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REVIEW ARTICLE

The promise and perils of HDAC inhibitors in neurodegeneration

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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.

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 Zn^{2+} 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 multiunit complexes. The complexes they form vary. Thus, HDACs 1 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[8]; 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]

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).[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.[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.[22] At a subcellular level, HDAC6 is present predominantly in the cytosol functioning as a potent deacetylase of α-tubulin,[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 β-catenin.[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.[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; H1F1α 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.[29–34] Their cytoplasmic substrates include myeloproliferative leukemia oncogene (MPL) and DNAJB8 – both deacetylated by HDAC4, tripartite motif-containing protein 29 (TRIM29) and heat shock protein 70 (HSP70), substrates of HDAC9 and HDAC10, respectively.[34–37]

The Class III NAD^+-dependent HDACs – called sirtuins, because of their homology to the yeast ortholog silent information regulator 2 (SIR2)[38] – comprise seven mammalian sirtuins, all expressed in the brain.[39] SIRT 1, 2, 6, and 7 are found in both the cytoplasm and nucleus, while SIRT 3, 4, and 5 are found localized to the mitochondria.[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-1α).[42–45] SIRT2 deacetylates cytosolic transcription factor p65, a subunit of nuclear factor kB (NF-kB), thus indirectly regulating the expression of NF-kB-dependent genes.[46] Interestingly, SIRT2 overlaps with HDAC6 in its ability to deacetylate α-tubulin.[47]

SIRT 3, 4, and 5 determine the global lysine-acetylation level, especially in mitochondria.[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.[48–50] SIRT3 also regulates apoptosis by deacetylating nicotinamide phosphoribosyltransferase (NAMPT) and mitochondrial ribosomal protein L10 (MRPL10) in mitochondria and Ku70 in the nucleus.[51–53] SIRT4 has recently been shown to regulate lipid metabolism by deacetylating malonyl CoA decarboxylase (MCD).[54] SIRT5 on the other hand regulates the urea cycle by deacetylating carbamoyl phosphate synthetase 1 (CPS1).[55] SIRT6 deacetylates the C-terminal-binding protein (CtBP) interacting protein and the acetyl transferase general control nonderepressible 5 (GCN5).[56,57] SIRT7 increases cellular resistance to cytotoxic and oxidative stress through p53 deacetylation.[58]

The Class IV HDAC family consists solely of HDAC11.[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.[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, trancription-promoting conformation of chromatin. In addition, the residues themselves provide docking sites for transcription factors/activators including ATP-dependent chromatin modulators.[62] By keeping histones deacetylated, HDACs repress gene expression.[9] 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

Table 1. The HDAC superfamily.

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)
		HDAC8	377 amino acids	Nucleus/Cytosol	Mainly expressed in muscle	Structural maintenance of chromosomes 3 (SMC3)
IIa	Zn^{2+}	HDAC4	1084 amino acids	Nucleus/Cytosol	Cortex, amigdala, hippocampus, locus coeruleus	p53, runt-related transcription factor 2 (RUNX2), myeloproliferative leukemia oncogene (MPL), DNAJB8
		HDAC5	1122 amino acids	Nucleus/Cytosol	Widely expressed	GATA1
		HDAC7	952 amino acids	Nucleus/Cytosol	Amigdala, hippocampus, substantia nigra pars compacta, locus coeruleus	H1F1α
		HDAC9	1011 amino acids	Nucleus/Cytosol	Hippocampus, substantia nigra pars compacta	Tripartite motif-containing protein 29 (TRIM29)
IIb	Zn^{2+}	HDAC6	1215 amino acids	Cytosol	Hippocampus, locus coeruleus	α-tubulin, heat shock protein 90 (HSP90), cortactin, β-catenin
		HDAC10	669 amino acids	Nucleus/Cytosol	Amigdala, hippocampus	Paired box 3 (Pax3), KRAB-associated protein-1 (KAP1), heat shock protein 70 (HSP70)
III	NAD^{+}	SIRT1	747 amino acids	Nucleus	Cortex, hippocampus, cerebellum, hypothalamus	TBP-associated factor 68 (TAF68), p53, p300, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)
		SIRT2	389 amino acids	Cytosol	Oligodendrocytes, olfactory neurons, hippocampus	p65, α-tubulin
		SIRT3	399 amino acids	Mitochondria	To be determined	Acetyl-coenzyme A synthase 2 (ACS2), glutamate dehydrogenase (GLDH), Isocitrate Dehydrogenase 2 (IDH2), electron-transport complex I, Nicotinamide phosphoribosyltransferase (NAMPT), mitochondrial ribosomal protein L10 (MRPL10), Ku70
		SIRT4	314 amino acids	Mitochondria	To be determined	Malonyl CoA decarboxylase (MCD)
		SIRT5	310 amino acids	Mitochondria	Cortex (layer II)	Carbamoyl phosphate synthetase 1 (CPS1)
		SIRT6	355 amino acids	Nucleus	To be determined	C-terminal-binding protein (CtBP) interacting protein, general control nonderepressible 5 (GCN5)
		SIRT7	400 amino acids	Nucleolus	To be determined	p53
IV	Zn^{2+}	HDAC11	347 amino acids	Nucleus	Widely distributed	To be determined

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.[63–65] 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.[66–68]

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[69]; 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.[70–75] These changes are accompanied by other epigenetic processes that interfere with transcription – in particular tri-methylation of histone lysine residues (including H3K9 and H3K27)[76]; enhanced cytosine methylation in the CpG residues in the DNA region upstream of the expanded triplet (as demonstrated by sodium bisulfite sequencing[72]); increased expression of a frataxin antisense transcript (FAST1) that promotes the spreading of DNA methylation (by decreasing the binding of the CTCF protein)[77]; and finally non-canonical structures subsumed by the locus itself because of the trinucleotide expansion.[75] 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%.[78] 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.[71] These inhibitors have shown promise in two FRDA models, given that they increase *FXN* expression in the brain and ameliorate the disease phenotype.[79,80] Since the inhibitors tend to target HDAC3[81] 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.[82] 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 FXN silencing, given that the sirtuin inhibitor nicotinamide increases histone H3 and H4 acetylation, decreases H3K9 and H3K27 trimethylation, and reverses the silencing at the *FXN* locus.[84] A recently concluded phase II clinical trial for nicotinamide corroborated this evidence by showing that daily doses induce a sustained upregulation of FXN expression along with reduced heterochromatin modifications at the *FXN* 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 metabolism[86] – is not expressed. Also unlike FRDA, the FXS expansion is a CGG expansion (not a GAA expansion) and occurs in the part of the gene encoding 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 1[92]; while others (H3K9Me3 and H4K20Me3) occur focally around the trinucleotide 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* oocytes[96]; 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-azadeocytidine – 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 excedes 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 α (PUR-α), Src-associated substrate in mitosis 68 (SAM68), and DiGeorge syndrome critical region 8 (DGCR8).[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 α-motor neurons in the anterior horn of the spinal cord and subsequent system-wide muscle wasting.[107] 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.[108,109]

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.[110] 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.[107]

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.[111]

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.[112–114] 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.[111] 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.[115,116]

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.[117–120] However, a subsequent phase II trial failed to show significant improvement in SMA children.[121,122] Also, a double-blind phase III trial in ambulatory SMA adults failed to shown any significant results.[123] Another randomized placebo-controlled phase III trial of valproate is in the recruiting phase (registered at ClinicalTrials.gov with identifier number NCT01671384).

Niemann-Pick type C

This disease is characterized by aberrant lipid accumulation in the endosomal/lysosomal compartment leading to progressive neurological degeneration.[124] 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.[125] NPC is caused by missense mutations in *NPC1* and *NPC2* genes (95% and 5% of cases, respectively),[126] encoding lysosomal proteins – NPC1 and NPC2, respectively – that bind cholesterol and promote its transfer to other cell membranes.[127,128] Studies on patient fibroblasts carrying the most common NPC mutation ($NPC1^{I1061T}$) 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.[129] Remarkably, the mutant protein is still functional, as evidenced by the finding that overexpression of $NPC1^{I1061T}$ is able to restore cholesterol trafficking in fibroblasts,[129] 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.[130,131] NPC2 appears to be less amenable to HDAC inhibition.[131] 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 (registered at ClinicalTrials.gov with identifier number NCT02124083).

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 examplars 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.[132–135] 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, α1A 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 similiaries 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

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-interactive 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 (A2BP1), 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	α1A	Transcription factor	cAMP response element-binding protein (CREB)	240
SCA17	TBP	Transcription factor	Transcription factor IIB (TFIIB), nuclear factor Y (NFY), TATA-binding protein-associated factor 172 (TAF-172)	241, 242
SBMA	AR	Transcription factor	p160, p300, transcription factor IIF (TFIIF), TBP, β-catenin	243, 244, 245, 246
DRPLA	Atrophin-1	Transcriptional repressor	SIN3A, eight twenty-one/myeloid translocation gene (ETO/MTG), 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.[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.[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[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.[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,[147] and *HDACs* 3, 4, and 7 in the case of Huntington's disease.[148,149] Only haploinsufficiency of *HDAC4* was able to improve the phenotype in the context of Huntington's disease mouse models.[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
Htn 150Q *Caenorhabditis elegans*	TSA	Reduced neuronal degeneration	251
R6/2 mouse	Phenyl-butyrate	Rescue of transcriptional aberrancies	252
Httex1p Q93 fly	Sirtinol, nicotinamide, niacin, butyrate	Reduced photoreceptor neuron degeneration	253
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 neurpathological features	256
N171-82Q mouse	Phenyl-butyrate	Extended survival, decreased brain atrophy	257
R6/2 mouse	4b	Ameliorated alterations in gene expression, improved motor performance, overall appearance, and body weight	212
R6/2 mouse, Httex1p Q93 fly	4b, 136, 233, 971, 974	Rescue of transcriptional aberrancies, reduced photoreceptor neuron degeneration	258
R6/2 mouse	SAHA	Reduced aggregate load and restoration of Bdnf transcript levels	259
N171-82Q mouse	4b	Prevention of body weight loss, improved motor functions, reduced cognitive decline, prevention of aggregate formation in the brain	260
N171-82Q mouse, YAC128 mouse	Valproate	Improved motor functions and decreased depressive behaviors	261
Httex1p Q93 fly, Htn 150Q *C. elegans*	AGK2, AK-1	Reduced photoreceptor neuron degeneration, improvement in touch response	262
R6/2 mouse, 140Q knock-in Htt mouse	AK-7	Improved motor function, extended survival, reduced brain atrophy, reduced brain aggregates	263
SCA3			
ATXN3-79Q mouse	Butyrate	Delayed disease onset, extended survival, improved neurological phenotype, reduced gene repression	264
ATXN3-78Q fly	Valproate	Extended survival, alleviated climbing disability, reduced photoreceptor neuron degeneration	265
ATXN3-79Q mouse	Butyrate	Prevention in long-term depression (LTD) induction impairment	266
SBMA			
AR-97Q mouse	Butyrate	Improved motor functions, improved neuropathological phenotype	267
DRPLA			
ATN1-118Q mouse	Butyrate	Extended survival, improved motor function	268

HDAC, histone deacetylase; SCA, spinocerebellar ataxia; SBMA, spinal bulbar muscular atrophy; DRPLA, dentatorubropallidoluysian atrophy.

does not always translate into a 50% reduction in protein levels – possibly on account of compensatory mechanisms.[147,148] In these mice, complete null phenotypes die either as embryos or in early perinatal life.[3] But even a complete knockdown where it can be achieved with minimal neuronal side effects – as was done with HDAC6 and SIR2 – does not rescue the polyglutamine phenotype as seen in the context of the R6/2 Huntington's disease mouse model.[151,152] 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 tubulin 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.[153] Undoubtedly, 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 prevents colchicine-induced axonal degeneration.[154,155] For this reason, such an approach has been tried in neurodegenerative disorders that affect neurons with particularly long neurites, especially considering that a reduction in acetylated α-tubulin levels is one of their pathological hallmarks.[156,157] Some of the best examples involve diseases 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.[158] More than 40 genes have been linked to CMT that can follow a pattern of autosomal dominant, autosomal recessive, or X-linked inheritance.[159] Despite the genetic heterogeneity, pathogenicity converges on defects in cytoskeletal dynamics and axonal transport of peripheral neurons.[160] 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.[161] The treatment of primary dorsal root ganglia (DRG) neurons from these mice with either TSA or the HDAC6-specific inhibitors tubacin and tubastatin A restored the number of total mitochondria and increased those that move along axons.[161] Remarkably, *in vivo* administration of TSA or tubastatin A to symptomatic mice rescued axonal transport defects via increasing acetylated α-tubulin levels in peripheral nerves and promoting muscle reinnervation as well.[161]

Amyotrophic lateral sclerosis

ALS, a devastating progressive neurodegenerative disorder, is characterized by muscle weakness, fasciculations, and spasticity leading ultimately to death.[162] Affecting both upper and lower motor neurons, axonal transport defects are highly relevant to pathogenesis.[163] 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*).[164–166] Most of the work testing the role of tubulin acetylation in ALS has been conducted in $SOD1^{G93A}$ 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.[167] Even though SIRT2 shares the ability to deacetylate tubulin *in vitro*, it does not appear to play a role in ALS, given that genetically depleting both copies of *SIRT2* in $SOD1^{G93A}$ 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*.[167]

It is interesting to note that the pan-HDAC inhibitors TSA or sodium phenylbutyrate ameliorated motoneuron death and axonal degeneration and enhanced motor functions in the $SOD1^{G93A}$ mouse model. This could be occurring via beneficial effects on gene transcription as described for the polyglutamine diseases or axonal transport through its effect on tubulin acetylation.[168,169] In recent phase II studies, phenyl-butyrate was demonstrated safe and able to increase histone acetylation in blood of

ALS patients at low dosage,[170] while valproic acid was also found safe, but showed no beneficial effects on survival or disease progression.[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[172] and impressively was also effective in rescuing cognitive deficits and reducing tau levels in a mouse model of AD (rTg4510 mice).[173] *HDAC6* null mutations were demonstrated to correct tau-induced microtubule defects in a fly model as well.[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.[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.[176]

In Parkinson's disease (PD), broad HDAC inhibitors rescue α-synuclein-dependent cytotoxicity both in cellular and fly models of the disease.[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).[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.[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.[182] Moreover, HDAC6 promotes the formation of an actin-network via cortactin deacetylation, inducing aggresome-lysosome fusion for autophagic degradation.[183] In addition, HDAC6 also plays a beneficial role in modulating the activity of the chaperone HSP90 via reversible acetylation.[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.[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.[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*).[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 analyis 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

Table 5. Roles of HDACs in the nervous system development.

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 $SIRT1^{H363T}$	Reduction in dendritic arbor complexity	279
SIRT1	Mouse neurospheres infected with SIRT1-targeting siRNA lentivirus	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 mice (myelin protein zero (MPZ)-Cre driver)	Delay in myelination of peripheral nerves	282

HDACs, histone deacetylases.

greatly improved cognitive performances in mice.[187,188] In contrast, the selective knockout of *HDAC4* in the forebrain impaired learning, memory formation, and long-term synaptic plasticity.[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.[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.[191] Similarly, ablation of *HDAC6* in serotonin neurons blocked the expression of social avoidance in mice exposed to chronic social defeat.[192] *SIRT1*-knockout mice exhibit impaired cognitive abilities associated with defects in synaptic plasticity.[193] Moreover, SIRT1 is expressed in several hypothalamic regions controlling endocrine functions and feeding behaviors, as well as the regulation of circadian rhythmicity.[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.[196] HDAC3 itself is highly neurotoxic, as demonstrated by overexpressing HDAC3 in cortical and granule neurons.[197] Also the overexpression of class II HDAC5 in cerebellar granule neurons compromises their survival via transcriptional repression of MEF2.[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.[199] Also, overexpressing HDAC9 was shown to rescue apoptosis in granule neurons. HDAC9 anti-apoptotic activity is connected to the inhibition of c-jun via direct interaction with c-jun N-terminal kinase (JNK).[200] Sirtuins play important functions in neuronal survival as well. Overexpression of SIRT1 and SIRT5 was shown to protect granule neurons from low potassium-

Table 6. Neuronal phenotypes of HDAC knockout mice.

Gene	Cre line/construct	Cell type/Brain region	Phenotype	References
HDAC1 (overexpression)	AAV- synapsin 1 (Syn1)-HDAC1	Hippocampus	Enhanced fear extinction learning	283
HDAC2	EIIa-Cre Nestin-Cre	All neurons	Enhanced memory formation and associative learning, increased synaptic plasticity	284
HDAC2 (overexpression)	Tau-HDAC2	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
HDAC3	AAV2/1–Cre	Nucleus accumbens	Enhanced cocaine-context-associated memory formation	286
HDAC4	Calcium/calmodulin-dependent protein kinase II (CaMKII)-Cre	Forebrain neurons	Impairment in long-term potentiation (LTP) induction, alteration in motor coordination and anxiety, deficits in learning	189
HDAC4 (overexpression)	HSV-HDAC4	Nucleus accumbens	Reduction in cocaine place conditioning	287
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
HDAC6	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 (overexpression)	Calcium/calmodulin-dependent protein kinase II (CaMKII)-SIRT1	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	Constitutive	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 (overexpression)	Proopiomelanocortin (Pomc)-Cre Agouti-related protein (Agrp)-Cre Rosa26-SIRT1	Hypothalamus	Prevention of age-associated weight gain	294
SIRT1 (overexpression)	Neuron-specific enolase (NSE)–SIRT1	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

(*Continued*)

Table 6. Continued.

Gene	Cre line/construct	Cell type/Brain region	Phenotype	References
SIRT1 (overexpression)	Prion protein (PrP)-SIRT1	All brain	Enhanced neural activation and physical activity in response to diet-restriction	299
SIRT1	Constitutive	All brain	Defects in neurobehavioral adaptation to diet-restricting conditions	299
SIRT1	Nestin-Cre	All neurons	Impaired memory and synaptic plasticity	300
SIRT1	AAV2-Cre	Nucleus accumbens	Decreased drug reward effects	301
SIRT1 and SIRT2 (overexpression)	HSV-SIRT1 HSV-SIRT2	Nucleus accumbens	Increased drug reward effects	301
SIRT4	Constitutive	Total brain	Enhanced seizure Phenotypes in response to kainic acid	302
SIRT6	Nestin-Cre	All neurons	Postnatal growth retardation and obesity due to somatotropic attenuation	303
SIRT6	Constitutive	All neurons	Retinal transmission defects and apoptosis of inner retina cells	304

HDAC, histone deacetylase.

induced apoptosis, while SIRT2, SIRT3, and SIRT6 overexpression promotes neuronal death.[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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References

1. Gregoretti IV, Lee YM, Goodson HV. Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis. J Mol Biol 2004;338:17–31.
2. Dokmanovic M, Clarke C, Marks PA. Histone deacetylase inhibitors: overview and perspectives. Mol Cancer Res 2007;5:981–989.
3. Haberland M, Montgomery RL, Olson EN. The many roles of histone deacetylases in development and physiology: implications for disease and therapy. Nat Rev Genet 2009;10:32–42.
4. de Ruijter AJ, van Gennip AH, Caron HN, et al. Histone deacetylases (HDACs): characterization of the classical HDAC family. Biochem J 2003;370(Pt 3):737–749.
5. Sauve AA, Wolberger C, Schramm VL, Boeke JD. The biochemistry of sirtuins. Annu Rev Biochem 2006;75:435–465.
6. Kazantsev AG, Thompson LM. Therapeutic application of histone deacetylase inhibitors for central nervous system disorders. Nat Rev Drug Discovery 2008;7:854–868.
7. Waltregny D, De Leval L, Glenisson W, et al. Expression of histone deacetylase 8, a class I histone deacetylase, is restricted to cells showing smooth muscle differentiation in normal human tissues. Am J Pathol 2004;165:553–564.
8. Yang XJ, Seto E. Collaborative spirit of histone deacetylases in regulating chromatin structure and gene expression. Curr Opin Genet Dev 2003;13:143–153.
9. Karagianni P, Wong J. HDAC3: taking the SMRT-N-CoRrect road to repression. Oncogene 2007;26:5439–5449.
10. Polesskaya A, Duquet A, Naguibneva I, et al. CREB-binding protein/p300 activates MyoD by acetylation. J Biol Chem 2000;275:34359–34364.

11. Ito A, Kawaguchi Y, Lai CH, et al. MDM2-HDAC1-mediated deacetylation of p53 is required for its degradation. EMBO J 2002;21:6236–6245.
12. Yao YL, Yang WM, Seto E. Regulation of transcription factor YY1 by acetylation and deacetylation. Mol Cell Biol 2001;21:5979–5991.
13. Kawai H, Yamada Y, Tatsuka M, et al. Down-regulation of nuclear factor kappaB is required for p53-dependent apoptosis in X-ray-irradiated mouse lymphoma cells and thymocytes. Cancer Res 1999;59:6038–6041.
14. Markham D, Munro S, Soloway J, et al. DNA-damage-responsive acetylation of pRb regulates binding to E2F-1. EMBO Rep 2006;7:192–198.
15. Marzio G, Wagener C, Gutierrez MI, et al. E2F family members are differentially regulated by reversible acetylation. J Biol Chem 2000;275:10887–10892.
16. Gregoire S, Xiao L, Nie J, et al. Histone deacetylase 3 interacts with and deacetylates myocyte enhancer factor 2. Mol Cell Biol 2007;27:1280–1295.
17. Blanco-Garcia N, Asensio-Juan E, de la Cruz X, Martinez-Balbas MA. Autoacetylation regulates P/CAF nuclear localization. J Biol Chem 2009;284:1343–1352.
18. Thevenet L, Mejean C, Moniot B, et al. Regulation of human SRY subcellular distribution by its acetylation/deacetylation. EMBO J 2004;23:3336–3345.
19. Kramer OH, Knauer SK, Greiner G, et al. A phosphorylation-acetylation switch regulates STAT1 signaling. Genes Dev 2009;23:223–235.
20. Yuan ZL, Guan YJ, Chatterjee D, Chin YE. Stat3 dimerization regulated by reversible acetylation of a single lysine residue. Science 2005;307:269–273.
21. Chen L, Fischle W, Verdin E, Greene WC. Duration of nuclear NF-kappaB action regulated by reversible acetylation. Science 2001;293:1653–1657.
22. Guedes-Dias P, Oliveira JM. Lysine deacetylases and mitochondrial dynamics in neurodegeneration. Biochim Biophys Acta 2013;1832:1345–1359.
23. Verdel A, Curtet S, Brocard MP, et al. Active maintenance of mHDA2/mHDAC6 histone-deacetylase in the cytoplasm. Curr Biol 2000;10:747–749.
24. Hubbert C, Guardiola A, Shao R, et al. HDAC6 is a microtubule-associated deacetylase. Nature 2002;417:455–458.
25. Kekatpure VD, Dannenberg AJ, Subbaramaiah K. HDAC6 modulates Hsp90 chaperone activity and regulates activation of aryl hydrocarbon receptor signaling. J Biol Chem 2009;284:7436–7445.
26. Zhang X, Yuan Z, Zhang Y, et al. HDAC6 modulates cell motility by altering the acetylation level of cortactin. Mol Cell 2007;27:197–213.
27. Li Y, Zhang X, Polakiewicz RD, et al. HDAC6 is required for epidermal growth factor-induced beta-catenin nuclear localization. J Biol Chem 2008;283:12686–12690.
28. Ellis JJ, Valencia TG, Zeng H, et al. CaM kinase IIdeltaC phosphorylation of 14-3-3beta in vascular smooth muscle cells: activation of class II HDAC repression. Mol Cell Biochem 2003;242:153–161.
29. Basile V, Mantovani R, Imbriano C. DNA damage promotes histone deacetylase 4 nuclear localization and repression of G2/M promoters, via p53 C-terminal lysines. J Biol Chem 2006;281:2347–2357.
30. Jeon EJ, Lee KY, Choi NS, et al. Bone morphogenetic protein-2 stimulates Runx2 acetylation. J Biol Chem 2006;281:16502–16511.
31. Glozak MA, Sengupta N, Zhang X, Seto E. Acetylation and deacetylation of non-histone proteins. Gene 2005;363:15–23.
32. Deardorff MA, Bando M, Nakato R, et al. HDAC8 mutations in Cornelia de Lange syndrome affect the cohesin acetylation cycle. Nature 2012;489:313–317.
33. Jeong JW, Bae MK, Ahn MY, et al. Regulation and destabilization of HIF-1alpha by ARD1-mediated acetylation. Cell 2002;111:709–720.
34. Lai IL, Lin TP, Yao YL, et al. Histone deacetylase 10 relieves repression on the melanogenic program by maintaining the deacetylation status of repressors. J Biol Chem 2010;285:7187–7196.
35. Gupta MP, Samant SA, Smith SH, Shroff SG. HDAC4 and PCAF bind to cardiac sarcomeres and play a role in regulating myofilament contractile activity. J Biol Chem 2008;283:10135–10146.
36. Hageman J, Rujano MA, van Waarde MA, et al. A DNAJB chaperone subfamily with HDAC-dependent activities suppresses toxic protein aggregation. Mol Cell 2010;37:355–369.
37. Yuan Z, Peng L, Radhakrishnan R, Seto E. Histone deacetylase 9 (HDAC9) regulates the functions of the ATDC (TRIM29) protein. J Biol Chem 2010;285:39329–39338.
38. Blander G, Guarente L. The Sir2 family of protein deacetylases. Annu Rev Biochem 2004;73:417–435.
39. Frye RA. Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins. Biochem Biophys Res Commun 2000;273:793–798.
40. Michishita E, Park JY, Burneskis JM, et al. Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins. Mol Biol Cell 2005;16:4623–4635.
41. Ramadori G, Lee CE, Bookout AL, et al. Brain SIRT1: anatomical distribution and regulation by energy availability. J Neurosci 2008;28:9989–9996.
42. Muth V, Nadaud S, Grummt I, Voit R. Acetylation of TAF(I)68, a subunit of TIF-IB/SL1, activates RNA polymerase I transcription. EMBO J 2001;20:1353–1362.
43. Bouras T, Fu M, Sauve AA, et al. SIRT1 deacetylation and repression of p300 involves lysine residues 1020/1024

within the cell cycle regulatory domain 1. J Biol Chem 2005;280:10264–10276.
44. Cheng HL, Mostoslavsky R, Saito S, et al. Developmental defects and p53 hyperacetylation in Sir2 homolog (SIRT1)-deficient mice. Proc Natl Acad Sci USA 2003;100:10794–10799.
45. Rodgers JT, Lerin C, Haas W, et al. Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. Nature 2005;434:113–118.
46. Rothgiesser KM, Erener S, Waibel S, et al. SIRT2 regulates NF-kappaB dependent gene expression through deacetylation of p65 Lys310. J Cell Sci 2010;123(Pt 24):4251–4258.
47. North BJ, Marshall BL, Borra MT, et al. The human Sir2 ortholog, SIRT2, is an NAD+-dependent tubulin deacetylase. Mol Cell 2003;11:437–444.
48. Schwer B, Bunkenborg J, Verdin RO, et al. Reversible lysine acetylation controls the activity of the mitochondrial enzyme acetyl-CoA synthetase 2. Proc Natl Acad Sci USA 2006;103:10224–10229.
49. Schlicker C, Gertz M, Papatheodorou P, et al. Substrates and regulation mechanisms for the human mitochondrial sirtuins Sirt3 and Sirt5. J Mol Biol 2008;382:790–801.
50. Ahn BH, Kim HS, Song S, et al. A role for the mitochondrial deacetylase Sirt3 in regulating energy homeostasis. Proc Natl Acad Sci USA 2008;105:14447–14452.
51. Sundaresan NR, Samant SA, Pillai VB, et al. SIRT3 is a stress-responsive deacetylase in cardiomyocytes that protects cells from stress-mediated cell death by deacetylation of Ku70. Mol Cell Biol 2008;28:6384–6401.
52. Yang H, Yang T, Baur JA, et al. Nutrient-sensitive mitochondrial NAD+ levels dictate cell survival. Cell 2007;130:1095–1107.
53. Yang Y, Cimen H, Han MJ, et al. NAD+-dependent deacetylase SIRT3 regulates mitochondrial protein synthesis by deacetylation of the ribosomal protein MRPL10. J Biol Chem 2010;285:7417–7429.
54. Laurent G, German NJ, Saha AK, et al. SIRT4 coordinates the balance between lipid synthesis and catabolism by repressing malonyl CoA decarboxylase. Mol Cell 2013;50:686–698.
55. Nakagawa T, Lomb DJ, Haigis MC, Guarente L. SIRT5 deacetylates carbamoyl phosphate synthetase 1 and regulates the urea cycle. Cell 2009;137:560–570.
56. Kaidi A, Weinert BT, Choudhary C, Jackson SP. Human SIRT6 promotes DNA end resection through CtIP deacetylation. Science 2010;329:1348–1353.
57. Dominy JE Jr, Lee Y, Jedrychowski MP, et al. The deacetylase Sirt6 activates the acetyltransferase GCN5 and suppresses hepatic gluconeogenesis. Mol Cell 2012;48:900–913.
58. Vakhrusheva O, Smolka C, Gajawada P, et al. Sirt7 increases stress resistance of cardiomyocytes and prevents apoptosis and inflammatory cardiomyopathy in mice. Circ Res 2008;102:703–710.
59. Gao L, Cueto MA, Asselbergs F, Atadja P. Cloning and functional characterization of HDAC11, a novel member of the human histone deacetylase family. J Biol Chem 2002;277:25748–25755.
60. Liu H, Hu Q, Kaufman A, et al. Developmental expression of histone deacetylase 11 in the murine brain. J Neurosci Res 2008;86:537–543.
61. Villagra A, Cheng F, Wang HW, et al. The histone deacetylase HDAC11 regulates the expression of interleukin 10 and immune tolerance. Nat Immunol 2009;10:92–100.
62. Cheung P, Allis CD, Sassone-Corsi P. Signaling to chromatin through histone modifications. Cell 2000;103:263–271.
63. Lill R. Function and biogenesis of iron-sulphur proteins. Nature 2009;460:831–838.
64. Martelli A, Napierala M, Puccio H. Understanding the genetic and molecular pathogenesis of Friedreich's ataxia through animal and cellular models. Dis Model Mech 2012;5:165–176.
65. Campuzano V, Montermini L, Molto MD, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 1996;271:1423–1427.
66. Chutake YK, Lam C, Costello WN, et al. Epigenetic promoter silencing in Friedreich ataxia is dependent on repeat length. Ann Neurol 2014;76:522–528.
67. Tan G, Chen LS, Lonnerdal B, et al. Frataxin expression rescues mitochondrial dysfunctions in FRDA cells. Hum Mol Genet 2001;10:2099–2107.
68. Perdomini M, Belbellaa B, Monassier L, et al. Prevention and reversal of severe mitochondrial cardiomyopathy by gene therapy in a mouse model of Friedreich's ataxia. Nat Med 2014;20:542–547.
69. Saveliev A, Everett C, Sharpe T, et al. DNA triplet repeats mediate heterochromatin-protein-1-sensitive variegated gene silencing. Nature 2003;422:909–913.
70. Dion V, Wilson JH. Instability and chromatin structure of expanded trinucleotide repeats. Trends Genet 2009;25:288–297.
71. Herman D, Jenssen K, Burnett R, et al. Histone deacetylase inhibitors reverse gene silencing in Friedreich's ataxia. Nat Chem Biol 2006;2:551–558.
72. Greene E, Mahishi L, Entezam A, et al. Repeat-induced epigenetic changes in intron 1 of the frataxin gene and its consequences in Friedreich ataxia. Nucleic Acids Res 2007;35:3383–3390.
73. Punga T, Buhler M. Long intronic GAA repeats causing Friedreich ataxia impede transcription elongation. EMBO Mol Med 2010;2:120–129.
74. Kumari D, Biacsi RE, Usdin K. Repeat expansion affects both transcription initiation and elongation

in Friedreich ataxia cells. J Biol Chem 2011;286:4209–4215.
75. Kim E, Napierala M, Dent SY. Hyperexpansion of GAA repeats affects post-initiation steps of FXN transcription in Friedreich's ataxia. Nucleic Acids Res 2011;39:8366–8377.
76. Peters AH, O'Carroll D, Scherthan H, et al. Loss of the Suv39h histone methyltransferases impairs mammalian heterochromatin and genome stability. Cell 2001;107:323–337.
77. De Biase I, Chutake YK, Rindler PM, Bidichandani SI. Epigenetic silencing in Friedreich ataxia is associated with depletion of CTCF (CCCTC-binding factor) and antisense transcription. PLoS One 2009;4:e7914.
78. Sarsero JP, Li L, Wardan H, et al. Upregulation of expression from the FRDA genomic locus for the therapy of Friedreich ataxia. J Gene Med 2003;5:72–81.
79. Rai M, Soragni E, Jenssen K, et al. HDAC inhibitors correct frataxin deficiency in a Friedreich ataxia mouse model. PLoS One 2008;3:e1958.
80. Sandi C, Pinto RM, Al-Mahdawi S, et al. Prolonged treatment with pimelic o-aminobenzamide HDAC inhibitors ameliorates the disease phenotype of a Friedreich ataxia mouse model. Neurobiol Dis 2011;42:496–505.
81. Xu C, Soragni E, Chou CJ, et al. Chemical probes identify a role for histone deacetylase 3 in Friedreich's ataxia gene silencing. Chem Biol 2009;16:980–989.
82. Rai M, Soragni E, Chou CJ, et al. Two new pimelic diphenylamide HDAC inhibitors induce sustained frataxin upregulation in cells from Friedreich's ataxia patients and in a mouse model. PLoS One 2010;5:e8825.
83. Soragni E, Miao W, Iudicello M, et al. Epigenetic therapy for Friedreich ataxia. Ann Neurol 2014;76:489–508.
84. Chan PK, Torres R, Yandim C, et al. Heterochromatinization induced by GAA-repeat hyperexpansion in Friedreich's ataxia can be reduced upon HDAC inhibition by vitamin B3. Hum Mol Genet 2013;22:2662–2675.
85. Libri V, Yandim C, Athanasopoulos S, et al. Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study. Lancet 2014;384:504–513.
86. Antar LN, Dictenberg JB, Plociniak M, et al. Localization of FMRP-associated mRNA granules and requirement of microtubules for activity-dependent trafficking in hippocampal neurons. Genes Brain Behav 2005;4:350–359.
87. Pieretti M, Zhang FP, Fu YH, et al. Absence of expression of the FMR-1 gene in fragile X syndrome. Cell 1991;66:817–822.
88. Coffee B, Zhang F, Warren ST, Reines D. Acetylated histones are associated with FMR1 in normal but not fragile X-syndrome cells. Nat Genet 1999;22:98–101.
89. Coffee B, Zhang F, Ceman S, et al. Histone modifications depict an aberrantly heterochromatinized FMR1 gene in fragile x syndrome. Am J Hum Genet 2002;71:923–932.
90. Pietrobono R, Tabolacci E, Zalfa F, et al. Molecular dissection of the events leading to inactivation of the FMR1 gene. Hum Mol Genet 2005;14:267–277.
91. Tabolacci E, Pietrobono R, Moscato U, et al. Differential epigenetic modifications in the FMR1 gene of the fragile X syndrome after reactivating pharmacological treatments. Eur J Hum Genet 2005;13:641–648.
92. Eiges R, Urbach A, Malcov M, et al. Developmental study of fragile X syndrome using human embryonic stem cells derived from preimplantation genetically diagnosed embryos. Cell Stem Cell 2007;1:568–577.
93. Kumari D, Usdin K. The distribution of repressive histone modifications on silenced FMR1 alleles provides clues to the mechanism of gene silencing in fragile X syndrome. Hum Mol Genet 2010;19:4634–4642.
94. Kumari D, Usdin K. Interaction of the transcription factors USF1, USF2, and alpha -Pal/Nrf-1 with the FMR1 promoter. Implications for fragile X mental retardation syndrome. J Biol Chem 2001;276:4357–4364.
95. Naumann A, Hochstein N, Weber S, et al. A distinct DNA-methylation boundary in the 5′- upstream sequence of the FMR1 promoter binds nuclear proteins and is lost in fragile X syndrome. Am J Hum Genet 2009;85:606–616.
96. Chandler SP, Kansagra P, Hirst MC. Fragile X (CGG)n repeats induce a transcriptional repression in cis upon a linked promoter: evidence for a chromatin mediated effect. BMC Mol Biol 2003;4:3.
97. Chiurazzi P, Pomponi MG, Pietrobono R, et al. Synergistic effect of histone hyperacetylation and DNA demethylation in the reactivation of the FMR1 gene. Hum Mol Genet 1999;8:2317–2323.
98. Tabolacci E, De Pascalis I, Accadia M, et al. Modest reactivation of the mutant FMR1 gene by valproic acid is accompanied by histone modifications but not DNA demethylation. Pharmacogenet Genomics 2008;18:738–741.
99. Biacsi R, Kumari D, Usdin K. SIRT1 inhibition alleviates gene silencing in fragile X mental retardation syndrome. PLoS Genet 2008;4:e1000017.
100. Hagerman RJ, Leavitt BR, Farzin F, et al. Fragile-X-associated tremor/ataxia syndrome (FXTAS) in females with the FMR1 premutation. Am J Hum Genet 2004;74:1051–1056.
101. Tassone F, Hagerman RJ, Taylor AK, et al. Elevated levels of FMR1 mRNA in carrier males: a new mechanism of involvement in the fragile-X syndrome. Am J Hum Genet 2000;66:6–15.
102. Sofola OA, Jin P, Qin Y, et al. RNA-binding proteins hnRNP A2/B1 and CUGBP1 suppress fragile X CGG premutation repeat-induced neurodegeneration in a Drosophila model of FXTAS. Neuron 2007;55:565–571.

103. Aumiller V, Graebsch A, Kremmer E, et al. Drosophila Pur-alpha binds to trinucleotide-repeat containing cellular RNAs and translocates to the early oocyte. RNA Biol 2012;9:633–643.
104. Sellier C, Rau F, Liu Y, et al. Sam68 sequestration and partial loss of function are associated with splicing alterations in FXTAS patients. EMBO J 2010;29:1248–1261.
105. Sellier C, Freyermuth F, Tabet R, et al. Sequestration of DROSHA and DGCR8 by expanded CGG RNA repeats alters microRNA processing in fragile X-associated tremor/ataxia syndrome. Cell Rep 2013;3:869–880.
106. Todd PK, Oh SY, Krans A, et al. Histone deacetylases suppress CGG repeat-induced neurodegeneration via transcriptional silencing in models of fragile X tremor ataxia syndrome. PLoS Genet 2010;6:e1001240.
107. Mohseni J, Zabidi-Hussin ZA, Sasongko TH. Histone deacetylase inhibitors as potential treatment for spinal muscular atrophy. Genet Mol Biol 2013;36:299–307.
108. Edens BM, Ajroud-Driss S, Ma L, Ma YC. Molecular mechanisms and animal models of spinal muscular atrophy. Biochim Biophys Acta 2014; In press.
109. Monani UR, Sendtner M, Coovert DD, et al. The human centromeric survival motor neuron gene (SMN2) rescues embryonic lethality in Smn(-/-) mice and results in a mouse with spinal muscular atrophy. Hum Mol Genet 2000;9:333–339.
110. Arnold WD, Burghes AH. Spinal muscular atrophy: development and implementation of potential treatments. Ann Neurol 2013;74:348–362.
111. Kernochan LE, Russo ML, Woodling NS, et al. The role of histone acetylation in SMN gene expression. Hum Mol Genet 2005;14:1171–1182.
112. Andreassi C, Angelozzi C, Tiziano FD, et al. Phenylbutyrate increases SMN expression in vitro: relevance for treatment of spinal muscular atrophy. Eur J Hum Genet 2004;12:59–65.
113. Brichta L, Hofmann Y, Hahnen E, et al. Valproic acid increases the SMN2 protein level: a well-known drug as a potential therapy for spinal muscular atrophy. Hum Mol Genet 2003;12:2481–2489.
114. Chang JG, Hsieh-Li HM, Jong YJ, et al. Treatment of spinal muscular atrophy by sodium butyrate. Proc Natl Acad Sci USA 2001;98:9808–9813.
115. Avila AM, Burnett BG, Taye AA, et al. Trichostatin A increases SMN expression and survival in a mouse model of spinal muscular atrophy. J Clin Invest 2007;117:659–671.
116. Riessland M, Ackermann B, Forster A, et al. SAHA ameliorates the SMA phenotype in two mouse models for spinal muscular atrophy. Hum Mol Genet 2010;19:1492–1506.
117. Weihl CC, Connolly AM, Pestronk A. Valproate may improve strength and function in patients with type III/IV spinal muscle atrophy. Neurology 2006;67:500–501.
118. Tsai LK, Yang CC, Hwu WL, Li H. Valproic acid treatment in six patients with spinal muscular atrophy. Eur J Neurol 2007;14:e8–e9.
119. Swoboda KJ, Scott CB, Reyna SP, et al. Phase II open label study of valproic acid in spinal muscular atrophy. PLoS One 2009;4:e5268.
120. Darbar IA, Plaggert PG, Resende MB, et al. Evaluation of muscle strength and motor abilities in children with type II and III spinal muscle atrophy treated with valproic acid. BMC Neurol 2011;11:36.
121. Swoboda KJ, Scott CB, Crawford TO, et al. SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. PLoS One 2010;5:e12140.
122. Kissel JT, Scott CB, Reyna SP, et al. SMA CARNIVAL TRIAL PART II: a prospective, single-armed trial of L-carnitine and valproic acid in ambulatory children with spinal muscular atrophy. PLoS One 2011;6:e21296.
123. Kissel JT, Elsheikh B, King WM, et al. SMA valiant trial: a prospective, double-blind, placebo-controlled trial of valproic acid in ambulatory adults with spinal muscular atrophy. Muscle Nerve 2014;49:187–192.
124. Vanier MT. [Niemann-Pick C disease: history, current research topics, biological and molecular diagnosis]. Arch Pediatr 2010;17(suppl 2):S41–S44.
125. Stern G. Niemann-Pick's and Gaucher's diseases. Parkinsonism Relat Disord 2014;20(suppl 1):S143–S146.
126. Blom TS, Linder MD, Snow K, et al. Defective endocytic trafficking of NPC1 and NPC2 underlying infantile Niemann-Pick type C disease. Hum Mol Genet 2003;12:257–272.
127. Liou HL, Dixit SS, Xu S, et al. NPC2, the protein deficient in Niemann-Pick C2 disease, consists of multiple glycoforms that bind a variety of sterols. J Biol Chem 2006;281:36710–36723.
128. Infante RE, Wang ML, Radhakrishnan A, et al. NPC2 facilitates bidirectional transfer of cholesterol between NPC1 and lipid bilayers, a step in cholesterol egress from lysosomes. Proc Natl Acad Sci USA 2008;105:15287–15292.
129. Gelsthorpe ME, Baumann N, Millard E, et al. Niemann-Pick type C1 I1061T mutant encodes a functional protein that is selected for endoplasmic reticulum-associated degradation due to protein misfolding. J Biol Chem 2008;283:8229–8236.
130. Gevry NY, Lalli E, Sassone-Corsi P, Murphy BD. Regulation of niemann-pick c1 gene expression by the 3′5′-cyclic adenosine monophosphate pathway in steroidogenic cells. Mol Endocrinol 2003;17:704–715.
131. Pipalia NH, Cosner CC, Huang A, et al. Histone deacetylase inhibitor treatment dramatically reduces

cholesterol accumulation in Niemann-Pick type C1 mutant human fibroblasts. Proc Natl Acad Sci USA 2011;108:5620–5625.
132. Cummings CJ, Zoghbi HY. Trinucleotide repeats: mechanisms and pathophysiology. Annu Rev Genomics Hum Genet 2000;1:281–328.
133. Nakamura K, Jeong SY, Uchihara T, et al. SCA17, a novel autosomal dominant cerebellar ataxia caused by an expanded polyglutamine in TATA-binding protein. Hum Mol Genet 2001;10:1441–1448.
134. Opal P, Zoghbi HY. The role of chaperones in polyglutamine disease. Trends Mol Med 2002;8:232–236.
135. Opal P, Zoghbi HY. The hereditary ataxias. Principle and practice of medical genetics 2013;118:1–32.
136. Steffan JS, Kazantsev A, Spasic-Boskovic O, et al. The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. Proc Natl Acad Sci USA 2000;97:6763–6768.
137. McCampbell A, Taylor JP, Taye AA, et al. CREB-binding protein sequestration by expanded polyglutamine. Hum Mol Genet 2000;9:2197–2202.
138. Sugars KL, Rubinsztein DC. Transcriptional abnormalities in Huntington disease. Trends Genet 2003;19:233–238.
139. Nucifora FC Jr, Sasaki M, Peters MF, et al. Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science 2001;291:2423–2428.
140. Palhan VB, Chen S, Peng GH, et al. Polyglutamine-expanded ataxin-7 inhibits STAGA histone acetyltransferase activity to produce retinal degeneration. Proc Natl Acad Sci USA 2005;102:8472–8477.
141. Li F, Macfarlan T, Pittman RN, Chakravarti D. Ataxin-3 is a histone-binding protein with two independent transcriptional corepressor activities. J Biol Chem 2002;277:45004–45012.
142. Cvetanovic M, Kular RK, Opal P. LANP mediates neuritic pathology in Spinocerebellar ataxia type 1. Neurobiol Dis 2012;48:526–532.
143. Cvetanovic M, Patel JM, Marti HH, et al. Vascular endothelial growth factor ameliorates the ataxic phenotype in a mouse model of spinocerebellar ataxia type 1. Nat Med 2011;17:1445–1447.
144. Kular RK, Cvetanovic M, Siferd S, et al. Neuronal differentiation is regulated by leucine-rich acidic nuclear protein (LANP), a member of the inhibitor of histone acetyltransferase complex. J Biol Chem 2009;284:7783–7792.
145. Hogarth P, Lovrecic L, Krainc D. Sodium phenylbutyrate in Huntington's disease: a dose-finding study. Mov Disord 2007;22:1962–1964.
146. Ebbel EN, Leymarie N, Schiavo S, et al. Identification of phenylbutyrate-generated metabolites in Huntington disease patients using parallel liquid chromatography/electrochemical array/mass spectrometry and off-line tandem mass spectrometry. Anal Biochem 2010;399:152–161.
147. Venkatraman A, Hu YS, Didonna A, et al. The histone deacetylase HDAC3 is essential for Purkinje cell function, potentially complicating the use of HDAC inhibitors in SCA1. Hum Mol Genet 2014;23:3733–3745.
148. Moumne L, Campbell K, Howland D, et al. Genetic knock-down of HDAC3 does not modify disease-related phenotypes in a mouse model of Huntington's disease. PLoS One 2012;7:e31080.
149. Benn CL, Butler R, Mariner L, et al. Genetic knock-down of HDAC7 does not ameliorate disease pathogenesis in the R6/2 mouse model of Huntington's disease. PLoS One 2009;4:e5747.
150. Mielcarek M, Landles C, Weiss A, et al. HDAC4 reduction: a novel therapeutic strategy to target cytoplasmic huntingtin and ameliorate neurodegeneration. PLoS Biol 2013;11:e1001717.
151. Bobrowska A, Paganetti P, Matthias P, Bates GP. Hdac6 knock-out increases tubulin acetylation but does not modify disease progression in the R6/2 mouse model of Huntington's disease. PLoS One 2011;6:e20696.
152. Bobrowska A, Donmez G, Weiss A, et al. SIRT2 ablation has no effect on tubulin acetylation in brain, cholesterol biosynthesis or the progression of Huntington's disease phenotypes in vivo. PLoS One 2012;7:e34805.
153. Hammond JW, Cai D, Verhey KJ. Tubulin modifications and their cellular functions. Curr Opin Cell Biol 2008;20:71–76.
154. Chen S, Owens GC, Makarenkova H, Edelman DB. HDAC6 regulates mitochondrial transport in hippocampal neurons. PLoS One 2010;5:e10848.
155. Suzuki K, Koike T. Mammalian Sir2-related protein (SIRT) 2-mediated modulation of resistance to axonal degeneration in slow Wallerian degeneration mice: a crucial role of tubulin deacetylation. Neuroscience 2007;147:599–612.
156. Hempen B, Brion JP. Reduction of acetylated alpha-tubulin immunoreactivity in neurofibrillary tangle-bearing neurons in Alzheimer's disease. J Neuropathol Exp Neurol 1996;55:964–972.
157. Dompierre JP, Godin JD, Charrin BC, et al. Histone deacetylase 6 inhibition compensates for the transport deficit in Huntington's disease by increasing tubulin acetylation. J Neurosci 2007;27:3571–3583.
158. Barisic N, Claeys KG, Sirotkovic-Skerlev M, et al. Charcot-Marie-Tooth disease: a clinico-genetic confrontation. Ann Hum Genet 2008;72(Pt 3):416–441.
159. Ostern R, Fagerheim T, Hjellnes H, et al. Diagnostic laboratory testing for Charcot Marie Tooth disease (CMT): the spectrum of gene defects in Norwegian patients with CMT and its implications for future genetic test strategies. BMC Med Genet 2013;14:94.

160. d'Ydewalle C, Benoy V, Van Den Bosch L. Charcot-Marie-Tooth disease: emerging mechanisms and therapies. Int J Biochem Cell Biol 2012;44:1299–1304.
161. d'Ydewalle C, Krishnan J, Chiheb DM, et al. HDAC6 inhibitors reverse axonal loss in a mouse model of mutant HSPB1-induced Charcot-Marie-Tooth disease. Nat Med 2011;17:968–974.
162. Robberecht W, Philips T. The changing scene of amyotrophic lateral sclerosis. Nat Rev Neurosci 2013;14:248–264.
163. Bilsland LG, Sahai E, Kelly G, et al. Deficits in axonal transport precede ALS symptoms in vivo. Proc Natl Acad Sci USA 2010;107:20523–20528.
164. Rosen DR. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature 1993;364:362.
165. Maruyama H, Morino H, Ito H, et al. Mutations of optineurin in amyotrophic lateral sclerosis. Nature 2010;465:223–226.
166. Deng HX, Chen W, Hong ST, et al. Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. Nature 2011;477:211–215.
167. Taes I, Timmers M, Hersmus N, et al. Hdac6 deletion delays disease progression in the SOD1G93A mouse model of ALS. Hum Mol Genet 2013;22:1783–1790.
168. Yoo YE, Ko CP. Treatment with trichostatin A initiated after disease onset delays disease progression and increases survival in a mouse model of amyotrophic lateral sclerosis. Exp Neurol 2011;231:147–159.
169. Ryu H, Smith K, Camelo SI, et al. Sodium phenylbutyrate prolongs survival and regulates expression of anti-apoptotic genes in transgenic amyotrophic lateral sclerosis mice. J Neurochem 2005;93:1087–1098.
170. Cudkowicz ME, Andres PL, Macdonald SA, et al. Phase 2 study of sodium phenylbutyrate in ALS. Amyotroph Lateral Scler 2009;10:99–106.
171. Piepers S, Veldink JH, de Jong SW, et al. Randomized sequential trial of valproic acid in amyotrophic lateral sclerosis. Ann Neurol 2009;66:227–234.
172. Kim C, Choi H, Jung ES, et al. HDAC6 inhibitor blocks amyloid beta-induced impairment of mitochondrial transport in hippocampal neurons. PLoS One 2012;7: e42983.
173. Selenica ML, Benner L, Housley SB, et al. Histone deacetylase 6 inhibition improves memory and reduces total tau levels in a mouse model of tau deposition. Alzheimers Res Ther 2014;6:12.
174. Xiong Y, Zhao K, Wu J, et al. HDAC6 mutations rescue human tau-induced microtubule defects in Drosophila. Proc Natl Acad Sci USA 2013;110:4604–4609.
175. Govindarajan N, Rao P, Burkhardt S, et al. Reducing HDAC6 ameliorates cognitive deficits in a mouse model for Alzheimer's disease. EMBO Mol Med 2013;5:52–63.
176. Cook C, Carlomagno Y, Gendron TF, et al. Acetylation of the KXGS motifs in tau is a critical determinant in modulation of tau aggregation and clearance. Hum Mol Genet 2014;23:104–116.
177. Kontopoulos E, Parvin JD, Feany MB. Alpha-synuclein acts in the nucleus to inhibit histone acetylation and promote neurotoxicity. Hum Mol Genet 2006;15:3012–3023.
178. Inden M, Kitamura Y, Takeuchi H, et al. Neurodegeneration of mouse nigrostriatal dopaminergic system induced by repeated oral administration of rotenone is prevented by 4-phenylbutyrate, a chemical chaperone. J Neurochem 2007;101:1491–1504.
179. Gardian G, Yang L, Cleren C, et al. Neuroprotective effects of phenylbutyrate against MPTP neurotoxicity. Neuromolecular Med 2004;5:235–241.
180. Ono K, Ikemoto M, Kawarabayashi T, et al. A chemical chaperone, sodium 4-phenylbutyric acid, attenuates the pathogenic potency in human alpha-synuclein A30P + A53T transgenic mice. Parkinsonism Relat Disord 2009;15:649–654.
181. Monti B, Mercatelli D, Contestabile A. Valproic acid neuroprotection in 6-OHDA lesioned rat, a model for Parkinson's disease. HOAJ Biol 2012;1:1–4.
182. Kawaguchi Y, Kovacs JJ, McLaurin A, et al. The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. Cell 2003;115:727–738.
183. Lee JY, Koga H, Kawaguchi Y, et al. HDAC6 controls autophagosome maturation essential for ubiquitin-selective quality-control autophagy. EMBO J 2010;29:969–980.
184. Kovacs JJ, Murphy PJ, Gaillard S, et al. HDAC6 regulates Hsp90 acetylation and chaperone-dependent activation of glucocorticoid receptor. Mol Cell 2005;18:601–607.
185. Pandey UB, Nie Z, Batlevi Y, et al. HDAC6 rescues neurodegeneration and provides an essential link between autophagy and the UPS. Nature 2007;447:859–863.
186. Roth M, Chen WY. Sorting out functions of sirtuins in cancer. Oncogene 2014;33:1609–1620.
187. Morris MJ, Mahgoub M, Na ES, et al. Loss of histone deacetylase 2 improves working memory and accelerates extinction learning. J Neurosci 2013;33:6401–6411.
188. McQuown SC, Barrett RM, Matheos DP, et al. HDAC3 is a critical negative regulator of long-term memory formation. J Neurosci 2011;31:764–774.
189. Kim MS, Akhtar MW, Adachi M, et al. An essential role for histone deacetylase 4 in synaptic plasticity and memory formation. J Neurosci 2012;32:10879–10886.
190. Sando R III, Gounko N, Pieraut S, et al. HDAC4 governs a transcriptional program essential for synaptic plasticity and memory. Cell 2012;151:821–834.
191. Renthal W, Maze I, Krishnan V, et al. Histone deacetylase 5 epigenetically controls behavioral

adaptations to chronic emotional stimuli. Neuron 2007;56:517–529.
192. Espallergues J, Teegarden SL, Veerakumar A, et al. HDAC6 regulates glucocorticoid receptor signaling in serotonin pathways with critical impact on stress resilience. J Neurosci 2012;32:4400–4416.
193. Michan S, Li Y, Chou MM, et al. SIRT1 is essential for normal cognitive function and synaptic plasticity. J Neurosci 2010;30:9695–9707.
194. Bellet MM, Nakahata Y, Boudjelal M, et al. Pharmacological modulation of circadian rhythms by synthetic activators of the deacetylase SIRT1. Proc Natl Acad Sci USA 2013;110:3333–3338.
195. Herskovits AZ, Guarente L. SIRT1 in neurodevelopment and brain senescence. Neuron 2014;81:471–483.
196. Bardai FH, Price V, Zaayman M, et al. Histone deacetylase-1 (HDAC1) is a molecular switch between neuronal survival and death. J Biol Chem 2012;287:35444–35453.
197. Bardai FH, D'Mello SR. Selective toxicity by HDAC3 in neurons: regulation by Akt and GSK3beta. J Neurosci 2011;31:1746–1751.
198. Linseman DA, Bartley CM, Le SS, et al. Inactivation of the myocyte enhancer factor-2 repressor histone deacetylase-5 by endogenous Ca(2 +)// calmodulin-dependent kinase II promotes depolarization-mediated cerebellar granule neuron survival. J Biol Chem 2003;278:41472–41481.
199. Majdzadeh N, Wang L, Morrison BE, et al. HDAC4 inhibits cell-cycle progression and protects neurons from cell death. Dev Neurobiol 2008;68:1076–1092.
200. Morrison BE, Majdzadeh N, Zhang X, et al. Neuroprotection by histone deacetylase-related protein. Mol Cell Biol 2006;26:3550–3564.
201. Pfister JA, Ma C, Morrison BE, D'Mello SR. Opposing effects of sirtuins on neuronal survival: SIRT1-mediated neuroprotection is independent of its deacetylase activity. PLoS One 2008;3:e4090.
202. Broide RS, Redwine JM, Aftahi N, et al. Distribution of histone deacetylases 1-11 in the rat brain. J Mol Neurosci 2007;31:47–58.
203. Donmez G. The neurobiology of sirtuins and their role in neurodegeneration. Trends Pharmacol Sci 2012;33:494–501.
204. Zhang F, Wang S, Gan L, et al. Protective effects and mechanisms of sirtuins in the nervous system. Prog Neurobiol 2011;95:373–395.
205. Marks PA, Breslow R. Dimethyl sulfoxide to vorinostat: development of this histone deacetylase inhibitor as an anticancer drug. Nat Biotechnol 2007;25:84–90.
206. Butler KV, Kalin J, Brochier C, et al. Rational design and simple chemistry yield a superior, neuroprotective HDAC6 inhibitor, tubastatin A. J Am Chem Soc 2010;132:10842–10846.
207. Glaser KB. HDAC inhibitors: clinical update and mechanism-based potential. Biochem Pharmacol 2007;74:659–671.
208. Haggarty SJ, Koeller KM, Wong JC, et al. Domain-selective small-molecule inhibitor of histone deacetylase 6 (HDAC6)-mediated tubulin deacetylation. Proc Natl Acad Sci USA 2003;100:4389–4394.
209. Furumai R, Matsuyama A, Kobashi N, et al. FK228 (depsipeptide) as a natural prodrug that inhibits class I histone deacetylases. Cancer Res 2002;62:4916–4921.
210. Xu WS, Parmigiani RB, Marks PA. Histone deacetylase inhibitors: molecular mechanisms of action. Oncogene 2007;26:5541–5552.
211. Vannini A, Volpari C, Filocamo G, et al. Crystal structure of a eukaryotic zinc-dependent histone deacetylase, human HDAC8, complexed with a hydroxamic acid inhibitor. Proc Natl Acad Sci USA 2004;101: 15064–15069.
212. Thomas EA, Coppola G, Desplats PA, et al. The HDAC inhibitor 4b ameliorates the disease phenotype and transcriptional abnormalities in Huntington's disease transgenic mice. Proc Natl Acad Sci USA 2008;105:15564–15569.
213. Sauve AA, Schramm VL. Sir2 regulation by nicotinamide results from switching between base exchange and deacetylation chemistry. Biochemistry 2003;42: 9249–9256.
214. Bedalov A, Gatbonton T, Irvine WP, et al. Identification of a small molecule inhibitor of Sir2p. Proc Natl Acad Sci USA 2001;98:15113–15118.
215. Grozinger CM, Chao ED, Blackwell HE, et al. Identification of a class of small molecule inhibitors of the sirtuin family of NAD-dependent deacetylases by phenotypic screening. J Biol Chem 2001;276:38837–38843.
216. Taylor DM, Balabadra U, Xiang Z, et al. A brain-permeable small molecule reduces neuronal cholesterol by inhibiting activity of sirtuin 2 deacetylase. ACS Chem Biol 2011;6:540–546.
217. Friden-Saxin M, Seifert T, Landergren MR, et al. Synthesis and evaluation of substituted chroman-4-one and chromone derivatives as sirtuin 2-selective inhibitors. J Med Chem 2012;55:7104–7113.
218. Li SH, Cheng AL, Zhou H, et al. Interaction of Huntington disease protein with transcriptional activator Sp1. Mol Cell Biol 2002;22:1277–1287.
219. Boutell JM, Thomas P, Neal JW, et al. Aberrant interactions of transcriptional repressor proteins with the Huntington's disease gene product, huntingtin. Hum Mol Genet 1999;8:1647–1655.
220. Takano H, Gusella JF. The predominantly HEAT-like motif structure of huntingtin and its association and coincident nuclear entry with dorsal, an NF-kB/Rel/dorsal family transcription factor. BMC Neurosci 2002;3:15.

221. Dunah AW, Jeong H, Griffin A, et al. Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease. Science 2002;296:2238–2243.
222. McFarland KN, Huizenga MN, Darnell SB, et al. MeCP2: a novel Huntingtin interactor. Hum Mol Genet 2014;23:1036–1044.
223. Steffan JS, Bodai L, Pallos J, et al. Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in Drosophila. Nature 2001;413:739–743.
224. Tsuda H, Jafar-Nejad H, Patel AJ, et al. The AXH domain of ataxin-1 mediates neurodegeneration through its interaction with Gfi-1/Senseless proteins. Cell 2005;122:633–644.
225. Lam YC, Bowman AB, Jafar-Nejad P, et al. ATAXIN-1 interacts with the repressor Capicua in its native complex to cause SCA1 neuropathology. Cell 2006;127:1335–1347.
226. Mizutani A, Wang L, Rajan H, et al. Boat, an AXH domain protein, suppresses the cytotoxicity of mutant ataxin-1. EMBO J 2005;24:3339–3351.
227. Serra HG, Duvick L, Zu T, et al. RORalpha-mediated Purkinje cell development determines disease severity in adult SCA1 mice. Cell 2006;127:697–708.
228. Matilla A, Koshy BT, Cummings CJ, et al. The cerebellar leucine-rich acidic nuclear protein interacts with ataxin-1. Nature 1997;389:974–978.
229. Davidson JD, Riley B, Burright EN, et al. Identification and characterization of an ataxin-1-interacting protein: A1Up, a ubiquitin-like nuclear protein. Hum Mol Genet 2000;9:2305–2312.
230. Shibata H, Huynh DP, Pulst SM. A novel protein with RNA-binding motifs interacts with ataxin-2. Hum Mol Genet 2000;9:1303–1313.
231. Elden AC, Kim HJ, Hart MP, et al. Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. Nature 2010;466:1069–1075.
232. Nonhoff U, Ralser M, Welzel F, et al. Ataxin-2 interacts with the DEAD/H-box RNA helicase DDX6 and interferes with P-bodies and stress granules. Mol Biol Cell 2007;18:1385–1396.
233. Damrath E, Heck MV, Gispert S, et al. ATXN2-CAG42 sequesters PABPC1 into insolubility and induces FBXW8 in cerebellum of old ataxic knock-in mice. PLoS Genet 2012;8:e1002920.
234. Araujo J, Breuer P, Dieringer S, et al. FOXO4-dependent upregulation of superoxide dismutase-2 in response to oxidative stress is impaired in spinocerebellar ataxia type 3. Hum Mol Genet 2011;20:2928–2941.
235. Doss-Pepe EW, Stenroos ES, Johnson WG, Madura K. Ataxin-3 interactions with rad23 and valosin-containing protein and its associations with ubiquitin chains and the proteasome are consistent with a role in ubiquitin-mediated proteolysis. Mol Cell Biol 2003;23:6469–6483.
236. Shimohata T, Nakajima T, Yamada M, et al. Expanded polyglutamine stretches interact with TAFII130, interfering with CREB-dependent transcription. Nat Genet 2000;26:29–36.
237. Evert BO, Araujo J, Vieira-Saecker AM, et al. Ataxin-3 represses transcription via chromatin binding, interaction with histone deacetylase 3, and histone deacetylation. J Neurosci 2006;26:11474–11486.
238. La Spada AR, Fu YH, Sopher BL, et al. Polyglutamine-expanded ataxin-7 antagonizes CRX function and induces cone-rod dystrophy in a mouse model of SCA7. Neuron 2001;31:913–927.
239. Lebre AS, Jamot L, Takahashi J, et al. Ataxin-7 interacts with a Cbl-associated protein that it recruits into neuronal intranuclear inclusions. Hum Mol Genet 2001;10:1201–1213.
240. Takahashi M, Obayashi M, Ishiguro T, et al. Cytoplasmic location of alpha1A voltage-gated calcium channel C-terminal fragment (Cav2.1-CTF) aggregate is sufficient to cause cell death. PLoS One 2013;8:e50121.
241. Lee LC, Chen CM, Wang HC, et al. Role of the CCAAT-binding protein NFY in SCA17 pathogenesis. PLoS One 2012;7:e35302.
242. Klejman MP, Zhao X, van Schaik FM, et al. Mutational analysis of BTAF1-TBP interaction: BTAF1 can rescue DNA-binding defective TBP mutants. Nucleic Acids Res 2005;33:5426–5436.
243. Alen P, Claessens F, Verhoeven G, et al. The androgen receptor amino-terminal domain plays a key role in p160 coactivator-stimulated gene transcription. Mol Cell Biol 1999;19:6085–6097.
244. Fu M, Wang C, Reutens AT, et al. p300 and p300/cAMP-response element-binding protein-associated factor acetylate the androgen receptor at sites governing hormone-dependent transactivation. J Biol Chem 2000;275:20853–20860.
245. Masiello D, Chen SY, Xu Y, et al. Recruitment of beta-catenin by wild-type or mutant androgen receptors correlates with ligand-stimulated growth of prostate cancer cells. Mol Endocrinol 2004;18:2388–2401.
246. McEwan IJ, Gustafsson J. Interaction of the human androgen receptor transactivation function with the general transcription factor TFIIF. Proc Natl Acad Sci USA 1997;94:8485–8490.
247. Wang L, Charroux B, Kerridge S, Tsai CC. Atrophin recruits HDAC1/2 and G9a to modify histone H3K9 and to determine cell fates. EMBO Rep 2008;9:555–562.
248. Wood JD, Yuan J, Margolis RL, et al. Atrophin-1, the DRPLA gene product, interacts with two families of WW domain-containing proteins. Mol Cell Neurosci 1998;11:149–160.

249. Wood JD, Nucifora FC Jr, Duan K, et al. Atrophin-1, the dentato-rubral and pallido-luysian atrophy gene product, interacts with ETO/MTG8 in the nuclear matrix and represses transcription. J Cell Biol 2000;150:939–948.
250. Hockly E, Richon VM, Woodman B, et al. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. Proc Natl Acad Sci USA 2003;100:2041–2046.
251. Bates EA, Victor M, Jones AK, et al. Differential contributions of *Caenorhabditis elegans* histone deacetylases to huntingtin polyglutamine toxicity. J Neurosci 2006;26:2830–2838.
252. Sadri-Vakili G, Bouzou B, Benn CL, et al. Histones associated with downregulated genes are hypo-acetylated in Huntington's disease models. Hum Mol Genet 2007;16:1293–1306.
253. Pallos J, Bodai L, Lukacsovich T, et al. Inhibition of specific HDACs and sirtuins suppresses pathogenesis in a Drosophila model of Huntington's disease. Hum Mol Genet 2008;17:3767–3775.
254. Zadori D, Geisz A, Vamos E, et al. Valproate ameliorates the survival and the motor performance in a transgenic mouse model of Huntington's disease. Pharmacol Biochem Behav 2009;94:148–153.
255. Hathorn T, Snyder-Keller A, Messer A. Nicotinamide improves motor deficits and upregulates PGC-1alpha and BDNF gene expression in a mouse model of Huntington's disease. Neurobiol Dis 2011;41:43–50.
256. Ferrante RJ, Kubilus JK, Lee J, et al. Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. J Neurosci 2003;23:9418–9427.
257. Gardian G, Browne SE, Choi DK, et al. Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington's disease. J Biol Chem 2005;280:556–563.
258. Jia H, Pallos J, Jacques V, et al. Histone deacetylase (HDAC) inhibitors targeting HDAC3 and HDAC1 ameliorate polyglutamine-elicited phenotypes in model systems of Huntington's disease. Neurobiol Dis 2012;46:351–361.
259. Mielcarek M, Benn CL, Franklin SA, et al. SAHA decreases HDAC 2 and 4 levels in vivo and improves molecular phenotypes in the R6/2 mouse model of Huntington's disease. PLoS One 2011;6:e27746.
260. Jia H, Kast RJ, Steffan JS, Thomas EA. Selective histone deacetylase (HDAC) inhibition imparts beneficial effects in Huntington's disease mice: implications for the ubiquitin-proteasomal and autophagy systems. Hum Mol Genet 2012;21:5280–5293.
261. Chiu CT, Liu G, Leeds P, Chuang DM. Combined treatment with the mood stabilizers lithium and valproate produces multiple beneficial effects in transgenic mouse models of Huntington's disease. Neuropsychopharmacology 2011;36:2406–2421.
262. Luthi-Carter R, Taylor DM, Pallos J, et al. SIRT2 inhibition achieves neuroprotection by decreasing sterol biosynthesis. Proc Natl Acad Sci USA 2010;107:7927–7932.
263. Chopra V, Quinti L, Kim J, et al. The sirtuin 2 inhibitor AK-7 is neuroprotective in Huntington's disease mouse models. Cell Rep 2012;2:1492–1497.
264. Chou AH, Chen SY, Yeh TH, et al. HDAC inhibitor sodium butyrate reverses transcriptional downregulation and ameliorates ataxic symptoms in a transgenic mouse model of SCA3. Neurobiol Dis 2011;41:481–488.
265. Yi J, Zhang L, Tang B, et al. Sodium valproate alleviates neurodegeneration in SCA3/MJD via suppressing apoptosis and rescuing the hypoacetylation levels of histone H3 and H4. PLoS One 2013;8:e54792.
266. Chou AH, Chen YL, Hu SH, et al. Polyglutamine-expanded ataxin-3 impairs long-term depression in Purkinje neurons of SCA3 transgenic mouse by inhibiting HAT and impairing histone acetylation. Brain Res 2014;1583:220–229.
267. Minamiyama M, Katsuno M, Adachi H, et al. Sodium butyrate ameliorates phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy. Hum Mol Genet 2004;13:1183–1192.
268. Ying M, Xu R, Wu X, et al. Sodium butyrate ameliorates histone hypoacetylation and neurodegenerative phenotypes in a mouse model for DRPLA. J Biol Chem 2006;281:12580–12586.
269. Montgomery RL, Hsieh J, Barbosa AC, et al. Histone deacetylases 1 and 2 control the progression of neural precursors to neurons during brain development. Proc Natl Acad Sci USA 2009;106:7876–7881.
270. Ye F, Chen Y, Hoang T, et al. HDAC1 and HDAC2 regulate oligodendrocyte differentiation by disrupting the beta-catenin-TCF interaction. Nat Neurosci 2009;12:829–838.
271. Jacob C, Lotscher P, Engler S, et al. HDAC1 and HDAC2 control the specification of neural crest cells into peripheral glia. J Neurosci 2014;34:6112–6122.
272. Chen B, Cepko CL. HDAC4 regulates neuronal survival in normal and diseased retinas. Science 2009;323:256–259.
273. Cho Y, Sloutsky R, Naegle KM, Cavalli V. Injury-induced HDAC5 nuclear export is essential for axon regeneration. Cell 2013;155:894–908.
274. Tapia M, Wandosell F, Garrido JJ. Impaired function of HDAC6 slows down axonal growth and interferes with axon initial segment development. PLoS One 2010;5:e12908.
275. Ageta-Ishihara N, Miyata T, Ohshima C, et al. Septins promote dendrite and axon development by negatively regulating microtubule stability via HDAC6-mediated deacetylation. Nat Commun 2013;4:2532.

276. Sugo N, Oshiro H, Takemura M, et al. Nucleocytoplasmic translocation of HDAC9 regulates gene expression and dendritic growth in developing cortical neurons. Eur J Neurosci 2010;31:1521–1532.
277. Li XH, Chen C, Tu Y, et al. Sirt1 promotes axonogenesis by deacetylation of Akt and inactivation of GSK3. Mol Neurobiol 2013;48:490–499.
278. Sugino T, Maruyama M, Tanno M, et al. Protein deacetylase SIRT1 in the cytoplasm promotes nerve growth factor-induced neurite outgrowth in PC12 cells. FEBS Lett 2010;584:2821–2826.
279. Codocedo JF, Allard C, Godoy JA, et al. SIRT1 regulates dendritic development in hippocampal neurons. PLoS One 2012;7:e47073.
280. Hisahara S, Chiba S, Matsumoto H, et al. Histone deacetylase SIRT1 modulates neuronal differentiation by its nuclear translocation. Proc Natl Acad Sci USA 2008;105:15599–15604.
281. Prozorovski T, Schulze-Topphoff U, Glumm R, et al. Sirt1 contributes critically to the redox-dependent fate of neural progenitors. Nat Cell Biol 2008;10:385–394.
282. Beirowski B, Gustin J, Armour SM, et al. Sir-two-homolog 2 (Sirt2) modulates peripheral myelination through polarity protein Par-3/atypical protein kinase C (aPKC) signaling. Proc Natl Acad Sci USA 2011;108:E952–E961.
283. Bahari-Javan S, Maddalena A, Kerimoglu C, et al. HDAC1 regulates fear extinction in mice. J Neurosci 2012;32:5062–5073.
284. Guan JS, Haggarty SJ, Giacometti E, et al. HDAC2 negatively regulates memory formation and synaptic plasticity. Nature 2009;459:55–60.
285. Jiang Y, Hsieh J. HDAC3 controls gap 2/mitosis progression in adult neural stem/progenitor cells by regulating CDK1 levels. Proc Natl Acad Sci USA 2014;111:13541–13546.
286. Rogge GA, Singh H, Dang R, Wood MA. HDAC3 is a negative regulator of cocaine-context-associated memory formation. J Neurosci 2013;33:6623–6632.
287. Kumar A, Choi KH, Renthal W, et al. Chromatin remodeling is a key mechanism underlying cocaine-induced plasticity in striatum. Neuron 2005;48: 303–314.
288. Fukada M, Hanai A, Nakayama A, et al. Loss of deacetylation activity of Hdac6 affects emotional behavior in mice. PLoS One 2012;7:e30924.
289. Lu M, Sarruf DA, Li P, et al. Neuronal Sirt1 deficiency increases insulin sensitivity in both brain and peripheral tissues. J Biol Chem 2013;288:10722–10735.
290. Wu D, Qiu Y, Gao X, et al. Overexpression of SIRT1 in mouse forebrain impairs lipid/glucose metabolism and motor function. PLoS One 2011;6:e21759.
291. Li Y, Xu W, McBurney MW, Longo VD. SirT1 inhibition reduces IGF-I/IRS-2/Ras/ERK1/2 signaling and protects neurons. Cell Metab 2008;8:38–48.
292. Saharan S, Jhaveri DJ, Bartlett PF. SIRT1 regulates the neurogenic potential of neural precursors in the adult subventricular zone and hippocampus. J Neurosci Res 2013;91:642–659.
293. Ramadori G, Fujikawa T, Fukuda M, et al. SIRT1 deacetylase in POMC neurons is required for homeostatic defenses against diet-induced obesity. Cell Metab 2010;12:78–87.
294. Sasaki T, Kikuchi O, Shimpuku M, et al. Hypothalamic SIRT1 prevents age-associated weight gain by improving leptin sensitivity in mice. Diabetologia 2014;57:819–831.
295. Kakefuda K, Fujita Y, Oyagi A, et al. Sirtuin 1 overexpression mice show a reference memory deficit, but not neuroprotection. Biochem Biophys Res Commun 2009;387:784–788.
296. Rafalski VA, Ho PP, Brett JO, et al. Expansion of oligodendrocyte progenitor cells following SIRT1 inactivation in the adult brain. Nat Cell Biol 2013;15:614–624.
297. Chang HC, Guarente L. SIRT1 mediates central circadian control in the SCN by a mechanism that decays with aging. Cell 2013;153:1448–1460.
298. Cohen DE, Supinski AM, Bonkowski MS, et al. Neuronal SIRT1 regulates endocrine and behavioral responses to calorie restriction. Genes Dev 2009;23:2812–2817.
299. Satoh A, Brace CS, Ben-Josef G, et al. SIRT1 promotes the central adaptive response to diet restriction through activation of the dorsomedial and lateral nuclei of the hypothalamus. J Neurosci 2010;30:10220–10232.
300. Gao J, Wang WY, Mao YW, et al. A novel pathway regulates memory and plasticity via SIRT1 and miR-134. Nature 2010;466:1105–1109.
301. Ferguson D, Koo JW, Feng J, et al. Essential role of SIRT1 signaling in the nucleus accumbens in cocaine and morphine action. J Neurosci 2013;33:16088–16098.
302. Shih J, Mason A, Liu L, et al. Loss of SIRT4 decreases GLT-1-dependent glutamate uptake and increases sensitivity to kainic acid. J Neurochem 2014;131:573–581.
303. Schwer B, Schumacher B, Lombard DB, et al. Neural sirtuin 6 (Sirt6) ablation attenuates somatic growth and causes obesity. Proc Natl Acad Sci USA 2010;107:21790–21794.
304. Silberman DM, Ross K, Sande PH, et al. SIRT6 is required for normal retinal function. PLoS One 2014;9:e98831.

