Minireview

Histone deacetylase-3: Friend and foe of the brain

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Impact statement

Brain development and degeneration are highly complex processes that are regulated by a large number of molecules and signaling pathways the identities of which are being unraveled. Accumulating evidence points to histone deacetylases and epigenetic mechanisms as being important regulators of these processes. In this review, we describe that histone deacetylase-3 (HDAC3) is a particularly crucial regulator of both neurodevelopment and neurodegeneration. In addition, HDAC3 regulates memory formation, synaptic plasticity, and the cognitive impairment associated with normal aging. Understanding how HDAC3 functions contributes to the normal development and functioning of the brain while also promoting neurodegeneration could lead to the development of therapeutic approaches for neurodevelopmental, neuropsychiatric, and neurodegenerative disorders.

Abstract

Histone deacetylases (HDACs) are a family of enzymes that deacetylate histones as well as a large number of other nuclear, cytoplasmic, and mitochondrial proteins. The deacetylation of histones transforms chromatin to a transcriptionally repressed state, whereas deacetylation of other cellular proteins regulates their functional activity through modulation of subcellular location, their interaction with other proteins, and in the case of transcription factors, their DNA-binding ability. A compelling body of evidence derived from the utilization of pharmacological inhibitors indicates that histone deacetylases are important regulators of brain development as well as the pathogenesis of neurodegenerative diseases. However, because most of the pharmacological inhibitors used are non-selective with regard to the different members of the HDAC family, the significance of individual HDAC proteins to brain development and degeneration has been difficult to delineate. This review focuses on HDAC3. Experiments conducted using more recently developed isoform selective inhibitors and molecular genetic approaches demonstrate that HDAC3 regulates different steps of neurodevelopment, including neurogenesis, gliogenesis, glial cell fate determination, and the myelination of oligodendrocytes and Schwann cells. However, specific posttranslational modifications and alterations in its binding partners transform HDAC3 from a protein that is beneficial to the brain to one that is neurotoxic. The role of HDAC3 in the promotion of neurodegeneration and the inhibition of recovery after nerve injury is reviewed. The role of HDAC3 in the regulation of memory in the adult and aging brain is also described.

Keywords: Histone deacetylases, histone deacetylase-3, neurodevelopment, neurodegenerative diseases, aging, learning and memory

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Introduction

Gene transcription is dependent on the state of chromatin, which is determined, in large part, on posttranslational modifications of residues within the tails of histones, the protein component of nucleosomes.[1] By regulating the associations of histones with other proteins and with DNA, these modifications determine whether chromatin is in a transcriptionally active or an inactive state. Over the past two decades, it has become clear that these chromatin-altering modifications may not only be dynamically regulated by environmental factors and experiences, but can also be heritable. Such regulation of gene expression, which is controlled not by the genetic "blueprint" but by histone modification-driven changes to chromatin is referred to as epigenetic regulation. Among the best studied of epigenetic modifications is the acetylation and deacetylation of lysine residues.[2] Acetylation neutralizes the positive charge of lysine residues within histone tails resulting in a weakening of the electrostatic interaction between histones and the negatively charged DNA with which they associate. This causes the relaxation of chromatin permitting the binding of DNA polymerase and transcription factors promoting transcription. On the other

hand, deacetylation of histone tails increases their interaction with DNA resulting in chromatin compacting and, consequently, a reduction of transcription. In addition to affecting chromatin structure, the acetylation and deacetylation of histone tails also regulate the recruitment of transcriptional regulatory factors to DNA.[2] Depending on the proteins that are recruited, and complexes assembled to the modified histones, chromatin can be remodeled, and transcription can be activated or repressed.

Acetylation and deacetylation of histones are regulated by two families of enzymes – histone acetyltransferases (HATS) and histone deacetylases (HDACs). The HDAC family of deacetylases is subdivided into four groups.[3,4] Class I HDACs includes HDAC1, HDAC2, HDAC3, and HDAC8. These are ubiquitously expressed nuclear proteins, except for HDAC3 which is both nuclear and cytoplasmic. Class II HDACs are expressed more selectively and subdivided into two subgroups, with Class IIa consisting of HDAC4, HDAC5, HDAC7, and HDAC9, whereas Class IIb is made up of HDAC6 and HDAC10. Class II HDACs can shuttle between the cytoplasm and the nucleus based on their phosphorylation status, except for HDAC6 which is cytoplasmic. Class III HDACs, generally called sirtuins, include SIRT1—7. SIRTs can be nuclear, cytoplasmic, or mitochondrial. Finally, HDAC11, localized predominantly in the nucleus, is the sole member of the Class IV HDAC family. Class I, II, and IV HDACs are commonly referred to as classical HDACs. Classical HDACs share structural similarity in their catalytic domains and require zinc as cofactor. In contrast, the structurally distinct sirtuins are NAD^+-dependent enzymes.[3,4]

Although histones were their first identified substrates, HDACS (and HATs) regulate the acetylation status of a last number of non-histone proteins in the nucleus, cytoplasm, and mitochondria and in doing so, regulate their structural conformation, subcellular localization, stability, interactions with other proteins and, in the case of transcription factors, DNA-binding activity.[3,4] Through such actions, HDACs regulate diverse physiological and pathophysiological processes. Much of the information on the involvement of HDACs in various biological processes has been obtained through the utilization of pharmacological inhibitors. The most commonly used inhibitors of classical HDACs belong to five groups: hydroximates, benzamides, cyclic tetrapeptides, aliphatic acids, and electrophilic ketones. A major limitation of these inhibitors, however, is that they are generally non-selective with respect to the different HDAC proteins at the doses at which they are typically used.

Epigenetic mechanisms, such as histone acetylation/deacetylation, regulate brain development and hence important brain-related functions including activity-dependent transcription, synaptic plasticity, and learning and memory formation.[5–10] Not surprisingly, impaired epigenetic regulation affects proper functioning of the brain and has been implicated in in the etiology of complex brain disorders such as depression, autism schizophrenia, and bipolar disorder.[11–13] Epigenetic mechanisms also play a critical role in brain activities during normal adulthood and in the progressive cognitive decline associated with aging.[14–16] This review describes the actions of HDACs in the brain, focusing on a single member of the family, the Class I HDAC, HDAC3. As described below, HDAC3 plays both helpful and damaging roles in the brain. Specifically, HDAC3 is critical to the proper brain development but can also promote neurodegeneration in the adult brain. Results from several recent studies also implicate HDACs in the etiology of neuropsychiatric disorders. While this review focuses on HDAC3, the reader is referred to other recent reviews for information on the role of other Class I HDACs in brain development and degeneration.[5,6,17]

HDAC3 is required for proper development of the brain

Conventional knockout of *Hdac3* results in early embryonic lethality.[18] Norwood *et al*.[19] were the first to describe the effects of conditional genetic ablation of *Hdac3* on the development of the CNS (Table 1). Mice in which *Hdac3* was deleted specifically in neural progenitor cells (NPCs) survived for less than 24 h after birth.[19] Examination of the cortex revealed severe lamination defects in the cortex along with loss of neurons in the superficial layers, which are the last cortical layers to be formed. The dentate gyrus was poorly formed. Similarly, the cerebellum of these *Hdac3*-deficient mice was underdeveloped and largely devoid of foliation. Purkinje neurons of the cerebellum were improperly positioned.[19] During brain development, the production of neurons (neurogenesis) precedes the production of glial cell generation (gliogenesis). Within the gliogenic phase, astrocytes are generated first and after a cell fate switch, NPCs differentiate to produce oligodendrocytes.[20–22] Examination of the status of glial cells in the cortex of *Hdac3* mutant mice on the day of birth suggested a defect in glial cell fate determination resulting in the overproduction of astrocytes at the cost of oligodendrocyte precursor cells.[19] Mice in which *Hdac3* was selectively ablated in forebrain neurons displayed progressive motor deficits and died within six weeks demonstrating an essential role in neuronal function. Although *Hdac3* ablated in developing neurons in these mice, the expression of GFAP, a marker

Table 1. Roles of HDAC3 in neurodevelopment.

Role	References
Regulation of NPC proliferation and differentiation in the neocortex and hippocampus	26–28
Experience-dependent NPC proliferation in the Xenopus tectum	29
Neocortical lamination, survival of neurons in the superficial layers of the cortex	19
Cerebellar morphogenesis and hippocampal formation	19
Auditory organ morphogenesis in zebrafish	32
Glial cell fate determination, production of oligodendrocytes	19,23–25
Development and myelination of Schwann cells	24,25

Note: Unless otherwise mentioned, all studies listed in the tables were performed in rodents or in vitro systems derived from rodent or human.

of astrocytes, was highly elevated in the cortex indicating overproduction of astrocytes.[19] The disruption of glial cell fate determination was confirmed and extended by Zhang *et al*.[23] (Table 1). These authors found that HDAC3 antagonized astrogliogenesis by inhibiting the acetylation of STAT3, a transcription factor necessary for astrogenesis, while activating the oligodendrocyte lineage.[23] Deletion of *Hdac3* in oligodendrocyte progenitors resulted in reduced production of oligodendrocytes demonstrating the requirement for HDAC3 for the generation of this glial cell type in proper numbers.[23] Oligodendrocytes that were produced were severely deficient in myelin.[23] In striking contrast to its role in oligodendrocyte development, HDAC3 inhibits the maturation and myelination of Schwann cells, the cellular equivalent of oligodendrocytes in the peripheral nervous system (PNS).[24] Deletion of *Hdac3* in the Schwann cell lineage resulted in premature myelination ending up in their hyper-myelination of Schwann cells. Moreover, *Hdac3* deletion stimulated re-myelination after nerve transection. An inhibitory role for HDAC3 in myelin formation as well as its regeneration after nerve injury was confirmed using pharmacological inhibitors of HDAC3.[24] Nerve conductivity after injury was enhanced in mice both by HDAC3 deletion and following administration of HDAC3 inhibitors.[24] *In vitro* experiments using pharmacological inhibition and genetic knockdown confirmed that HDAC3 inhibits Schwann cell differentiation and maturation and revealed that the inhibitory action of HDAC3 was mediated by inhibition of myelination genes through the antagonization of the NRG1-PI 3 kinase-Akt signaling pathway.[24] Although some of the findings of He *et al.* were confirmed by another group, other findings were not. Specifically, Rosenberg *et al.*[25] found that HDAC3 is not required for the production of myelinated Schwann cells during development, but plays a critical role in maintaining a proper level of myelination through adulthood. Deletion of *Hdac3* led to hypertrophy and hyper-myelination of the Schwann cells during adulthood resulting in progressive neuropathy.[25] The different conclusion with regard to the generation of properly myelinated Schwann cells is unclear but may be related in part to the utilization of different Cre constructs for *Hdac3* ablation in the two studies. While He *et al*. used 2′,3′-cyclic nucleotide 3′ phosphodiesterase (Cnp) promoter, Rosenberg *et al.* utilized the P0 promoter, which like the Cnp promoter is also expressed in Schwann cell progenitors.

As described above, mice in which *Hdac3* is deleted in neural progenitors show impaired cerebellar morphogenesis[19] (Table 1). Another study described that knockdown of *Hdac3* in the zebrafish using morpholinos impaired morphogenesis of the auditory system which was accompanied by decreased cell proliferation and increased apoptosis.[30] The effect of HDAC3 in enabling auditory organ morphogenesis was found to be mediated by the stimulation basic FGF/FGF2. Administration of FGF2, a mitotic factor and morphogen, compensated for the lack of HDAC3 and promoted proper auditory organ development.[30] Even in the mouse, FGF2 stimulates proliferation of NPCs in the cortex as well as in other areas including the hippocampus, cerebellum, and spinal cord, regions of the brain which are all affected in mice lacking *Hdac3* in NPCs.[31–36] Whether FGF2 mediates the morphogenetic actions of HDAC3 in the mammalian brain has not yet been examined. It is possible, however, that the absence of HDAC3 reduces FGF2-mediated proliferation NPCs that generate late-developing neuronal populations in the cortex (upper-layer neurons), hippocampus (dentate gyrus), and the cerebellum. This would explain the selective impact on neurons in these brain regions.

Other studies have also found that HDAC3 stimulates NPC proliferation, which could then contribute to the regulation morphogenetic actions. Using neural NPCs cultured from the adult mice lacking HDAC3 in the hippocampus, Jiang and Hsieh described that HDAC3 was necessary for cell cycle progression acting at the G2/M boundary. This stimulatory effect on cell cycle progression in these adult was found to be due to the post-translational stabilization of the mitotic cyclin-dependent kinase, CDK1.[26] The reduction in NPC proliferation was confirmed in mice in which *Hdac3* was inducibly deleted in the hippocampus.[26] A similar proliferation defect leading to apoptotic death or increased differentiation was described in embryonic cortical NPCs cultured from mice lacking *Hdac3* and normal NPCs in which *Hdac3* was knocked down.[27,28] A role for HDAC3 in the stimulation of NPC proliferation was also reported in studies of the zebrafish retina suggesting that this proliferative activity of HDAC3 is conserved.[29]

In sum, based on the defective migration in the cortex, the loss of later-born neurons in the cortex, the underdeveloped cerebellum and mispositioning of Purkinje neurons,[19] the impaired glial cell fate determination,[19,23] and this regulation of myelination of oligodendrocytes and Schwann cell,[23–25] it is clear that HDAC3 is a critical mediator of brain development regulating multiple neurodevelopmental processes possibly through distinct signaling partners and mechanisms.

HDAC3 as a key contributor to neurodegenerative disease

The first indication that HDACs contribute to neurodegenerative disease came from a study by Steffan *et al.*[37] in 2001 which showed that pharmacological inhibition of HDACs suppressed polyglutamine-dependent neurotoxicity in *Drosophila* (Table 2). Since then a large number of studies have demonstrated the ability of structurally distinct HDAC inhibitors to protect in diverse cell culture, invertebrate, and mammalian models of neurodegenerative conditions.[17,38–40] However, because these pharmacological inhibitors are generally non-selective with respect to the HDAC family, the identity of the specific HDAC(s) that trigger neurodegeneration and that are targeted by the inhibitors to afford protection has been unresolved. A growing and compelling body of evidence points to HDAC3 being a particularly important player in the promotion of neurodegeneration in a variety of disease models. The first evidence of HDAC3 as a promoter of neurodegeneration came from *C. Elegans* in which it was shown that knockdown *Had-3*, considered to be the

Table 2. HDAC3 in the promotion of neurodegeneration.

Role	References
Polyglutamine-induced neurotoxicity in *Drosophila* and *C. Elegans*	37,41
Low potassium and HCA-induced neuronal death in cultured cerebellar granule and cortical neurons	48–50
Huntington's disease	48,51–57
Alzheimer's disease	58—61
Parkinson's disease	62
Friedreich's ataxia	63–65
Spinocerebellar ataxia-3	66
Ischemic stroke	67–69
Spinal cord injury	70
Retinal ganglion cell degeneration	71,72

Note: Unless otherwise mentioned, all studies listed in the tables were performed in rodents or *in vitro* systems derived from rodent or human. Not shown in the table but described are the negative effects of HDAC3 in synaptic plasticity, learning and memory.[73–77]

ortholog of mammalian *Hdac3*, suppressed toxicity resulting from the expression of a human huntingtin (Htt) fragment with an expanded polyglutamine tract (Htt-Q150).[41] PolyQ-expansion of Htt is the cause of Huntington's disease (HD), an inherited neurodegenerative disorder characterized by neuronal loss in the striatum and to a lesser extent, the cortex.[42,43] Interestingly, the knockdown of other HDAC genes in *C. Elegans* caused an enhancement of Htt-Q150 neurotoxicity. This is consistent with the finding that some HDAC proteins, particularly those belonging to the Class IIa family, are neuroprotective in mammals.[44–46] The first compelling report that HDAC3 is neurotoxic in mammalian neurons came from a study conducted in cultured cerebellar granule neurons (CGNs) and cortical neurons in which it was shown that elevating HDAC3 expression resulted in cell death[47] (Table 2). Interestingly, this toxicity was selective for neurons and cell lines of neuronal origin, as the viability of other cell types was unaffected by elevated HDAC3. Knockdown of endogenous HDAC3 protected against death expression resulting from oxidative stress, low potassium treatment, and overexpression of polyQ-Htt, indicating that HDAC3 is required for neuronal death in response to diverse neurotoxic stimuli.[47]

Pharmacological studies using more recently developed HDAC3-selective inhibitors confirm its requirement for neurodegeneration in HD. The Thomas lab was the first to demonstrate that administration of the HDAC3/HDAC1-selective inhibitor, HDACi 4 b, improved disease-associated body weight loss, motor dysfunction, and cognitive decline in different models of HD.[51–53] Interestingly, the protective effect was transgenerational in that it was also seen in first filial generation (F1) offspring of HDACi 4 b-administered male HD transgenic mice.[54] The transgenerational protection was attributed to changes in the DNA methylation pattern elicited from the administration of the inhibitor resulting in elevated expression of several genes including Gadd45b, Parp, Mbd3, and Rnf4. Protection in transgenic mouse models of HD through HDAC3 inhibition was confirmed in a follow-up study by the same group as well as by another group using a different HDAC inhibitor, RGFP966.[48,55] More recently HDAC3 has been shown to reduce degeneration and improve behavioral performance in a variety of other serious neurodegenerative conditions. This includes Alzheimer's disease (AD),[58,59,73] Parkinson's disease (PD),[62] Friedreich's ataxia,[63,64] ischemic stroke,[67–69] and spinal cord injury[70] (Table-2). In AD, the beneficial effect of pharmacological inhibition was confirmed using lentivirally expressed shRNA against *Hdac3*, which reduced spatial memory deficits, decreased amyloid plaque load and Aβ levels, and increased dendritic spine density.[78] ShRNA-mediated knockdown of *Hdac3* inhibition also reduces lipid peroxidation, and oxidation of protein and nuclei acid in the hippocampus of AD mice.[60] Similarly, in optic nerve crush-induced retinal ganglion cells (RGC) degeneration, protection by pharmacological HDAC3 inhibition was confirmed using RGC-specific conditional knockout of *Hdac3*.

Neuroinflammation, which exacerbates neuronal loss in neurodegenerative diseases as well as other neurological conditions such as stroke and spinal cord injury, is also suppressed by pharmacological HDAC inhibition.[68,70,78] For example, in a rat spinal cord injury model, Chen *et al.*[79] described an upregulation of HDAC3 expression in glial cells after injury which was blocked by valproic acid, a pan-HDAC inhibitor. These authors showed that pharmacological inhibition of HDAC3 inhibited the transformation of microglia from the anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype, thus reducing neuroinflammation.[79] The anti-inflammatory effect was mediated by acetylation of NF-κB, which reduced its inflammatory activity. Additionally, nuclear localization of HDAC3 in neurons was reduced by HDAC3 inhibition.[79]

Surprisingly in view of the effectiveness of pharmacological inhibitors in HD, hemizygous deletion of *Hdac3* in the R6/2 mouse model of HD does not reduce neuropathology or improve behavioral performance.[80] One possibility is that, at least in this aggressive mouse model of HD, a 50% reduction in HDAC3 level is insufficient to provide significant benefit. Alternatively, and given that neurotoxicity by HDAC3 requires altered posttranslational modifications, protein–protein interactions, and subcellular localization (see below), these pathological alterations could be enhanced in the *Hdac3* hemizygous mice to compensate for the reduction of expression. In other words, although present at reduced levels, the remaining HDAC3 may have enhanced neurotoxic activity.

Although knockdown of *Hdac3* is protective in cell culture models of HD and other neurotoxic stimuli, neither *Hdac3* mRNA or protein levels are altered in dying neurons.[47] A similar lack of alteration of HDAC3 expression has been reported in other cell culture and *in vivo* models of neurodegeneration.[47,60,71] This suggests that rather than increased expression, the posttranslational modification of existing HDAC3 converts it to a neurotoxic protein. Indeed, the phosphorylation of HDAC3 by GSK3β is necessary for its neurotoxic activity.[47] This finding is interesting because increased activity of GSK3β has been described in a variety of neurodegenerative diseases, although exactly how this activation triggers neuronal loss is unclear.[81–84] The findings of Bardai *et al.* suggest that HDAC3 is a substrate and

effector of GSK3β in its neurodegeneration-promoting action. Another kinase that stimulates the neurotoxic activity of HDAC3 through direct phosphorylation is leucine-rich repeat kinase 2 (LRRK2), mutations of which are the major cause of inherited PD.[62] This finding raises the possibility that neurodegeneration in PD in patients with LRRK2 mutations could be mediated by HDAC3.

Besides phosphorylation, HDAC3 neurotoxicity requires its interaction with HDAC1, another Class-I HDAC.[49] A large body of experimental data describe that HDAC1 and HDAC3 are components of distinct multi-protein complexes.[3,4] Whereas HDAC1 (and HDAC2) are components of the Co-REST (co-repressor for element-1-silencing transcription factor), NuRD (nucleosome remodeling and deacetylation) and Sin3 complexes Kelly and Cowley 2013), HDAC3 associates with either NCOR1 (Nuclear Receptor Corepressor-1) or NCOR2 (also known as silencing mediator of retinoid and thyroid receptors, or SMRT) together with the WD40 protein, TBL1, and GPS2, a signaling protein.[85–87] Consistent with the large number of studies performed in non-neuronal cell types, HDAC1-HDAC3 interaction is not detectable in healthy neurons.[49] However, robust interaction is seen in cultured neurons primed to die.[49] Robust HDAC1-HDAC3 interaction is also observed in the striatum of HD mice, but not in other brain regions that are not affected in HD. Furthermore, HDAC1-HDAC3 interaction in HD mice coincides with the appearance of neuropathology and behavioral deficits. Demonstrating the requirement for HDAC1 in HDAC3-mediated neuronal death is the finding that shRNA-mediated knockdown of HDAC1 protects against the neurotoxic effect of mut-Htt and other stimuli. It deserves pointing out that RGFP966, the HDAC3 inhibitor shown to be neuroprotective in many models of neurodegenerative disease, also inhibits HDAC1 significantly.[55] HDAC1/HDAC3 selective inhibition also protects in a mouse model of Friedreich's ataxia, a neurological disorder caused by the silencing of the (FXN) frataxin gene.[63–65] In this case, administration of the inhibitors resulted in the upregulation on FXN expression. Likewise, genetic knockdown of either HDAC1 or HDAC3 increases FXN mRNA synthesis in Friedreich's ataxia cells. Interestingly, the transgenerational protections provided by HDACi 4 b in HD mice are not observed with RGFP966. A difference between these two HDAC3 inhibitors is that while HDACi 4 b also inhibits HDAC1 effectively, RGFP966 is much more selective for HDAC3.[74] This suggests that transgenerational protection requires efficient inhibition of the HDAC1-HDAC3 complex.

While expression of HDAC3 does not increase during neuronal death in cell culture models or in mouse models of HD or AD, HDAC1 expression does increase in these models.[49] Whether the increase in HDAC1 facilitates the interaction with HDAC3 is not known, but possible. Increased expression of HDAC1 has also been described in the spinal cord in a mouse model nerve injury-induced neuropathic pain.[88] In this study, increased HDAC1 expression stimulated the JNK-c-jun signaling pathway resulting in increased phosphorylation of c-jun, a transcription factor involved in promoting neuronal death, and an interaction between c-jun and HDAC1. This interaction was not detectable in the brains of control mice. Pharmacological inhibition using an HDAC1-selective inhibitor protects against spinal cord injury and prevents activation of JNK-c-jun signaling.[88] Whether HDAC3 is part of the HDAC1-c-jun complex in the injured spinal cord has not been looked at. Direct evidence that HDAC3 inhibits recovery from nerve injury comes from a study that described that either pharmacological inhibition of HDAC3 or shRNA-mediated knockdown robustly stimulates regeneration of the peripheral axons of dorsal root neurons (DRGs) within damaged sciatic nerve.[89] Although the kinase responsible was not identified, the repressive action of HDAC3 on peripheral axonal regeneration depends on its phosphorylation. Axonal regeneration requires the dephosphorylation by protein phosphatase-4 (PP4), which inactivates HDAC3.[89] In contrast to the sciatic nerve, axonal regeneration of CNS nerves is known to be poor because of inhibitory signals. It was found that the central axonal branch of the DRG neurons that lie within spinal cord do not regenerate following spinal cord injury because PP4 is not activated and consequently HDAC4 remains phosphorylated inhibiting the regeneration program.[89]

Bardai *et al.*[56] described that in healthy neurons HDAC3 associates with Htt, which is predominantly a cytoplasmic protein. The HDAC3-Htt interaction is reduced in cultured neurons induced to die likely freeing HDAC3 to translocate to the nucleus. HDAC3-Htt interaction is also reduced in the striatum, and to a lesser degree the cortex, of symptomatic HD mice.[56] In contrast HDAC3-Htt interaction was elevated in the cerebellum. This is noteworthy because neurodegeneration in HD is highest in the striatum with a lesser amount in the cortex, whereas the cerebellum is largely unaffected.[43] Interestingly, polyQ-Htt does not bind to HDAC3. However, the presence of polyQ-expanded Htt disrupts the binding between HDAC3 and wild-type Htt.[56] This finding along with the correlation between the reduction in HDAC3-Htt interaction and neuropathology suggests that the loss of interaction is causally involved in HD pathogenesis. It may be noted that like HDAC3, conventional knockout of Htt leads to embryonic lethality, whereas conditional deletion in the brain causes abnormalities including neurodegeneration.[90,91] Taken together, these findings indicate that along with its phosphorylation, the replacement of Htt with HDAC1 as a binding partner converts HDAC3 to a neurotoxic protein.

Whereas HDAC1 is normally nuclear in neurons and most other cell types, HDAC3 localizes to both the nucleus and the cytoplasm.[92] This would suggest that the interaction with HDAC1 involves HDAC3 that normally localizes to the nucleus and/or cytoplasmic HDAC3 that translocates to the nucleus in response to neurotoxic stimuli. Evidence from studies that have analyzed subcellular localization of HDAC3 indicate that its neurotoxicity is mediated in the nucleus as a result of translocation from the cytoplasm.[57,71,72,78] For example, in an *in vivo* model of retinal ganglion cell (RGC) degeneration triggered by excitotoxicity, the total level of HDAC3 was unchanged through the degenerative process, although nuclear localization of HDAC3 was significantly elevated concomitant with

neuronal loss.[71] This translocation is normally blocked by its cleavage within the C-terminus region by calpain1/calpain2, which results in the retention of HDAC3 in the cytoplasm. A similar nuclear translocation of HDAC3 in hippocampal neurons, coincident with neuropathology, was described in the APP/PS1 transgenic mouse model of AD.[60] It is likely that translocation of HDAC3 may by itself be insufficient for neuronal death. One study described that c-fos, an immediate-early gene regulated by neuronal activity, interacts with HDAC3 and can inhibit its neurotoxic action.[50] Under conditions of neuronal death, c-fos expression is reduced.[50] Such a reduction would permit HDAC3 to interact with HDAC1 unhindered by c-fos. C-fos expression is also reduced in the striatum of HD mice.[50] Interestingly, the interaction of c-fos with HDAC3 does not require its transcriptional activity but involves a 20 amino acid region at the C-terminus of the protein. Overexpression of this HDAC3-interacting motif of c-fos is sufficient to protect against HDAC3 toxicity in cultured neurons.[50]

Two other that HDAC3 interacts with is ataxin-3 and ataxin-7, abnormal polyglutamine expansion of which causes spinocerebellar ataxia-7 (SCA3) and SCA7, respectively.[66,93] In contrast to its inability to interact with polyQ-Htt however, HDAC3 interacts similarly with normal and mutant ataxin-3 and ataxin-7.[66,93] Although stabilizing both wild-type and mutant ataxin-7, HDAC3 caused an accumulation of mutant ataxin-7 in the nucleus and enhanced its neurotoxicity.[66] While interacting with HDAC3, ataxin-3 also regulates HDAC3 expression. Mouse embryonic fibroblasts from mice ataxin-3 knockout mice show reduced expression of HDAC3 as well as NCoR1, with which it complexes.[94] In this study, it was shown that HDAC3 bound and repressed the promoter of the Eph receptor A3(*Efna3*) gene, a key component of Eph-ephrin signaling. The reduction of HDAC3 in ataxin-3 knockout mice leads to the de-repression of *Efna* gene transcription leading to a robust increase in its expression which likely alters Eph-Ephrin signaling pathways. Besides playing a key role in brain development, Eph-Ephrin signaling regulates neurodegeneration.[95]

How does nuclear HDAC3 (likely is association with HDAC1) promote neurodegeneration? Given that both HDAC1 and HDAC3 are transcriptional repressors, it is likely that neurotoxicity is triggered by the repression of genes which have critical functions, including the promotion of neuronal survival. Several potential targets of HDAC3 were recently identified using ChIP-Seq in cultured cerebellar granule neurons.[96] Among these were Bdnf and Npas4 genes.[96] Conventional ChIP assays confirmed that the interaction of HDAC3 with the Bdnf and Npas4 gene promoters was greatly increased in neurons primed to die.[96] Binding of HDAC3 represses the promoters of these two genes. Whereas overexpression of HDAC3 inhibits Bdnf and Npas4 expression, treatment of cells with RGFP966 stimulates expression confirming that these two genes are transcriptional targets of HDAC3-mediated repression.[96] The neuroprotective effects of BDNF are well-established.[97–103] A number of studies have found *Npas4*, best known as a gene expressed specifically in neurons and in response to neuronal activity, also promotes neuroprotection.[104–108] Using mass spectrometric-based proteomic analyses, Qu *et al*. identified several proteins that were deregulated by HDAC3 expression in cultured cerebellar granule neurons. Among these were *Nptx1* (neuronal pentraxin-1), which was upregulated and *Hip1r*, and *Hdac9*, which were repressed by HDAC3. The deregulation of these genes by HDAC3 expression was confirmed by standard ChIP assays and by qPCR.[109] Interestingly, NPTX1 is involved in promoting neuronal death in different models of human neurodegenerative conditions, including in *in vivo* models of hypoxic-ischemic brain injury and a cell culture model of AD.[110–119] In contrast, HIP1R is involved in dendritic and synaptic development, whereas an alternatively spliced form of HDRP is neuroprotective.[45,120,121]

Using ChIP assays to probe specific promoters bound by HDAC3 in a cell culture model of ischemic stroke, *Hsp1a, Bcl2l1,* and *Prdx2* were found to be targets of HDAC3-mediated transcriptional repression.[69] Both treatments with RGFP966 or pre-conditioning, which also has a strong protective effect against subsequent ischemic insult, reduced recruitment of HDAC3 to the promoters of these genes and increased their expression. On the other hand, pharmacological inhibition of calpains promoted nuclear localization and reduced the protective effect of pre-conditioning.[69]

A recent study described that the protective effect of enriched environment (EE) against the synaptotoxic effect of oligomeric Aβ protein was mediated by the suppression of HDAC3 expression.[61] This suppressive effect involved an upregulation of miRNA-132. Overexpressing miR-132 or injecting an HDAC3 inhibitor into mice mimicked the protective effect of EE.[61] Another recently published study conducted in mice described that upregulation of HDAC3 expression is involved in the cognitive decline and neurodegenerative changes caused by diabetes mellitus.[122]

HDAC3 as a contributor to memory impairment and neurodevelopmental and neuropsychiatric disorders

HDAC3 negatively regulates memory formation in the mature brain. This has been demonstrated by focal deletion of *Hdac3* in the hippocampus of adult mice as well as by the administration of RGFP966.[75,76] The negative regulation of memory was described to be due to the transcriptional repression of the immediate-early genes (IEGs) *c-fos* and *Nr4a2*, both of which are known to be involved in memory formation and promoting synaptic plasticity.[123–126] HDAC3 associates with the promoters of the *c-fos* and *Nr4a2* gene promoters and deletion of *Hdac3* increases the expression of these genes.[76] While ablation of *Hdac3* in hippocampal neurons improves memory, another group described that focal ablation of *Hdac3* in neurons within the lateral hypothalamus, a part that communicates with the hippocampus to regulate memory, causes learning and memory impairment indicating that HDAC3 can also facilitate memory formation.[77] Interestingly, it was found that the enhancement of

memory by HDAC3 requires its interaction with NCOR1/SMRT but that its deacetylase activity was not necessary.[77] Recent studies have demonstrated that many functions of HDAC3 outside of the nervous, particularly during development, are independent of its enzymatic activity.[127] Given this, it remains to be rigorously determined whether the neurodegeneration-promoting action of HDAC3 is dependent on its enzymatic activity.

HDAC3 has also been implicated in different neurodevelopmental and neuropsychiatric disorders. One of these disorders is schizophrenia. Several studies have shown that the expression of dysbindin-1, a schizophrenia-susceptibility protein that can localize to both the nucleus and cytoplasm, is reduced in the prefrontal cortex and hippocampus of schizophrenia patients.[128–131] Schizophrenia-like symptoms and cognitive impairment have also been described in dysbindin-1-deficient mice.[132–135] HDAC3 interacts with two of the three isoforms of dysbindin-1 in human neuroblastoma cells and in mouse brain.[136] These authors showed that dysbindin-1B expression was increased in the nucleus in the presence of HDAC3, while the phosphorylation of HDAC3 increased in the presence of dysbindin-1B without a change in expression.[136]

Although there is no indication that the expression of HDAC3 is deregulated in rodent models of schizophrenia or in patients with the disorder, HDAC1 expression is substantially higher in the prefrontal cortex (PFC) in mouse models of schizophrenia.[137,138] HDAC1 expression is also increased in the PFC and hippocampus of patients with schizophrenia.[137,139,140] Whether this increase is followed by interaction with HDAC3, as observed in models of neurodegeneration, has not been specifically examined. The well-documented alterations in gene expression in the brains of patients with schizophrenia would be consistent with such an interaction.

In developing NPCs, HDAC3 has been found to colocalize and associate with Ankrd11, mutations or deletion of which results in cognitive dysfunction and autism spectrum disorder in humans.[141–143] Like HDAC3, Ankrd11 is a transcriptional co-repressor and can localize to both the nucleus and cytoplasm and acts as a repressor of transcription.[144,145] Also like HDAC3, Ankrd11 is essential for brain development and function.[146] In the embryonic mouse cortex, Ankrd11 promotes proliferation of neural progenitors a function that involves association with HDAC3.[146] This raises the possibility that the mutations/deletion of Ankrd11 affects the functioning of HDAC3 in brain development resulting in cognitive impairment and autism. Consistent with such a possibility, HDAC3 also interacts with TBL1XR1, a component of the NCOR1 complex and a protein that also causes cognitive impairment and autism when mutated.[147–149] HDAC3 may also contribute to depressive disorder. At least two studies utilizing distinct anti-depressants described that these drugs downregulate HDAC3 activity.[150,151] In one of these studies, the reduced HDAC3 activity resulted in increased expression of NR2B, a subunit of the NMDA receptor.[151] However, another study found that *Hdac3* was one of many genes that was upregulated following treatment with a subset of anti-depressants.[152]

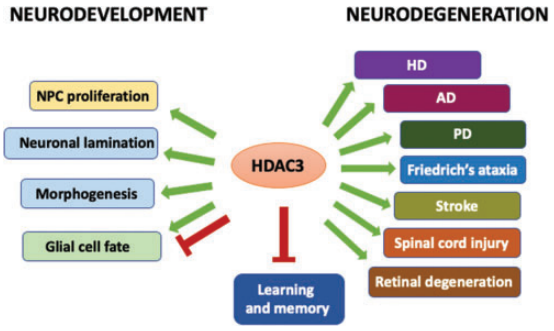

Figure 1. Figure depicts stimulatory and inhibitory actions of HDAC3 during brain development, on learning and memory and in neurodegenerative diseases. NPC: neural progenitor cell; AD: Alzheimer's disease, HD: Huntington's disease; PD: Parkinson's disease. (A color version of this figure is available in the online journal.)

HDAC3 in aging

Gene expression is reduced in the brain during normal aging. Although the precise reasons for this are not known, the adoption a more repressive chromatin state is likely to be an important factor. For example, it is known that learning and memory require new gene expression, a requirement that would not be adequately met in the aging brain. It has been suggested that this impairment results from the epigenetic modification of chromatin in aging neurons. Indeed, work done by Kwapis *et al.*[153] has shown that this is the case and that HDAC3 plays a key role in driving the decline in learning and memory. Specifically, it was shown that deletion of *Hdac3* in the dorsal hippocampus of mice ameliorates age-related impairments in both long-term memory and synaptic plasticity. The findings were confirmed using a dominant-negative form of HDAC3 to disrupt normal HDAC3 activity. Furthermore, deletion of *Hdac3* reversed age-related reduction of LTP in hippocampal slices. Interestingly, rather than restoring the gene expression profile of the young brain, deleting HDAC3 in the aging brain prevented the reduction in expression of a few key genes that are critically important for long-term memory formation. One of these genes is circadian clock gene Period1 (*Per1*) gene. HDAC3 binds to the promoter of the Per1 gene repressing its transcription.[153] The importance of *Per1* for memory formation in the younger brain has been documented.[154,155] Another gene that is transcriptionally repressed by HDAC3 in the aged hippocampus is *Nr4a2*, which as described above, is also targeted by HDAC3 in the non-aged adult brain.[156] Overexpression of Nr4a2 in the dorsal hippocampus ameliorated age-related memory impairment memory. Pharmacological inhibition of Class I HDACs, which includes HDAC3, stimulates Nr4a expression and enhanced long-term memory.[157,158] This enhancement by HDAC inhibition was prevented by blocking Nr4a signaling supporting the idea that HDAC3 impairs long-term memory by inhibiting Nr4a expression.[157]

Conclusions

HDAC3 is necessary for the regulation of critical events in the development of the mammalian CNS (Figure 1).

The absence or reduction of HDAC3 levels results in disrupted regulation of the proliferation of NPCs, mislocalization of neurons, abnormal cell death, deregulated production of astrocytes and oligodendrocytes, and morphogenetic abnormalities in the brain. Additionally, emerging evidence suggests that HDAC3 dysfunction can cause memory impairment and likely contribute to neurodevelopmental and neuropsychiatric disorders in humans (Figure 1). Compelling evidence from experimental models points to HDAC3 being a key player in promoting neurodegeneration in the mature brain (Figure 1). HDAC3 also inhibits regeneration after nerve injury. The detrimental effects of HDAC3 on brain function and health are caused not by changes in its expression, but by posttranslational modifications, altered subcellular localization, and abnormal protein–protein interactions. Therefore, a better understanding of how HDAC3 modification, subcellular localization, and interaction with other proteins is regulated could provide the knowledge necessary for developing therapeutic approaches for nerve injury and neurodegenerative disorders.

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REFERENCES

1. Berger SL. Histone modifications in transcriptional regulation. *Curr Opin Genet Dev* 2002;**12**:142–8
2. Gräff J, Tsai L-H. Histone acetylation: molecular mnemonics on the chromatin. *Nat Rev Neurosci* 2013;**14**:97–111
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. Yang X-J, Seto E. The Rpd3/Hda1 family of lysine deacetylases: from bacteria and yeast to mice and men. *Nat Rev Mol Cell Biol* 2008;**9**:206–18
5. D'Mello SR. Regulation of central nervous system development by class I histone deacetylases. *Dev Neurosci* 2019;**41**:149–65
6. D'Mello SR. Histone deacetylases 1, 2 and 3 in nervous system development. *Curr Opin Pharmacol* 2020;**50**:74–81
7. Goodman JV, Bonni A. Regulation of neuronal connectivity in the mammalian brain by chromatin remodeling. *Curr Opin Neurobiol* 2019;**59**:59–68
8. Pavlou MAS, Grandbarbe L, Buckley NJ, Niclou SP, Michelucci A. Transcriptional and epigenetic mechanisms underlying astrocyte identity. *Prog Neurobiol* 2019;**174**:36–52
9. Hoffmann A, Spengler D. Chromatin remodeling complex NuRD in neurodevelopment and neurodevelopmental disorders. *Front Genet* 2019;**10**:682
10. Herre M, Korb E. The chromatin landscape of neuronal plasticity. *Curr Opin Neurobiol* 2019;**59**:79–86
11. Smigielski L, Jagannath V, Rössler W, Walitza S, Grünblatt E. Epigenetic mechanisms in schizophrenia and other psychotic disorders: a systematic review of empirical human findings. *Mol Psychiatry* 2020. (in press) doi: 10.1038/s41380-019-0601-3
12. Kuehner JN, Bruggeman EC, Wen Z, Yao B. Epigenetic regulations in neuropsychiatric disorders. *Front Genet* 2019;**10**:268
13. Lamonica JM, Zhou Z. Disentangling chromatin architecture to gain insights into the etiology of brain disorders. *Curr Opin Genet Dev* 2019;**55**:76–81
14. Harman MF, Martín MG. Epigenetic mechanisms related to cognitive decline during aging. *J Neurosci Res* 2020;**98**:234–46
15. Lopez-Atalaya JP, Barco A. Can changes in histone acetylation contribute to memory formation? *Trends Genet* 2014;**30**:529–39
16. Barter JD, Foster TC. Aging in the brain: new roles of epigenetics in cognitive decline. *Neuroscientist* 2018;**24**:516–25
17. Thomas EA, D'Mello SR. Complex neuroprotective and neurotoxic effects of histone deacetylases. *J Neurochem* 2018;**145**:96–110
18. Montgomery RL, Potthoff MJ, Haberland M, Qi X, Matsuzaki S, Humphries KM, Richardson JA, Bassel-Duby R, Olson EN. Maintenance of cardiac energy metabolism by histone deacetylase 3 in mice. *J Clin Invest* 2008;**118**:3588–97
19. Norwood J, Franklin JM, Sharma D, DS. Histone deacetylase 3 is necessary for proper brain development. *J Biol Chem* 2014;**289**:34569–82
20. Molnár Z, Kaas JH, de Carlos JA, Hevner RF, Lein E, Němec P. Evolution and development of the mammalian cerebral cortex. *Brain Behav Evol* 2014;**83**:126–39
21. Molnár Z, Clowry GJ, Šestan N, Alzu'bi A, Bakken T, Hevner RF, Hüppi PS, Kostović I, Rakic P, Anton ES, Edwards D, Garcez P, Hoerder-Suabedissen A, Kriegstein A. New insights into the development of the human cerebral cortex. *J Anat* 2019;**235**:432–51
22. Sun YE, Martinowich K, Ge W. Making and repairing the mammalian brain–signaling toward neurogenesis and gliogenesis. *Semin Cell Dev Biol* 2003;**14**:161–8
23. Zhang L, He X, Liu L, Jiang M, Zhao C, Wang H, He D, Zheng T, Zhou X, Hassan A, Ma Z, Xin M, Sun Z, Lazar MA, Goldman SA, Olson EN, Lu QR. Hdac3 interaction with p300 histone acetyltransferase regulates the oligodendrocyte and astrocyte lineage fate switch. *Dev Cell* 2016;**36**:316–30
24. He X, Zhang L, Queme LF, Liu X, Lu A, Waclaw RR, Dong X, Zhou W, Kidd G, Yoon S-O, Buonanno A, Rubin JB, Xin M, Nave K-A, Trapp BD, Jankowski MP, Lu QR. A histone deacetylase 3-dependent pathway delimits peripheral myelin growth and functional regeneration. *Nat Med* 2018;**24**:338–51
25. Rosenberg LH, Cattin A-L, Fontana X, Harford-Wright E, Burden JJ, White IJ, Smith JG, Napoli I, Quereda V, Policarpi C, Freeman J, Ketteler R, Riccio A, Lloyd AC. HDAC3 regulates the transition to the homeostatic myelinating Schwann cell state. *Cell Rep* 2018;**25**:2755–65.e5
26. Jiang Y, Hsieh J. HDAC3 controls gap 2/mitosis progression in adult neural stem/progenitor cells by regulating CDK1 levels. *Proc Natl Acad Sci U S A* 2014;**111**:13541–6
27. Li L, Jin J, Yang X-J. Histone deacetylase 3 governs perinatal cerebral development via neural stem and progenitor cells. *iScience* 2019;**20**:148–67
28. Castelo-Branco G, Lilja T, Wallenborg K, Falcão AM, Marques SC, Gracias A, Solum D, Paap R, Walfridsson J, Teixeira AI, Rosenfeld MG, Jepsen K, Hermanson O. Neural stem cell differentiation is dictated by distinct actions of nuclear receptor corepressors and histone deacetylases. *Stem Cell Rep* 2014;**3**:502–15
29. Gao J, Ruan H, Qi X, Tao Y, Guo X, Shen W. HDAC3 but not HDAC2 mediates visual experience-dependent radial glia proliferation in the developing xenopus tectum. *Front Cell Neurosci* 2016;**10**:221

30. He Y, Wang Z, Sun S, Tang D, Li W, Chai R, Li H. HDAC3 is required for posterior lateral line development in zebrafish. *Mol Neurobiol* 2016;**53**:5103–17
31. Gensburger C, Labourdette G, Sensenbrenner M. Brain basic fibroblast growth factor stimulates the proliferation of rat neuronal precursor cells in vitro. *FEBS Lett* 1987;**217**:1–5
32. Vescovi AL, Reynolds BA, Fraser DD, Weiss S. bFGF regulates the proliferative fate of unipotent (neuronal) and bipotent (neuronal/astroglial) EGF-generated CNS progenitor cells. *Neuron* 1993;**11**:951–66
33. Ray J, Gage FH. Spinal cord neuroblasts proliferate in response to basic fibroblast growth factor. *J Neurosci* 1994;**14**:3548–64
34. Raballo R, Rhee J, Lyn-Cook R, Leckman JF, Schwartz ML, Vaccarino FM. Basic fibroblast growth factor (Fgf2) is necessary for cell proliferation and neurogenesis in the developing cerebral cortex. *J Neurosci* 2000;**20**:5012–23
35. Naruse M, Shibasaki K, Ishizaki Y. FGF-2 signal promotes proliferation of cerebellar progenitor cells and their oligodendrocytic differentiation at early postnatal stage. *Biochem Biophys Res Commun* 2015;**463**:1091–6
36. Vaccarino FM, Schwartz ML, Raballo R, Rhee J, Lyn-Cook R. Fibroblast growth factor signaling regulates growth and morphogenesis at multiple steps during brain development. *Curr Top Dev Biol* 1999;**46**:179–200
37. Steffan JS, Bodai L, Pallos J, Poelman M, McCampbell A, Apostol BL, Kazantsev A, Schmidt E, Zhu YZ, Greenwald M, Kurokawa R, Housman DE, Jackson GR, Marsh JL, Thompson LM. Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in *Drosophila*. *Nature* 2001;**413**:739–43
38. Sharma S, Sarathlal KC, Taliyan R. Epigenetics in neurodegenerative diseases: the role of histone deacetylases. *CNS Neurol Disord Drug Targets* 2019;**18**:11–8
39. Gupta R, Ambasta RK, Kumar P. Pharmacological intervention of histone deacetylase enzymes in the neurodegenerative disorders. *Life Sci* 2020;**243**:117278
40. De Simone A, Milelli A. Histone deacetylase inhibitors as multitarget ligands: new players in Alzheimer's disease drug discovery? *Chem Med Chem* 2019;**14**:1067–73
41. Bates EA, Victor M, Jones AK, Shi Y, Hart AC. Differential contributions of Caenorhabditis elegans histone deacetylases to huntingtin polyglutamine toxicity. *J Neurosci* 2006;**26**:2830–8
42. Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, Nance M, Ross CA, Scahill RI, Wetzel R, Wild EJ, Tabrizi SJ. Huntington disease. *Nat Rev Dis Primers* 2015;**1**:15005
43. Zuccato C, Cattaneo E. Huntington's disease. *Handb Exp Pharmacol* 2014;**220**:357–409
44. Majdzadeh N, Wang L, Morrison BE, Bassel-Duby R, Olson EN, D'Mello SR. HDAC4 inhibits cell-cycle progression and protects neurons from cell death. *Dev Neurobiol* 2008;**68**:1076–92
45. Morrison BE, Majdzadeh N, Zhang X, Lyles A, Bassel-Duby R, Olson EN, D'Mello SR. Neuroprotection by histone deacetylase-related protein. *Mol Cell Biol* 2006;**26**:3550–64
46. Ma C, D'Mello SR. Neuroprotection by histone deacetylase-7 (HDAC7) occurs by inhibition of c-jun expression through a deacetylase-independent mechanism. *J Biol Chem* 2011;**286**:4819–28
47. Bardai FH, D'Mello SR. Selective toxicity by HDAC3 in neurons: regulation by akt and GSK3beta. *J Neurosci* 2011;**31**:1746–51
48. Suelves N, Kirkham-McCarthy L, Lahue RS, Ginés S. A selective inhibitor of histone deacetylase 3 prevents cognitive deficits and suppresses striatal CAG repeat expansions in Huntington's disease mice. *Sci Rep* 2017;**7**:6082
49. Bardai FH, Price V, Zaayman M, Wang L, D'Mello SR. Histone deacetylase-1 (HDAC1) is a molecular switch between neuronal survival and death. *J Biol Chem* 2012;**287**:35444–53
50. Rawat V, Goux W, Piechaczyk M, D'Mello SR. c-Fos protects neurons through a noncanonical mechanism involving HDAC3 interaction: identification of a 21-Amino acid fragment with neuroprotective activity. *Mol Neurobiol* 2016;**53**:1165–80
51. 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**:5280–93
52. Thomas EA. Involvement of HDAC1 and HDAC3 in the pathology of polyglutamine disorders: therapeutic implications for selective HDAC1/HDAC3 inhibitors. *Pharmaceuticals* 2014;**7**:634–61
53. Thomas EA, Coppola G, Desplats PA, Tang B, Soragni E, Burnett R, Gao F, Fitzgerald KM, Borok JF, Herman D, Geschwind DH, Gottesfeld JM. The HDAC inhibitor 4b ameliorates the disease phenotype and transcriptional abnormalities in Huntington's disease transgenic mice. *Proc Natl Acad Sci U S A* 2008;**105**:15564–9
54. Jia H, Morris CD, Williams RM, Loring JF, Thomas EA. HDAC inhibition imparts beneficial transgenerational effects in Huntington's disease mice via altered DNA and histone methylation. *Proc Natl Acad Sci U S A* 2015;**112**:E56–64
55. Jia H, Wang Y, Morris CD, Jacques V, Gottesfeld JM, Rusche JR, Thomas EA. The effects of pharmacological inhibition of histone deacetylase 3 (HDAC3) in Huntington's disease mice. *PLoS One* 2016;**11**:e0152498
56. Bardai FH, Verma P, Smith C, Rawat V, Wang L, D'Mello SR. Disassociation of histone deacetylase-3 from normal Huntingtin underlies mutant Huntingtin neurotoxicity. *J Neurosci* 2013;**33**:11833–8
57. Jia H, Pallos J, Jacques V, Lau A, Tang B, Cooper A, Syed A, Purcell J, Chen Y, Sharma S, Sangrey GR, Darnell SB, Plasterer H, Sadri-Vakili G, Gottesfeld JM, Thompson LM, Rusche JR, Marsh JL, Thomas EA. Histone deacetylase (HDAC) inhibitors targeting HDAC3 and HDAC1 ameliorate polyglutamine-elicited phenotypes in model systems of Huntington's disease. *Neurobiol Dis* 2012;**46**:351–61
58. Janczura KJ, Volmar C-H, Sartor GC, Rao SJ, Ricciardi NR, Lambert G, Brothers SP, Wahlestedt C. Inhibition of HDAC3 reverses Alzheimer's disease-related pathologies in vitro and in the 3xTg-AD mouse model. *Proc Natl Acad Sci U S A* 2018;**115**:E11148–57
59. Krishna K, Behnisch T, Sajikumar S. Inhibition of histone deacetylase 3 restores amyloid-β Oligomer-Induced plasticity deficit in hippocampal CA1 pyramidal neurons. *J Alzheimers Dis* 2016;**51**:783–91
60. Yu L, Liu Y, Jin Y, Cao X, Chen J, Jin J, Gu Y, Bao X, Ren Z, Xu Y, Zhu X. Lentivirus-mediated HDAC3 inhibition attenuates oxidative stress in APPswe/PS1dE9 mice. *J Alzheimers Dis* 2018;**61**:1411–24
61. Wei Z, Meng X, El Fatimy R, Sun B, Mai D, Zhang J, Arora R, Zeng A, Xu P, Qu S, Krichevsky AM, Selkoe DJ, Li S. Environmental enrichment prevents Aβ oligomer-induced synaptic dysfunction through mirna-132 and hdac3 signaling pathways. *Neurobiol Dis* 2019;**134**:104617
62. Han KA, Shin WH, Jung S, Seol W, Seo H, Ko C, Chung KC. Leucine-rich repeat kinase 2 exacerbates neuronal cytotoxicity through phosphorylation of histone deacetylase 3 and histone deacetylation. *Hum Mol Genet* 2017;**26**:1–18
63. Rai M, Soragni E, Chou CJ, Barnes G, Jones S, Rusche JR, Gottesfeld JM, Pandolfo M. 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
64. Shan B, Xu C, Zhang Y, Xu T, Gottesfeld JM, Yates JR. Quantitative proteomic analysis identifies targets and pathways of a 2-aminobenzamide HDAC inhibitor in Friedreich's ataxia patient iPSC-derived neural stem cells. *J Proteome Res* 2014;**13**:4558–66
65. Soragni E, Chou CJ, Rusche JR, Gottesfeld JM. Mechanism of action of 2-aminobenzamide HDAC inhibitors in reversing gene silencing in Friedreich's. *Ataxia. Front Neurol* 2015;**6**:44
66. Duncan CE, An MC, Papanikolaou T, Rugani C, Vitelli C, Ellerby LM. Histone deacetylase-3 interacts with ataxin-7 and is altered in a spinocerebellar ataxia type 7 mouse model. *Mol Neurodegener* 2013;**8**:42
67. Matheson R, Chida K, Lu H, Clendaniel V, Fisher M, Thomas A, Lo EH, Selim M, Shehadah A. Neuroprotective effects of selective inhibition of histone deacetylase 3 in experimental stroke. *Transl Stroke Res* 2020. (in press). doi: 10.1007/s12975-020-00783-3
68. Zhao H, Li G, Zhang S, Li F, Wang R, Tao Z, Ma Q, Han Z, Yan F, Fan J, Li L, Ji X, Luo Y. Inhibition of histone deacetylase 3 by MiR-494

alleviates neuronal loss and improves neurological recovery in experimental stroke. *J Cereb Blood Flow Metab* 2019;**39**:2392–405
69. Yang X, Wu Q, Zhang L, Feng L. Inhibition of histone deacetylase 3 (HDAC3) mediates ischemic preconditioning and protects cortical neurons against ischemia in rats. *Front Mol Neurosci* 2016;**9**:131
70. Kuboyama T, Wahane S, Huang Y, Zhou X, Wong JK, Koemeter-Cox A, Martini M, Friedel RH, Zou H. HDAC3 inhibition ameliorates spinal cord injury by immunomodulation. *Sci Rep* 2017;**7**:8641
71. Schlüter A, Aksan B, Fioravanti R, Valente S, Mai A, Mauceri D. Histone deacetylases contribute to excitotoxicity-triggered degeneration of retinal ganglion cells in vivo. *Mol Neurobiol* 2019;**56**:8018–34
72. Schmitt HM, Pelzel HR, Schlamp CL, Nickells RW. Histone deacetylase 3 (HDAC3) plays an important role in retinal ganglion cell death after acute optic nerve injury. *Mol Neurodegener* 2014;**9**:39
73. Rumbaugh G, Sillivan SE, Ozkan ED, Rojas CS, Hubbs CR, Aceti M, Kilgore M, Kudugunti S, Puthanveettil SV, Sweatt JD, Rusche J, Miller CA. Pharmacological selectivity within class I histone deacetylases predicts effects on synaptic function and memory rescue. *Neuropsychopharmacology* 2015;**40**:2307–16
74. Malvaez M, McQuown SC, Rogge GA, Astarabadi M, Jacques V, Carreiro S, Rusche JR, Wood MA. HDAC3-selective inhibitor enhances extinction of cocaine-seeking behavior in a persistent manner. *Proc Natl Acad Sci U S A* 2013;**110**:2647–52
75. McQuown SC, Barrett RM, Matheos DP, Post RJ, Rogge GA, Alenghat T, Mullican SE, Jones S, Rusche JR, Lazar MA, Wood MA. HDAC3 is a critical negative regulator of long-term memory formation. *J Neurosci* 2011;**31**:764–74
76. Rogge GA, Singh H, Dang R, Wood MA. HDAC3 is a negative regulator of cocaine-context-associated memory formation. *J Neurosci* 2013;**33**:6623–32
77. Zhou W, He Y, Rehman AU, Kong Y, Hong S, Ding G, Yalamanchili HK, Wan Y-W, Paul B, Wang C, Gong Y, Zhou W, Liu H, Dean J, Scalais E, O'Driscoll M, Morton JEV, Study DDD, Hou X, Wu Q, et al. Loss of function of NCOR1 and NCOR2 impairs memory through a novel GABAergic hypothalamus-CA3 projection. *Nat Neurosci* 2019;**22**:205–17
78. Zhu X, Wang S, Yu L, Jin J, Ye X, Liu Y, Xu Y. HDAC3 negatively regulates spatial memory in a mouse model of Alzheimer's disease. *Aging Cell* 2017;**16**:1073–82
79. Chen S, Ye J, Chen X, Shi J, Wu W, Lin W, Lin W, Li Y, Fu H, Li S. Valproic acid attenuates traumatic spinal cord injury-induced inflammation via STAT1 and NF-κB pathway dependent of HDAC3. *J Neuroinammation* 2018;**15**:150
80. Moumné L, Campbell K, Howland D, Ouyang Y, Bates GP. Genetic knock-down of HDAC3 does not modify disease-related phenotypes in a mouse model of Huntington's disease. *PLoS One* 2012;**7**:e31080
81. Duda P, Wiśniewski J, Wójtowicz T, Wójcicka O, Jaśkiewicz M, Drulis-Fajdasz D, Rakus D, McCubrey JA, Gizak A. Targeting GSK3 signaling as a potential therapy of neurodegenerative diseases and aging. *Expert Opin Ther Targets* 2018;**22**:833–48
82. Llorens-Martín M, Jurado J, Hernández F, Avila J. GSK-3β, a pivotal kinase in Alzheimer disease. *Front Mol Neurosci* 2014;**7**:46
83. Avila J, Wandosell F, Hernández F. Role of glycogen synthase kinase-3 in Alzheimer's disease pathogenesis and glycogen synthase kinase-3 inhibitors. *Expert Rev Neurother* 2010;**10**:703–10
84. Li D-W, Liu Z-Q, Chen W, Yao M, Li G-R. Association of glycogen synthase kinase-3β with Parkinson's disease (review). *Mol Med Rep* 2014;**9**:2043–50
85. Guenther MG, Barak O, Lazar MA. The SMRT and N-CoR corepressors are activating cofactors for histone deacetylase 3. *Mol Cell Biol* 2001;**21**:6091–101
86. Karagianni P, Wong J. HDAC3: taking the SMRT-N-CoRrect road to repression. *Oncogene* 2007;**26**:5439–49
87. Li J, Wang J, Wang J, Nawaz Z, Liu JM, Qin J, Wong J. Both corepressor proteins SMRT and N-CoR exist in large protein complexes containing HDAC3. *EMBO J* 2000;**19**:4342–50
88. Sanna MD, Galeotti N. The HDAC1/c-JUN complex is essential in the promotion of nerve injury-induced neuropathic pain through JNK signaling. *Eur J Pharmacol* 2018;**825**:99–106
89. Hervera A, Zhou L, Palmisano I, McLachlan E, Kong G, Hutson TH, Danzi MC, Lemmon VP, Bixby JL, Matamoros-Angles A, Forsberg K, De Virgiliis F, Matheos DP, Kwapis J, Wood MA, Puttagunta R, Del Río JA, Di Giovanni S. PP4-dependent HDAC3 dephosphorylation discriminates between axonal regeneration and regenerative failure. *EMBO J* 2019;**38**:e101032
90. Liu J-P, Zeitlin SO. Is Huntingtin dispensable in the adult brain? *J Huntingtons Dis* **6**:1–17
91. Saudou F, Humbert S. The biology of Huntingtin. *Neuron* 2016;**89**:910–26
92. Emmett MJ, Lazar MA. Integrative regulation of physiology by histone deacetylase 3. *Nat Rev Mol Cell Biol* 2019;**20**:102–15
93. Evert BO, Araujo J, Vieira-Saecker AM, de Vos RAI, Harendza S, Klockgether T, Wüllner U. Ataxin-3 represses transcription via chromatin binding, interaction with histone deacetylase 3, and histone deacetylation. *J Neurosci* 2006;**26**:11474–86
94. Zeng L, Zhang D, McLoughlin HS, Zalon AJ, Aravind L, Paulson HL. Loss of the spinocerebellar ataxia type 3 disease protein ATXN3 alters transcription of multiple signal transduction pathways. *PLoS One* 2018;**13**:e0204438
95. Park S. Brain-Region specific apoptosis triggered by Eph/ephrin signaling. *Exp Neurobiol* 2013;**22**:143–8
96. Louis Sam Titus ASC, Sharma D, Kim MS, D'Mello SR. The Bdnf and Npas4 genes are targets of HDAC3-mediated transcriptional repression. *BMC Neurosci* 2019;**20**:65
97. Zuccato C, Cattaneo E. Brain-derived neurotrophic factor in neurodegenerative diseases. *Nat Rev Neurol* 2009;**5**:311–22
98. Palasz E, Wysocka A, Gasiorowska A, Chalimoniuk M, Niewiadomski W, Niewiadomska G. BDNF as a promising therapeutic agent in Parkinson's *disease. Int J Mol Sci* 2020;**21**: pii: E1170
99. Lanuza MA, Just-Borràs L, Hurtado E, Cilleros-Mañé V, Tomàs M, Garcia N, Tomàs J. The impact of kinases in amyotrophic lateral sclerosis at the neuromuscular synapse: insights into BDNF/TrkB and PKC signaling. *Cells* 2019;**8**:pii: E1578
100. Chen S-D, Wu C-L, Hwang W-C, Yang D-I. More insight into BDNF against neurodegeneration: anti-apoptosis, anti-oxidation, and suppression of autophagy. *Int J Mol Sci* 2017;**18**:545
101. Chen A, Xiong L-J, Tong Y, Mao M. The neuroprotective roles of BDNF in hypoxic ischemic brain injury. *Biomed Rep* 2013;**1**:167–76
102. Benussi L, Binetti G, Ghidoni R. Loss of neuroprotective factors in neurodegenerative dementias: the end or the starting point? *Front Neurosci* 2017;**11**:672
103. Daly C, Ward R, Reynolds AL, Galvin O, Collery RF, Kennedy BN. Brain-derived neurotrophic factor as a treatment option for retinal degeneration. *Adv Exp Med Biol* 2018;**1074**:465–71
104. Choy FC, Klarić TS, Koblar SA, Lewis MD. The role of the neuroprotective factor Npas4 in cerebral ischemia. *Int J Mol Sci* 2015;**16**:29011–28
105. Choy FC, Klarić TS, Leong WK, Koblar SA, Lewis MD. Reduction of the neuroprotective transcription factor Npas4 results in increased neuronal necrosis, inflammation and brain lesion size following ischaemia. *J Cereb Blood Flow Metab* 2016;**36**:1449–63
106. Woitecki AMH, Müller JA, van Loo KMJ, Sowade RF, Becker AJ, Schoch S. Identification of synaptotagmin 10 as effector of NPAS4-mediated protection from excitotoxic neurodegeneration. *J Neurosci* 2016;**36**:2561–70
107. Ooe N, Motonaga K, Kobayashi K, Saito K, Kaneko H. Functional characterization of basic helix-loop-helix-PAS type transcription factor NXF in vivo: putative involvement in an "on demand" neuroprotection system. *J Biol Chem* 2009;**284**:1057–63
108. Zhang S-J, Zou M, Lu L, Lau D, Ditzel DAW, Delucinge-Vivier C, Aso Y, Descombes P, Bading H. Nuclear calcium signaling controls expression of a large gene Pool: identification of a gene program for acquired neuroprotection induced by synaptic activity. *PLoS Genet* 2009;**5**: e1000604
109. Qu Z, D'Mello SR. Proteomic analysis identifies NPTX1 and HIP1R as potential targets of histone deacetylase-3-mediated neurodegeneration. *Exp Biol Med* 2018;**243**:627–38

110. Abad MA, Enguita M, DeGregorio-Rocasolano N, Ferrer I, Trullas R. Neuronal pentraxin 1 contributes to the neuronal damage evoked by amyloid-beta and is overexpressed in dystrophic neurites in Alzheimer's brain. *J Neurosci* 2006;**26**:12735–47
111. Clayton KB, Podlesniy P, Figueiro-Silva J, López-Doménech G, Benitez L, Enguita M, Abad MA, Soriano E, Trullas R. NP1 regulates neuronal activity-dependent accumulation of BAX in mitochondria and mitochondrial dynamics. *J Neurosci* 2012;**32**:1453–66
112. Figueiro-Silva J, Gruart A, Clayton KB, Podlesniy P, Abad MA, Gasull X, Delgado-García JM, Trullas R. Neuronal pentraxin 1 negatively regulates excitatory synapse density and synaptic plasticity. *J Neurosci* 2015;**35**:5504–21
113. Hooper AWM, Alamilla JF, Venier RE, Gillespie DC, Igdoura SA. Neuronal pentraxin 1 depletion delays neurodegeneration and extends life in Sandhoff disease mice. *Hum Mol Genet* 2017;**26**:661–73
114. Yeste-Velasco M, Folch J, Trullàs R, Abad MA, Enguita M, Pallàs M, Camins A. Glycogen synthase kinase-3 is involved in the regulation of the cell cycle in cerebellar granule cells. *Neuropharmacology* 2007;**53**:295–307
115. Hossain MA, Russell JC, O'Brien R, Laterra J. Neuronal pentraxin 1: a novel mediator of hypoxic-ischemic injury in neonatal brain. *J Neurosci* 2004;**24**:4187–96
116. Al Rahim M, Hossain MA. Genetic deletion of NP1 prevents hypoxic-ischemic neuronal death via reducing AMPA receptor synaptic localization in hippocampal neurons. *J Am Heart Assoc* 2013;**2**:e006098
117. Russell JC, Kishimoto K, O'Driscoll C, Hossain MA. Neuronal pentraxin 1 induction in hypoxic-ischemic neuronal death is regulated via a glycogen synthase kinase-3α/β dependent mechanism. *Cell Signal* 2011;**23**:673–82
118. Thatipamula S, Hossain MA. Critical role of extracellularly secreted neuronal pentraxin 1 in ischemic neuronal death. *BMC Neurosci* 2014;**15**:133
119. Thatipamula S, Al Rahim M, Zhang J, Hossain MA. Genetic deletion of neuronal pentraxin 1 expression prevents brain injury in a neonatal mouse model of cerebral hypoxia-ischemia. *Neurobiol Dis* 2015;**75**:15–30
120. Peng L, Yang Q, Xu X, Du Y, Wu Y, Shi X, Xu J, Zhu L, Luo J. Huntingtin-Interacting protein 1-Related protein plays a critical role in dendritic development and excitatory synapse formation in hippocampal neurons. *Front Mol Neurosci* 2017;**10**:186
121. Yang Q, Peng L, Wu Y, Li Y, Wang L, Luo J-H, Xu J. Endocytic adaptor protein HIP1R controls intracellular trafficking of epidermal growth factor receptor in neuronal dendritic development. *Front Mol Neurosci* 2018;**11**:447
122. Bao Y, Chen H, Cai Z, Zheng J, Zou J, Shi Y, Jiang L. Advanced glycation end products inhibit neural stem cell differentiation via upregualtion of HDAC3 expression. *Brain Res Bull* 2020;**159**:1–8
123. Miyamoto E. Molecular mechanism of neuronal plasticity: induction and maintenance of long-term potentiation in the hippocampus. *J Pharmacol Sci* 2006;**100**:433–42
124. Gallo FT, Katche C, Morici JF, Medina JH, Weisstaub NV. Immediate early genes, memory and psychiatric disorders: focus on c-Fos, Egr1 and arc. *Front Behav Neurosci* 2018;**12**:79
125. Hawk JD, Abel T. The role of NR4A transcription factors in memory formation. *Brain Res Bull* 2011;**85**:21–9
126. Bridi MS, Hawk JD, Chatterjee S, Safe S, Abel T. Pharmacological activators of the NR4A nuclear receptors enhance LTP in a CREB/CBP-Dependent manner. *Neuropsychopharmacology* 2017;**42**:1243–53
127. Sun Z, Feng D, Fang B, Mullican SE, You S-H, Lim H-W, Everett LJ, Nabel CS, Li Y, Selvakumaran V, Won K-J, Lazar MA. Deacetylase-independent function of HDAC3 in transcription and metabolism requires nuclear receptor corepressor. *Mol Cell* 2013;**52**:769–82
128. Talbot K, Eidem WL, Tinsley CL, Benson MA, Thompson EW, Smith RJ, Hahn C-G, Siegel SJ, Trojanowski JQ, Gur RE, Blake DJ, Arnold SE. Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia. *J Clin Invest* 2004;**113**:1353–63
129. Tang J, LeGros RP, Louneva N, Yeh L, Cohen JW, Hahn C-G, Blake DJ, Arnold SE, Talbot K. Dysbindin-1 in dorsolateral prefrontal cortex of schizophrenia cases is reduced in an isoform-specific manner unrelated to dysbindin-1 mRNA expression. *Hum Mol Genet* 2009;**18**:3851–63
130. Weickert CS, Rothmond DA, Hyde TM, Kleinman JE, Straub RE. Reduced DTNBP1 (dysbindin-1) mRNA in the hippocampal formation of schizophrenia patients. *Schizophr Res* 2008;**98**:105–10
131. Weickert CS, Straub R, Kleinman J, Hyde T, Rothmond D. Reduced dysbindin (DTNBP1) mRNA in hippocampus of patients with schizophrenia. *Acta Neuropsychiatr* 2006;**18**:307–8
132. Carlson GC, Talbot K, Halene TB, Gandal MJ, Kazi HA, Schlosser L, Phung QH, Gur RE, Arnold SE, Siegel SJ. Dysbindin-1 mutant mice implicate reduced fast-phasic inhibition as a final common disease mechanism in schizophrenia. *Proc Natl Acad Sci U S A* 2011;**108**:E962–970
133. Cox MM, Tucker AM, Tang J, Talbot K, Richer DC, Yeh L, Arnold SE. Neurobehavioral abnormalities in the dysbindin-1 mutant, sandy, on a C57BL/6J genetic background. *Genes Brain Behav* 2009;**8**:390–7
134. Bhardwaj SK, Baharnoori M, Sharif-Askari B, Kamath A, Williams S, Srivastava LK. Behavioral characterization of dysbindin-1 deficient sandy mice. *Behav Brain Res* 2009;**197**:435–41
135. Carr GV, Jenkins KA, Weinberger DR, Papaleo F. Loss of dysbindin-1 in mice impairs reward-based operant learning by increasing impulsive and compulsive behavior. *Behav Brain Res* 2013;**241**:173–84
136. Soma M, Wang M, Suo S, Ishiura S. Dysbindin-1, a schizophrenia-related protein, interacts with HDAC3. *Neurosci Lett* 2014;**582**:120–4
137. Bahari-Javan S, Varbanov H, Halder R, Benito E, Kaurani L, Burkhardt S, Anderson-Schmidt H, Anghelescu I, Budde M, Stilling RM, Costa J, Medina J, Dietrich DE, Figge C, Folkerts H, Gade K, Heilbronner U, Koller M, Konrad C, Nussbeck SY, Scherk H, Spitzer C, Stierl S, Stöckel J, Thiel A, von Hagen M, Zimmermann J, Zitzelsberger A, Schulz S, Schmitt A, Delalle I, Falkai P, Schulze TG, Dityatev A, Sananbenesi F, Fischer A.. HDAC1 links early life stress to schizophrenia-like phenotypes. *Proc Natl Acad Sci U S A* 2017;**114**:E4686–94
138. Večeřa J, Bártová E, Krejčí J, Legartová S, Komůrková D, Rudá-Kučerová J, Štark T, Dražanová E, Kašpárek T, Šulcová A, Dekker FJ, Szymanski W, Seiser C, Weitzer G, Mechoulam R, Micale V, Kozubek S. HDAC1 and HDAC3 underlie dynamic H3K9 acetylation during embryonic neurogenesis and in schizophrenia-like animals. *J Cell Physiol* 2018;**233**:530–48
139. Benes FM, Lim B, Matzilevich D, Walsh JP, Subburaju S, Minns M. Regulation of the GABA cell phenotype in hippocampus of schizophrenics and bipolars. *Proc Natl Acad Sci U S A* 2007;**104**:10164–9
140. Sharma RP, Grayson DR, Gavin DP. Histone deactylase 1 expression is increased in the prefrontal cortex of schizophrenia subjects: analysis of the national brain databank microarray collection. *Schizophr Res* 2008;**98**:111–7
141. Lo-Castro A, Brancati F, Digilio MC, Garaci FG, Bollero P, Alfieri P, Curatolo P. Neurobehavioral phenotype observed in KBG syndrome caused by ANKRD11 mutations. *Am J Med Genet B Neuropsychiatr Genet* 2013;**162B**:17–23
142. Sirmaci A, Spiliopoulos M, Brancati F, Powell E, Duman D, Abrams A, Bademci G, Agolini E, Guo S, Konuk B, Kavaz A, Blanton S, Digilio MC, Dallapiccola B, Young J, Zuchner S, Tekin M. Mutations in ANKRD11 cause KBG syndrome, characterized by intellectual disability, skeletal malformations, and macrodontia. *Am J Hum Genet* 2011;**89**:289–94
143. Sacharow S, Li D, Fan YS, Tekin M. Familial 16q24.3 microdeletion involving ANKRD11 causes a KBG-like syndrome. *Am J Med Genet A* 2012;**158A**:547–52
144. Zhang A, Li C-W, Tsai S-C, Chen JD. Subcellular localization of ankyrin repeats cofactor-1 regulates its corepressor activity. *J Cell Biochem* 2007;**101**:1301–15
145. Zhang A, Li C-W, Chen JD. Characterization of transcriptional regulatory domains of ankyrin repeat cofactor-1. *Biochem Biophys Res Commun* 2007;**358**:1034–40
146. Gallagher D, Voronova A, Zander MA, Cancino GI, Bramall A, Krause MP, Abad C, Tekin M, Neilsen PM, Callen DF, Scherer SW, Keller GM, Kaplan DR, Walz K, Miller FD. Ankrd11 is a chromatin regulator

involved in autism that is essential for neural development. *Dev Cell* 2015;**32**:31–42
147. Yoon H-G, Chan DW, Huang Z-Q, Li J, Fondell JD, Qin J, Wong J. Purification and functional characterization of the human N-CoR complex: the roles of HDAC3, TBL1 and TBLR1. *EMBO J* 2003;**22**:1336–46
148. Pons L, Cordier MP, Labalme A, Till M, Louvrier C, Schluth-Bolard C, Lesca G, Edery P, Sanlaville D. A new syndrome of intellectual disability with dysmorphism due to TBL1XR1 deletion. *Am J Med Genet A* 2015;**167A**:164–8
149. Li JY, Daniels G, Wang J, Zhang X. TBL1XR1 in physiological and pathological states. *Am J Clin Exp Urol* 2015;**3**:13–23
150. Mao X, Hou T, Cao B, Wang W, Li Z, Chen S, Fei M, Hurren R, Gronda M, Wu D, Trudel S, Schimmer AD. The tricyclic antidepressant amitriptyline inhibits D-cyclin transactivation and induces myeloma cell apoptosis by inhibiting histone deacetylases: in vitro and in silico evidence. *Mol Pharmacol* 2011;**79**:672–80
151. Nghia NA, Hirasawa T, Kasai H, Obata C, Moriishi K, Mochizuki K, Koizumi S, Kubota T. Long-term imipramine treatment increases N-methyl-d-aspartate receptor activity and expression via epigenetic mechanisms. *Eur J Pharmacol* 2015;**752**:69–77
152. Ookubo M, Kanai H, Aoki H, Yamada N. Antidepressants and mood stabilizers effects on histone deacetylase expression in C57BL/6 mice: brain region specific changes. *J Psychiatr Res* 2013;**47**:1204–14
153. Kwapis JL, Alaghband Y, Kramár EA, López AJ, Vogel Ciernia A, White AO, Shu G, Rhee D, Michael CM, Montellier E, Liu Y, Magnan CN, Chen S, Sassone-Corsi P, Baldi P, Matheos DP, Wood MA. Epigenetic regulation of the circadian gene Per1 contributes to age-related changes in hippocampal memory. *Nat Commun* 2018;**9**:3323
154. Rawashdeh O, Jilg A, Maronde E, Fahrenkrug J, Stehle JH. Period1 gates the circadian modulation of memory-relevant signaling in mouse hippocampus by regulating the nuclear shuttling of the CREB kinase pP90RSK. *J Neurochem* 2016;**138**:731–45
155. Rawashdeh O, Jilg A, Jedlicka P, Slawska J, Thomas L, Saade A, Schwarzacher SW, Stehle JH. PERIOD1 coordinates hippocampal rhythms and memory processing with daytime. *Hippocampus* 2014;**24**:712–23
156. Kwapis JL, Alaghband Y, López AJ, Long JM, Li X, Shu G, Bodinayake KK, Matheos DP, Rapp PR, Wood MA. HDAC3-Mediated repression of the Nr4a family contributes to Age-Related impairments in Long-Term memory. *J Neurosci* 2019;**39**:4999–5009
157. Hawk JD, Bookout AL, Poplawski SG, Bridi M, Rao AJ, Sulewski ME, Kroener BT, Manglesdorf DJ, Abel T. NR4A nuclear receptors support memory enhancement by histone deacetylase inhibitors. *J Clin Invest* 2012;**122**:3593–602
158. Hawk JD, Florian C, Abel T. Post-training intrahippocampal inhibition of class I histone deacetylases enhances long-term object-location memory. *Learn Mem* 2011;**18**:367–70