) |
|       |           | HDAC3   | 428 amino acids | Nucleus/Cytosol                    | Widely expressed                                  | Myocyte enhancer factor-2 (MEF2), sex-determining region Y (SRY), P300/CBP-associated factor (PCAF), p65, signal transducers, and activators of transcription 1 (STAT1) and 3 (STAT3) |
|       |           | HDAC4   | 1084 amino acids | Nucleus/Cytosol                    | Cortex, amigdala, hippocampus, locus coeruleus    | Structural maintenance of chromosomes 3 (SMC3) |
|       |           | HDAC5   | 1122 amino acids | Nucleus/Cytosol                    | Widely expressed                                  | p53, runt-related transcription factor 2 (RUNX2), myeloproliferative leukemia oncogene (MPL), DNAJB8 |
|       |           | HDAC6   | 952 amino acids | Nucleus/Cytosol                    | Amigdala, hippocampus, substantia nigra pars compacta, locus coeruleus | GATA1 |
|       |           | HDAC7   | 1215 amino acids | Cytosol                            | Hippocampus, substantia nigra pars compacta      | H1F1x |
|       |           | HDAC10  | 669 amino acids | Nucleus/Cytosol                    | Amigdala, hippocampus                             | |
|       |           | SIRT1   | 747 amino acids | Nucleus                            | Cortex, hippocampus, cerebellum, hypothalamus    | Tripartite motif-containing protein 29 (TRIM29) |
|       |           | SIRT2   | 389 amino acids | Cytosol                            | Oligodendrocytes, olfactory neurons, hippocampus | Acetyl-coenzyme A synthase 2 (AC52), glutamate dehydrogenase (GLDH), isocitrate dehydrogenase 2 (IDH2), electron-transport complex I, Nicotinamide phosphoribosyltransferase (NAMPT), mitochondrial ribosomal protein L10 (MRPL10), Ku70 |
|       |           | SIRT3   | 399 amino acids | Mitochondria                       | To be determined                                  | Malonyl CoA decarboxylase (MCD) |
|       |           | SIRT4   | 314 amino acids | Mitochondria                       | To be determined                                  | Carbamoyl phosphate synthetase 1 (CPS1) |
|       |           | SIRT5   | 310 amino acids | Mitochondria                       | Cortex (layer II)                                 | C-terminal-binding protein (CtBP) interacting protein, general control nonderepressible 5 (GCN5) |
|       |           | SIRT6   | 355 amino acids | Nucleus                            | To be determined                                  | p53 |
|       |           | SIRT7   | 400 amino acids | Nucleolus                          | To be determined                                  | To be determined |
|       |           | HDAC11  | 347 amino acids | Nucleus                            | Widely distributed                                | |

HDAC, histone deacetylase; NAD, nicotinamide adenine dinucleotide.
decrease in the level of a certain protein, resulting in disease by a “loss of function” mechanism. In the second, the mutation causes widespread transcriptional deficits across the genome. These are best explained in the context of specific neurological disorders, as described below.

**HDACs and gene silencing at a specific locus**

**Friedreich ataxia**

Friedreich ataxia (FRDA), the most common autosomal recessive ataxia, is an excellent example of the scenario where HDAC-dependent transcriptional silencing at a particular disease locus causes loss of expression of a crucial protein to result in neurodegeneration.

FRDA is characterized by ataxia and sensorimotor neuropathy, sometimes associated with vision and hearing loss, along with non-neurological manifestations of cardiomyopathy and diabetes. It is caused by a pathogenic GAA tri-nucleotide expansion in the first intron of the frataxin (FXN) gene. The product of this gene participates in the mitochondrial biogenesis of Fe-S clusters – essential cofactors involved in many metabolic pathways. How this function relates to neurodegeneration is still unclear. Regardless, there is growing evidence in FRDA cell and mouse models that GAA triplet expansion induces the FXN gene to be silenced, leading to FRDA by loss of its function.

FXN silencing takes place through a mechanism of heterochromatinization mediated by histone hypoacetylation. This inference stems from the finding that long GAA repeats suppress transcription of a nearby reporter gene; moreover, chromatin immunoprecipitation (ChIP) experiments show a significant enrichment in heterochromatin marks such as hypoacetylation of specific lysine residues on histones around the trinucleotide repeats and on the promoter. This enrichment has been observed on residues H3K9 and H3K14 of histone H3, and H4K8, H4K12, and H4K16 of histone H4. These changes are accompanied by other epigenetic processes that interfere with transcription – in particular tri-methylation of histone lysine residues (including H3K9 and H3K27); enhanced cytosine methylation in the CpG residues in the DNA region upstream of the expanded triplet (as demonstrated by sodium bisulfite sequencing); increased expression of a frataxin antisense transcript (FAST1) that promotes the spreading of DNA methylation (by decreasing the binding of the CTCF protein); and finally non-canonical structures subsumed by the locus itself because of the trinucleotide expansion. The relative importance of each of these events to silencing is unclear, but histone hypoacetylation is clearly important, given that inhibiting HDACs can rescue FXN expression.

One of the first studies evaluating HDAC inhibitors showed that the broad spectrum Class I and II HDAC inhibitor sodium butyrate (see Table 2) produced an increase in the activity of a FXN-EGFP reporter enhancing EGFP expression by ~15%. Subsequent experiments on primary lymphocytes from FRDA patients treated with novel benzamide-derived HDAC inhibitors showed even greater effects on FXN expression with potentially less toxicity compared to previously available inhibitors; moreover, ChIP assays mechanistically demonstrated that FXN reactivation was coupled with increased acetylation of histones H3 and H4 in the chromatin region immediately upstream of the GAA repeats. These inhibitors have shown promise in two FRDA models, given that they increase FXN expression in the brain and ameliorate the disease phenotype. Since the inhibitors tend to target HDAC3 and have shown the most promise in the FRDA mouse models, a concerted effort has been directed at developing yet more potent and specific inhibitors for HDAC3. A phase I clinical trial for one of these compounds (109/RG2833) has been recently completed, demonstrating that the drug increases FXN mRNA levels.

| Table 2. Classification of the most common HDAC inhibitors. |
|------------------|------------------|------------------|------------------|
| HDACi class      | Representative HDACi | Specificity | References |
| Hydroxamates     | Trichostatin A (TSA), vorinostat, panobinostat, tubastatin A, tubacin | Pan-inhibitors for class I-II HDACs (TSA, vorinostat, panobinostat), HDAC6 specific (tubastatin A and tubacin) | 205, 206, 207, 208 |
| Cyclic peptides  | Romidepsin, apicidin, cyclic hydroxamic acid-containing peptides (CHAPs) | Class I HDAC selectivity | 209 |
| Aliphatic acids  | Butyrate, phenyl-butyrate, valproate | Pan-inhibitors for class I-II HDACs | 210 |
| Benzamides       | MS-275, 4b, 106, 109 | Class I specific | 211, 212 |
| Sirtuin inhibitors | Nicotinamide, sirtinol, AGK-2, AK-7, splitomicin | Pan-inhibitor (nicotinamide), SIRT2 specific (sirtinol, AK-7, splitomicin) | 213, 214, 215, 216, 217 |

HDAC, histone deacetylase.
and H3K9 acetylation in peripheral blood mononuclear cells (PBMCs) of FRDA patients.83 There is also evidence to suggest that Class III HDACs are equally important in FNX silencing, given that the sirtuin inhibitor nicotinamide increases histone H3 and H4 acetylation, decreases H3K9 and H3K27 trimethylation, and reverses the silencing at the FNX locus.84 A recently concluded phase II clinical trial for nicotinamide corroborated this evidence by showing that daily doses induce a sustained upregulation of FNX expression along with reduced heterochromatin modifications at the FNX locus in PBMCs of FRDA patients.85

Fragile X syndrome

Fragile X syndrome (FXS) – an X-linked disease characterized by mental retardation, neurobehavioral abnormalities and autistic features – is another disease where silencing of a specific gene product is caused by histone hypoacetylation alongside other epigenetic events. As with FRDA, FXS is caused by a trinucleotide expansion, though this time in the FMR1 gene, and the gene product fragile X mental retardation protein (FMRP) – a protein that regulates neuronal mRNA metabolism86 – is not expressed. Also unlike FRDA, the FXS expansion is a CGG expansion (not a GAA expansion) and occurs in the 5′-UTR (not in the intron).

There are many similarities between FXS and FRDA with respect to the complex, spatio-temporally regulated heterochromatinization process that causes silencing at the FMR1 locus.87–91 These events have been best elucidated in a human embryonic FXS stem cell line that recapitulates the developmental hallmarks of gene expression.92 ChIP experiments demonstrate that histones H3 and H4 undergo progressively greater hypoacetylation accompanied by histone hypermethylation marks that are associated with gene silencing. It is interesting to note that some of the methylation changes (H3K9Me2, H3K27Me3) occur along the entire exon 192; while others (H3K9Me3 and H4K20Me3) occur focally around the tri-nucleotide repeat expansion.89,93 Later, aberrant DNA methylation takes place at CpG residues within CGG repeats and spreads to the upstream promoter region,92 preventing the binding of transcription factors such as α-PAL/nuclear respiratory factor 1 (NRF1), that are required for FMR1 expression.94,95

HDAC inhibitors as in FRDA have been tested for their ability to rescue expression at the FMR1 locus. Results have varied. Trichostatin A (TSA), a pan-inhibitor for HDAC classes I-II, was able to rescue the expression of a thymidine kinase TK-(CGG)n reporter in Xenopus oocytes96; however, TSA, as well as the pan-inhibitors valproate and butyrate, showed only minimal success in reactivating the FTR1 gene in FXS patients’ lymphoblastoid cells.97,98 Notably, better results were obtained with the class III inhibitor nicotinamide compared to class I-II inhibitors, suggesting that sirtuins are the preferential HDACs for the FMR1 locus.99 Interestingly, when 5-azadeoxycytidine – a DNA methylation inhibitor – was combined with HDAC inhibitors, a much greater rescue on FMR1 transcription was observed.97 Altogether, these results suggest that DNA methylation rather than histone deacetylation may be the primary epigenetic mechanism to cause repression at this locus.

Fragile X tremor ataxia syndrome

Fragile X tremor ataxia syndrome (FXTAS) is a late onset neurodegenerative disorder characterized by global brain atrophy, progressive gait ataxia, tremor, dementia, and neuropsychological deficits.100 FXTAS is related to FXS in that it also results from a pathogenic GAA expansion in the FMR1 gene. However, while in FXS the expansion exceeds 200 repeats, the number of GAA repeats in the context of FXTAS is limited to 55–200 units. Unlike the full mutation in FXS, this smaller expansion – known as “pre-mutation” – does not induce FMR1 gene silencing. On the contrary, the premutated gene is transcribed at 2- to 10-fold higher levels than the normal allele.101 As a consequence, expanded FMR1 transcript accumulates within the nucleus where it sequesters important RNA-binding proteins such as heterogeneous nuclear ribonucleoprotein (hnRNP) A2/B1, purine-rich single-stranded DNA-binding protein π (PUR-π), Src-associated substrate in mitosis 68 (SAM68), and DiGeorge syndrome critical region 8 (DGR8).102–105 This RNA toxic gain-of-function mechanism is believed to trigger neurodegeneration in FXTAS.

Recent evidence suggests that alteration in chromatin structure at the FMR1 locus rather than increased RNA stability is the main cause for enhanced expression of the premutated gene. Indeed, ChIP experiments on both lymphoblastoid cell lines and fibroblasts from premutation carriers and FXTAS patients have highlighted increased levels of acetylated H3K9 and H4 in the regions directly surrounding the CGG repeats.106 Consistent with this model, pharmacologic inhibition of HATs was shown to decrease FMR1 expression in lymphoblastoid lines from premutation carriers.106 Furthermore, the overexpression of several HDACs (HDAC 3, 6, and 11) was able to suppress the accumulation of (CGG)90-eGFP mRNA and rescue neurodegeneration in a fly model of FXTAS.106 These results suggest that the treatment strategy in FXTAS – unlike FXS – would be to increase HDAC activity rather than suppress it by inhibitors.
Reversing gene silencing at a specific locus by decreasing HDAC activity

Besides the aforementioned diseases, there are others where HDACs are not implicated in silencing at a gene locus per se; yet inhibiting HDACs can promote the expression of a protein with translational potential. Spinal muscular atrophy (SMA) and Niemann Pick type C (NPC) are two such examples.

Spinal muscular atrophy

SMA is a pediatric neuromuscular disorder characterized by the destruction of z-motor neurons in the anterior horn of the spinal cord and subsequent system-wide muscle wasting. SMA is caused by insufficient levels of the protein SMN (survival motor neuron), a protein implicated in pre-mRNA splicing, mRNA transport, and axonal growth.

In humans, two genes encode for SMN: the telomeric survival motor neuron 1 (SMN1) gene and its centromeric paralog survival motor neuron 2 (SMN2). In SMA, SMN1 is disrupted by either homozygous deletions or nonsense mutations. Thus, in the disease state SMN levels are determined entirely by SMN2 activity. However, over evolution a single-nucleotide substitution has affected the splicing of exon 7 at the SMN2 locus, resulting in reduced levels of functional SMN. Since SMN2 copy number differs in the population (ranging from 1 to 5 copies), the severity of the disease inversely correlates with this variable and the relative SMN amount. Thus, a tantalizing strategy for improving the disease might be to increase SMN protein levels from the SMN2 locus.

Detailed ChIP analysis of the SMN2 promoter in embryonic and adult mouse tissues have revealed that SMN2 expression is downregulated during development by HDAC1-2 activity through the deacetylation of histones H3 and H4 in the vicinity of the transcriptional start site.

Several inhibitors of class I and II HDACs (including butyrate, valproate, phenyl-butyrate, and vorinostat) have proved effective in upregulating SMN2 expression in fibroblasts from SMA patients. In a study employing a motor neuron-derived cell line, vorinostat and valproate enhanced SMN2 promoter activity by increasing histone H3 and H4 acetylation in its upstream regions. HDAC inhibitors can activate SMN2 expression in SMA mice as well, with TSA and vorinostat causing an increase in SMN2 transcript and SMN protein levels in neural and muscle tissues associated with improved survival, weight loss, and motor behavior.

Valproate has been tested on both pediatric and adult SMA patients with mixed results. Four initial open label trials highlighted a potential benefit for strength and motor function. However, a subsequent phase II trial failed to show significant improvement in SMA children. Also, a double-blind phase III trial in ambulatory SMA adults failed to shown any significant results. Another randomized placebo-controlled phase III trial of valproate is in the recruiting phase.

Niemann-Pick type C

This disease is characterized by aberrant lipid accumulation in the endosomal/lysosomal compartment leading to progressive neurological degeneration. Together with Niemann Pick Types A and B, NPC is part of a group of inherited disorders whose phenotypes are classified based upon the organs involved and the age of onset. NPC is caused by missense mutations in NPC1 and NPC2 genes (95% and 5% of cases, respectively), encoding lysosomal proteins – NPC1 and NPC2, respectively – that bind cholesterol and promote its transfer to other cell membranes. Studies on patient fibroblasts carrying the most common NPC mutation (NPC1I1061T) have shown that the mutated protein is retained in the endoplasmic reticulum and is subjected to proteosomal degradation. This results in an 85% reduction in protein levels. Remarkably, the mutant protein is still functional, as evidenced by the finding that overexpression of NPC1I1061T is able to restore cholesterol trafficking in fibroblasts, suggesting that an effective strategy might well be to promote the expression of just the mutant protein.

Since NPC1 expression depends on histone acetylation, attempts have been made to increase NPC1 levels by HDAC inhibitors. Experiments in vitro using fibroblasts from human patients show that panobinostat, TSA, butyrate, and vorinostat – and the more selective class I inhibitor thiophene benzamide – can promote NPC1 expression and correct cholesterol accumulation. NPC2 appears to be less amenable to HDAC inhibition. Nevertheless, since 95% of Niemann Pick patients have a mutation in NPC1, a phase I study has been started with the HDAC inhibitor vorinostat in this patient population.

Histone acetylation and HDAC involvement at multiple loci across the genome

Another mode of transcriptional dysregulation consists in an HDAC-dependent transcriptional misregulation of genes other than the gene bearing the mutation. The mechanism of transcriptional derangements is thought to
occur because of a build up of mutant protein that tends to cause transcriptional repression by a “gain of function” mechanism. Polyglutamine diseases are exemplars of this mechanism.

**Polyglutamine diseases**

Polyglutamine disorders are a group of nine neurodegenerative syndromes where a cytosine, alanine and guanine (CAG) nucleotide expansion in the protein-coding region of the culprit gene causes a pathogenic glutamine repeat. These diseases have several features in common including a typical midlife delayed onset and a tendency for the repeat tract to expand on transmission to offspring, causing more severe disease and earlier onset over generations. The proteins that carry polyglutamine mutations are otherwise unrelated; they include huntingtin in Huntington’s disease, ataxins 1, 2, 3, and 7 in the respective numbered spinocerebellar ataxia (SCA) syndromes, z1A calcium channel subunit in SCA6, TATA-binding protein (TBP) in SCA17, androgen receptor (AR) in spinal bulbar muscular atrophy (SBMA), and atrophin-1 in dentatorubropallidoluysian atrophy (DRPLA). Even though the proteins involved and indeed the neuronal populations can be quite distinct, there are many similarities at a molecular level. There is a growing theme, for instance, of altered clearance and build up of mutant proteins that lead to toxicity. This build up was first noticed by the evidence of protein aggregates or inclusions. Although the role of inclusions is still debated, the consensus in the field is that the polyglutamine disease belongs to the broader class of protein misfolding diseases where the misfolded proteins defy clearance by the normal chaperone assisted degradation systems, be they proteasomal or lysosomal, to cause toxicity by a gain-of-function mechanism.

Even though we do not yet know how pathogenesis ensues, one compelling mechanism is transcriptional misregulation stemming from alteration in histone acetylation. The evidence for this is compelling. First, all the disease-causing polyglutamine proteins are either transcriptional activators or repressors or indirectly involved with gene expression (see Table 3). In many of the polyglutamine diseases, HATs such as CREB-binding protein (CBP), PCAF, and GCN5 (a component of the STAGA complex),

### Table 3. Role and interactors of the polyglutamine proteins.

| Disease | Protein | Role | Interactors | References |
|---------|---------|------|-------------|------------|
| Huntington’s disease | Huntingtin | Transcriptional repressor | Specificity protein 1 (SP1), transcription initiation factor II 130 kDa (TAFII130), CREB-binding protein (CBP), p53, SIN3A, RE1-silencing transcription factor (REST), nuclear receptor co-repressor (NCoR), nuclear factor kb (NF-kb), methyl-CpG-binding protein 2 (MeCP2), p300 | 218, 120, 219, 220, 221, 222, 223 |
| SCA1 | Ataxin-1 | Transcriptional repressor | Silencing mediator for retinoid or thyroid-hormone receptor (SMRT), nuclear receptor corepressor (NCoR), SIN3A, growth factor independent 1 (GFI1), Tat-interactitve protein 60 kDa (TIP60), capicua (CIC), leucine-rich acidic nuclear protein (LANP), ubiquilin 4 | 224, 225, 226, 227, 228, 229 |
| SCA2 | Ataxin-2 | Translation regulator | Ataxin 2-binding protein 1 (A2BPL), transactive response DNA-binding protein 43 kDa (TDP-43), DEAD/H box RNA helicase (DDX6), poly-adenylate-binding protein cytoplasmic 1 (PABPC1) | 230, 231, 232, 233 |
| SCA3 | Ataxin-3 | Transcriptional repressor | Forkhead box O4 (FOXO4), transcription initiation factor II 130 kDa (TAFII130), nuclear receptor corepressor (NCoR), radiation-sensitive 23 (RAD23), CREB-binding protein (CBP) | 234, 235, 236, 237, 137 |
| SCA7 | Ataxin-7 | Transcriptional repressor | Cone-rod homeobox (CRX), R85, general control nonderepressible 5 (GCN5) | 238, 239, 140 |
| SCA6 | z1A | Transcription factor | cAMP response element-binding protein (CREB) | 240 |
| SCA17 | TBP | Transcription factor | Transcription factor IIβ (TFIIβ), nuclear factor Y (NFY), TATA-binding protein-associated factor 172 (TAF-172) | 241, 242 |
| SBMA | AR | Transcription factor | p160, p300, transcription factor IIβ (TFIIβ), TBP, β-catenin | 243, 244, 245, 246 |
| DRPLA | Atrophin-1 | Transcriptional repressor | SIN3A, eight twenty-one/myeloid translocation gene (ETOMTG), G9a, Nedd-4, CREB-binding protein (CBP) | 247, 248, 249, 139 |

SCA, spinocerebellar ataxia; SBMA, spinal bulbar muscular atrophy; DRPLA, dentatorubropallidoluysian atrophy.
transcription coactivator complex) are sequestered from their normal functions.\textsuperscript{136–140} Furthermore, in some instances, polyglutamine proteins can inhibit HAT activity by masking the access of HATs to their histone substrates through direct interactions with histones.\textsuperscript{141–144}

Several attempts have been made to pharmacologically reverse hypoacetylation of downregulated genes by inhibiting HDAC activity (see Table 4). So far, phase II trials have been encouraging. Low doses of phenyl-butyrate have been shown to correct transcriptional abnormalities in the blood of Huntington’s disease patients\textsuperscript{145} and increase the renal excretion of potentially neurotoxic indole metabolites as seen in a recent phase II study on individuals with early symptomatic Huntington’s disease.\textsuperscript{146} This last finding might represent a secondary therapeutic effect of phenyl-butyrate in addition to its HDAC inhibition activity.

It is interesting to note that genetic rescue of different HDACs using haploinsufficiency has been tested for HDAC3 in SCA1,\textsuperscript{147} and HDACs 3, 4, and 7 in the case of Huntington’s disease.\textsuperscript{148,149} Only haploinsufficiency of HDAC4 was able to improve the phenotype in the context of Huntington’s disease mouse models.\textsuperscript{150} It should be pointed out that, haploinsufficiency at the genomic locus,

### Table 4. Pharmacologic HDAC inhibition of polyglutamine diseases.

| Disease model                  | HDAC inhibitor          | Outcome                                                                 | References |
|-------------------------------|-------------------------|-------------------------------------------------------------------------|------------|
| Huntington’s disease          |                         |                                                                         |            |
| Httex1p Q93 fly               | Vorinostat, butyrate    | Reduced photoreceptor neuron degeneration, increased viability         | 223        |
| R6/2 mouse                    | Vorinostat              | Improved motor functions                                               | 250        |
| Htt 150Q                      | TSA                     | Reduced neuronal degeneration                                           | 251        |
| \textit{Caenorhabditis elegans}|                         |                                                                         |            |
| R6/2 mouse                    | Phenyl-butyrate         | Rescue of transcriptional aberrancies                                   | 252        |
| Httex1p Q93 fly               | Sirtinol, nicotinamide, | Reduced photoreceptor neuron degeneration                               | 253        |
|                               | niacin, butyrate        |                                                                         |            |
| N171-82Q mouse                | Valproate               | Extended survival, improved motor functions                           | 254        |
| R6/1 mouse                    | Nicotinamide            | Improved motor functions, increased BDNF brain levels                  | 255        |
| R6/2 mouse                    | Butyrate                | Extended survival, improved body weight and motor performance, delayed  | 256        |
|                               |                         | neuropathological features                                             |            |
| N171-82Q mouse                | Phenyl-butyrate         | Extended survival, decreased brain atrophy                             | 257        |
| R6/2 mouse                    | 4b                      | Ameliorated alterations in gene expression, improved motor performance, | 212        |
|                               |                         | overall appearance, and body weight                                    |            |
| N171-82Q mouse, Httex1p Q93   | 4b, 136, 233, 971, 974  | Rescue of transcriptional aberrancies, reduced photoreceptor neuron    | 258        |
| R6/2 mouse, Httex1p Q93 fly   | SAHA                    | Reduced aggregate load and restoration of Bdnf transcript levels        | 259        |
| N171-82Q mouse                | 4b                      | Prevention of body weight loss, improved motor functions, reduced     | 260        |
|                               |                         | cognitive decline, prevention of aggregate formation in the brain     |            |
| N171-82Q mouse, YAC128 mouse  | Valproate               | Improved motor functions and decreased depressive behaviors            | 261        |
| Httex1p Q93 fly, Htt 150Q C.  | AGK2, AK-1              | Reduced photoreceptor neuron degeneration, improved in touch response  | 262        |
| \textit{elegans}              |                         |                                                                         |            |
| R6/2 mouse, 140Q knock-in     | AK-7                    | Improved motor function, extended survival, reduced brain atrophy,     | 263        |
| Htt mouse                     |                         | reduced brain aggregates                                               |            |
| SCA3                          | Butyrate                | Delayed disease onset, extended survival, improved neurological        | 264        |
|                               |                         | phenotype, reduced gene repression                                    |            |
| ATXN3-79Q mouse               | Butyrate                | Extended survival, alleviated climbing disability, reduced photoreceptor | 265        |
|                               |                         | neuron degeneration                                                    |            |
| ATXN3-78Q fly                 | Valproate               | Prevention in long-term depression (LTD) induction impairment           | 266        |
| ATXN3-79Q mouse               | Butyrate                | Improved motor functions, improved neuropathological phenotype        | 267        |
| SBMA                          | Butyrate                | Extended survival, improved motor function                             | 268        |
| AR-97Q mouse                  |                         |                                                                         |            |
| DRPLA                         | Butyrate                |                                                                         |            |

HDAC, histone deacetylase; SCA, spinocerebellar ataxia; SBMA, spinal bulbar muscular atrophy; DRPLA, dentatorubral pallidoluysian atrophy.
does not always translate into a 50% reduction in protein levels—possibly on account of compensatory mechan-
isms. In these mice, complete null phenotypes die either as embryos or in early perinatal life. But even a
complete knockdown where it can be achieved with mini-

imal neuronal side effects—as was done with HDAC6 and
SIRT2—does not rescue the polyglutamine phenotype as
seen in the context of the R6/2 Huntington’s disease
to study, one must admit that genetic studies
are not the same as pharmacological studies where the
dosages and length of duration of drugs can be altered.

Nevertheless, the relative genetic lack of amelioration does
raise the possibility that HDAC inhibitors might have off-
target beneficial effects as well.

Nonhistone substrates and additional role
for HDACs

As mentioned earlier, HDACs also deacetylate proteins
other than histones, thus playing a broader role in cell
biology. The most relevant to neurodegeneration is tubu-
lin deacetylation mediated by HDAC6 and SIRT2 that
modulates the properties of microtubules. It appears that
acetylation at a conserved lysine K40 on tubulin must be
tightly regulated for movement of organelles mediated by
the molecular motors kinesin and dynein. Undoubt-
edly, this is especially important for neurons that must
transport cargo along long distances. Indeed, increasing
tubulin acetylation by drugs that inhibit HDAC6 and
SIRT2 activity (tubacin and nicotinamide, respectively)
improves axonal transport in primary neurons and pre-

vents colchicine-induced axonal degeneration. For this
reason, such an approach has been tried in neurode-
genator disorders that affect neurons with particularly
long neurites, especially considering that a reduction in
acetylated α-tubulin levels is one of their pathological
hallmarks. Some of the best examples involve dis-
erases where long neurons are affected such as Charcot-
Marie-Tooth disorders (CMT) and amyotrophic lateral

sclerosis (ALS).

CMT disease

CMT is the term given to a group of genetic diseases that
affect the peripheral nervous system to cause progressive
distal muscle weakness and atrophy associated with
sensory problems. More than 40 genes have been
linked to CMT that can follow a pattern of autosomal
dominant, autosomal recessive, or X-linked inheritance.
Despite the genetic heterogeneity, pathogenicity converges
on defects in cytoskeletal dynamics and axonal transport
of peripheral neurons. The role of tubulin acetylation has
been recently addressed in a mouse model of CMT-
expressing mutant HSPB1—one of the 27 kDa small heat

shock proteins—that recapitulates several features of the
CMT phenotype including severe axonal transport defects
coupled with reduced levels of acetylated α-tubulin. The
treatment of primary dorsal root ganglia (DRG) neu-
rons from these mice with either TSA or the HDAC6-spe-
cific inhibitors tubacin and tubastatin A restored the
number of total mitochondria and increased those that
move along axons. Remarkably, in vivo administration of
TSA or tubastatin A to symptomatic mice rescued axo-
nal transport defects via increasing acetylated α-tubulin
levels in peripheral nerves and promoting muscle reinnerv-
ation as well.

Amyotrophic lateral sclerosis

ALS, a devastating progressive neurodegenerative disorder,
is characterized by muscle weakness, fasciculations, and
spasticity leading ultimately to death. Affecting both
upper and lower motor neurons, axonal transport defects
are highly relevant to pathogenesis. Besides sporadic
ALS, a growing number of ALS-genes have been identified
including superoxide dismutase 1 (SOD1), optineurin
(OPT), ubiquilin 2 (UBQLN2), chromosome 9 open reading
frame 72 (C9orf72), TAR DNA-binding protein (TARDBP),
fused in sarcoma (FUS), angiogenin (ANG), amyotrophic lateral sclerosis 2 (ALS2), and senataxin
(SETX). Most of the work testing the role of tubu-
lin acetylation in ALS has been conducted in SOD1G93A
mice that represent the best studied model of familial
ALS. Genetic ablation of HDAC6 positively affected the
levels of acetylated tubulin in the central and peripheral
nervous system and maintained motor axon integrity.
There was a significant increase in the compound muscle
action potential (CMAP) and an improvement in the
number of quantified neurons in the ventral horn of the
spinal cord, along with a significant improvement in
survival. Even though SIRT2 shares the ability to de-
acetylate tubulin in vitro, it does not appear to play a role
in ALS, given that genetically depleting both copies of
SIRT2 in SOD1G93A mice did not change either tubulin
acetylation levels or ALS phenotype, suggesting that
HDAC6 is the principal tubulin deacetylating enzyme of
the nervous system in vivo.

It is interesting to note that the pan-HDAC inhibitors
TSA or sodium phenylbutyrate ameliorated motoneuron
death and axonal degeneration and enhanced motor func-
tions in the SOD1G93A mouse model. This could be
occurring via beneficial effects on gene transcription as
described for the polyglutamine diseases or axonal trans-
port through its effect on tubulin acetylation. In recent
phase II studies, phenyl-butyrate was demonstrated
safe and able to increase histone acetylation in blood of
ALS patients at low dosage,\textsuperscript{170} while valproic acid was also found safe, but showed no beneficial effects on survival or disease progression.\textsuperscript{171} 

**Alzheimer’s, Parkinson’s diseases and polyglutamine diseases**

Given the importance of axonal transport to all neurons, it is likely that modulating tubulin acetylation might be an approach to other disorders of the nervous system. For instance, in Alzheimer’s disease (AD) the HDAC6-specific inhibitor tubastatin A was shown to recover mitochondrial axonal transport in primary hippocampal neurons exposed to the neurotoxic Aβ-peptide\textsuperscript{172} and impressively was also effective in rescuing cognitive deficits and reducing tau levels in a mouse model of AD (rTg4510 mice).\textsuperscript{173} HDAC6 null mutations were demonstrated to correct tau-induced microtubule defects in a fly model as well.\textsuperscript{174} Genetic depletion supports these pharmacological studies, given that complete knockout of HDAC6 restored learning and memory in a severe AD model (APPPS1-21 mice) by rescuing axonal transport.\textsuperscript{175} However, the beneficial effects of depleting HDAC6 might not just stem from its action on microtubules per se, but also from its effects on tau, which, once acetylated, is protected from pathogenic hyperphosphorylation and aggregation.\textsuperscript{176}

In Parkinson’s disease (PD), broad HDAC inhibitors rescue α-synuclein-dependent cytotoxicity both in cellular and fly models of the disease.\textsuperscript{177} They also alleviate motor deficits and attenuate depletion of striatal dopaminergic neurons in PD mouse models —be they neurotoxic (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-, rotenone- and 6-hydroxydopamine-induced) or genetic (A30P–A53T α-synuclein double transgenic mice).\textsuperscript{178–181} Given that alterations in axonal transport have been observed in PD models, these beneficial effects are likely to occur also via inhibition of HDAC6 — although HDAC6 has yet to be tested directly.

In this context, it is possible that the beneficial effects of HDAC inhibition discussed earlier in polyglutamine disease also occur to some extent because of an improvement in axonal transport mediated by HDAC6 inhibition. Indeed, tubacin ameliorates axonal transport of brain-derived neurotrophic factor (BDNF) in primary striatal neurons from HdhQ109 knock-in mice.\textsuperscript{157} However, inhibiting HDAC6 in the context of misfolding disorders appears to be a double edged sword, given that HDAC6 binds both ubiquitinated proteins and dynein motors, facilitating their transport to aggresomes.\textsuperscript{182} Moreover, HDAC6 promotes the formation of an actin-network via cortactin deacetylation, inducing aggresome-lysosome fusion for autophagic degradation.\textsuperscript{183} In addition, HDAC6 also plays a beneficial role in modulating the activity of the chaperone HSP90 via reversible acetylation.\textsuperscript{184} Thus, HDAC6 might prevent aberrant protein accumulation in the nervous system as demonstrated in a fly model of SBMA characterized by neuronal-mutant AR aggregates.\textsuperscript{185}

**Future Trends and Concluding Remarks**

HDACs appear to be important players in neurodegeneration. Surprisingly, despite their promise, the functions of HDACs in the nervous system have not been comprehensively studied. Although pharmacological HDAC inhibition is one way to learn about the functions of HDACs, genetic depletion studies, particularly in neurons, are probably easier to interpret, given that there are no confounding off-target effects — since even the most selective drugs are not absolute in their specificity.

This research program is still lagging. For instance, only recently, we have found that depleting HDAC3 in post-mitotic neurons can be quite deleterious.\textsuperscript{147} Our experiments were performed by deleting HDAC3 in Purkinje neurons and it is not clear at this point whether these neurons are more vulnerable to HDAC depletion than others. But it certainly suggests that deleting HDAC3 in some neuronal populations for a long period is likely to have side effects. It is important to perform similar experiments for additional neuronal populations and for all neuronal HDACs individually to see whether these are also essential for neuronal health. A by-product of these studies will be that we will learn about the genetic networks that are regulated by individual HDACs using RNA-seq or microarray experiments. These studies are still in their infancy. This is largely because time-consuming conditional approaches have to be used, given that most of the HDAC constitutive knockout mice are embryonic lethal (HDAC1, HDAC3, and HDAC7) or die within a few weeks after birth (HDAC2, HDAC4, HDAC8, and SIRT6).\textsuperscript{3,186} Those where HDACs have been depleted in neuronal tissues have often focused on early developmental stages that are not so applicable to insights into neurodegeneration (see Table 5). A thorough analysis of HDAC depletion in the adult nervous system should provide a reasonable idea of what to discern in terms of side effects and how they might be prevented. These studies then could be carefully interpreted in conjunction with cell-based mechanistic studies or in vivo studies manipulating HDAC levels in mice. For instance, conditional deletion studies in the adult brain have highlighted the opposite effects of class I and II HDACs on memory formation. Indeed, selective ablation of HDAC2 in the forebrain or HDAC3 focal deletion in the hippocampus
greatly improved cognitive performances in mice.\textsuperscript{187,188} In contrast, the selective knockout of HDAC4 in the forebrain impaired learning, memory formation, and long-term synaptic plasticity.\textsuperscript{189} The positive effects of HDAC4 on cognitive functions seem to be mediated via the repression of a specific set of genes encoding constituents of central synapses.\textsuperscript{190} Interestingly, although HDAC5 is closely related to HDAC4, its genetic ablation in the adult brain did not impair cognitive performances, but otherwise affected behavioral adaptations to chronic emotional stimuli.\textsuperscript{191} Similarly, ablation of HDAC6 in serotonin neurons blocked the expression of social avoidance in mice exposed to chronic social defeat.\textsuperscript{192} SIRT1-knockout mice exhibit impaired cognitive abilities associated with defects in synaptic plasticity.\textsuperscript{193} Moreover, SIRT1 is expressed in several hypothalamic regions controlling endocrine functions and feeding behaviors, as well as the regulation of circadian rhythmicity.\textsuperscript{194,195} A list of neuronal phenotypes for all knockout mice is shown in Table 6.

In addition, cell-based studies on primary neurons suggest that some HDACs regulate neuronal survival and death. For instance, HDAC1 can be either neuroprotective or neurotoxic, based on whether it interacts with HDAC9 or HDAC3.\textsuperscript{196} HDAC3 itself is highly neurotoxic, as demonstrated by overexpressing HDAC3 in cortical and granule neurons.\textsuperscript{197} Also the overexpression of class II HDAC5 in cerebellar granule neurons compromises their survival via transcriptional repression of MEF2.\textsuperscript{198} In contrast, overexpression of HDAC4 protects granule neurons from low potassium-induced apoptosis. HDAC4’s neuroprotective effects seem to be mediated through the inhibition of cyclin-dependent kinase 1 (CDK1) activity and cell cycle progression.\textsuperscript{199} Also, overexpressing HDAC9 was shown to rescue apoptosis in granule neurons. HDAC9’s anti-apoptotic activity is connected to the inhibition of c-jun via direct interaction with c-jun N-terminal kinase (JNK).\textsuperscript{200} Sirtuins play important functions in neuronal survival as well. Overexpression of SIRT1 and SIRT5 was shown to protect granule neurons from low potassium-induced apoptosis.

| Gene         | Experimental model                                                                 | Phenotype                                                                                                                                                                                                 | References |
|--------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| HDAC1/HDAC2  | HDAC1/HDAC2 conditional knockout mice (glial fibrillary acidic protein (GFAP)-Cre driver) | Abnormal Purkinje cell migration, blockade of neuronal differentiation, aberrant cell death in neuronal progenitors                                                                                      | 269        |
| HDAC1/HDAC2  | HDAC1/HDAC2 conditional knockout mice (Olig1-Cre driver)                            | Defects in oligodendrocytes differentiation                                                                                                                                                    | 270        |
| HDAC1/HDAC2  | HDAC1/HDAC2 conditional knockout mice (Wnt1-Cre driver)                             | Defects in neural crest cells differentiation                                                                                                                                         | 271        |
| HDAC4        | HDAC4 constitutive knockout mice                                                    | Purkinje cell death, duplication of Purkinje cell soma, defects in Purkinje cell arborization                                                                                                    | 199        |
| HDAC4        | P0 mouse retinas transfected with HDAC4-targeting shRNA vector by in vivo electroporation | Increased apoptosis of photoreceptors and interneurons during retinal development                                                                                                                  | 272        |
| HDAC5        | Primary mouse dorsal root ganglia (DRG) neurons infected with HDAC5-targeting shRNA lentivirus | Impaired axon regeneration                                                                                                                                   | 273        |
| HDAC6        | Primary mouse hippocampal neurons transfected with HDAC6-targeting shRNA vector    | Impaired axonal growth and axonal initial segment development                                                                                                                      | 274        |
| HDAC6        | Primary mouse cortical neurons treated with tubacin                                  | Impaired axon projections and dendritogenesis                                                                                                           | 275        |
| HDAC9        | Primary mouse cortical neurons transfected with HDAC9-targeting shRNA vector       | Increased dendrite length and more complex branching pattern                                                                                                                 | 276        |
| SIRT1        | Primary rat hippocampal neurons transfected with SIRT1-targeting siRNA            | Retarded axonal elongation and branching                                                                                                                                         | 277        |
| SIRT1        | Rat pheochromocytoma PC12 cell line transfected with SIRT1-targeting siRNA         | Reduced neurite outgrowth                                                                                                                                         | 278        |
| SIRT1        | Primary rat hippocampal neurons overexpressing the dominant negative SIRT1\textsuperscript{H363T} | Reduction in dendritic arbor complexity                                                                                                                                             | 279        |
| SIRT1        | Mouse neurospheres infected with SIRT1-targeting siRNA                            | Impaired neuronal differentiation                                                                                                                            | 280        |
| SIRT1        | Primary cortical neural progenitor cells (NPCs) from Sirt1 knockout mice           | Prevention of oxidation-mediated suppression of neurogenesis                                                                                                           | 281        |
| SIRT2        | Sirt2 conditional knockout mouse (myelin protein zero (MPZ)-Cre driver)            | Delay in myelination of peripheral nerves                                                                                                                                       | 282        |

HDACs, histone deacetylases.
Table 6. Neuronal phenotypes of HDAC knockout mice.

| Gene   | Cre line/construct                          | Cell type/Brain region                  | Phenotype                                                                 | References |
|--------|--------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------|------------|
| HDAC1  | AAV- synapsin 1 (Syn1)-HDAC1 (overexpression) | Hippocampus                             | Enhanced fear extinction learning                                         | 283        |
| HDAC2  | EIIa-Cre                                    | All neurons                             | Enhanced memory formation and associative learning, increased synaptic plasticity | 284        |
| HDAC2  | Nestin-Cre                                  | All brain                               | Decreased synaptic plasticity and memory formation                        | 284        |
| HDAC2  | Calcium/calmodulin-dependent protein kinase II (CaMKII)-Cre | Forebrain neurons                     | Enhanced hippocampal long-term potentiation (LTP), improved associative learning | 187        |
| HDAC3  | Purkinje cell protein 2 (PCP2)-Cre          | Purkinje neurons                        | Cell death                                                               | 147        |
| HDAC3  | AAV2/1-Cre                                  | Hippocampus (CA1)                       | Enhanced long-term memory                                               | 188        |
| HDAC3  | Nestin-Cre                                  | All neurons                             | Decrease in proliferation of adult neural stem cells                     | 285        |
| HDAC4  | Calcium/calmodulin-dependent protein kinase II (CaMKII)-Cre | Nucleus accumbens                     | Enhanced cocaine-context-associated memory formation                    | 286        |
| HDAC4  | HSV-HDAC4                                   | Nucleus accumbens                       | Impairment in long-term potentiation (LTP) induction, alteration in motor coordination and anxiety, deficits in learning | 189        |
| HDAC5  | Constitutive                                | Total brain                             | Hypersensitive responses to chronic cocaine or stress                     | 191        |
| HDAC6  | PC12 ETS domain-containing transcription factor 1 (Pet-1)-Cre | Serotonin neurons                     | Block in the expression of social avoidance induced by chronic social defeat, reduced anxiogenic effects of corticosterone | 192        |
| SIRT1  | Constitutive                                | Total brain                             | Abnormal emotional behaviors                                            | 288        |
| SIRT1  | Synapsin 1 (Syn1)-Cre                      | All neurons                             | Increased systemic insulin sensitivity, increased central insulin signaling in the hypothalamus | 289        |
| SIRT1  | Calcium/calmodulin-dependent protein kinase II (CaMKII)-SIRT1 (overexpression) | Striatum and hippocampus               | Impaired motor functions and lipid/glucose metabolism                   | 290        |
| SIRT1  | Constitutive                                | Total brain                             | Cognitive deficits, defects in synaptic plasticity, decrease in dendritic branching | 193        |
| SIRT1  | Nestin-Cre                                  | Total brain                             | Reduced oxidative brain damage and life span                            | 291        |
| SIRT1  | Nestin-Cre                                  | Hippocampus and subventricular zone     | Increased production of adult neural precursor                           | 292        |
| SIRT1  | Pro-opiomelanocortin (Pomc)-Cre            | Proopiomelanocortin neurons             | Hypersensitivity to diet-induced obesity due to reduced energy expenditure | 293        |
| SIRT1  | Proopiomelanocortin (Pomc)-Cre (overexpression) | Hypothalamus                         | Prevention of age-associated weight gain                                | 294        |
| SIRT1  | Neuron-specific enolase (NSE)-SIRT1 (overexpression) | All neurons                           | Reference memory deficits                                              | 295        |
| SIRT1  | Nestin-Cre                                  | Neural progenitors and neural stem cells  | Expansion of proliferating oligodendrocyte precursor cells, enhanced remyelination | 296        |
| SIRT1  | Nestin-Cre                                  | All neurons                             | Altered circadian rhythms                                              | 297        |
| SIRT1  | Nestin-Cre                                  | All neurons                             | Defects in somatotropic signaling, defects in the endocrine and behavioral responses to calorie-restriction | 298        |
induced apoptosis, while SIRT2, SIRT3, and SIRT6 over-expression promotes neuronal death.\textsuperscript{201} A thorough evaluation of HDAC function in the nervous system, particularly with a loss of function approach, would allow a better understanding of the potential side effects of these drugs and how best to avert them. Indeed, the gained knowledge could serve as a guide for designing HDAC inhibitors with improved selectivity, specificity, pharmacological properties (pharmacokinetics and dynamics), and with the least possible side effects. Alternatively, pulsed dosing to allow neurons to recover from side effects could be part of the treatment strategy.

Conflict of Interest

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