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Regulation of CNS Development by Class I HDACs

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Abstract

Neurodevelopment is a highly complex process composed of several carefully regulated events starting from the proliferation of neuroepithelial cells and culminating with and refining of neural networks and synaptic transmission. Improper regulation of any of these neurodevelopmental events often results in severe brain dysfunction. Accumulating evidence indicates that epigenetic modifications of chromatin plays a key role in neurodevelopmental regulation. Among these modifications are histone acetylation and deacetylation, which control access of transcription factors to DNA thereby regulating gene transcription. Histone deacetylation, which restricts access of transcription factor repressing gene transcription, involves the action of members of a family of 18 enzymes, the histone deacetylases (HDACs), which are subdivided in four subgroups. This review focuses on the Group 1 HDACs – HDAC 1, 2, 3 and 8. Although much of the evidence for HDAC involvement in neurodevelopment has come from the use of pharmacological inhibitors, because these agents are generally non-selective with regard to their effects on individual members of the HDAC family, this review is limited to evidence garnered from the use of molecular genetic approaches. Our review describes that Class I HDACs play essential roles in all phases of neurodevelopment. Modulation of the activity of individual HDACs could be an important therapeutic approach for neurodevelopmental and psychiatric disorders.

Keywords

Cerebellum; Conditional knockout (cKO); Histone deactylase (HDAC); Neocortex; Neural progenitor cells (NPCs); Neurodevelopment; Neurodevelopmental disorders

The development of the vertebrate central nervous system (CNS) is a highly complex process involving several discreet phases, each requiring careful and coordinated regulation of a large number of specific genes, the expression of which are regulated by transcription factors often in association with protein complexes. A key regulatory feature of transcription is chromatin structure which can be modified to promote or prevent accessibility to transcription factors and the RNA polymerase complex. A family of enzymes that modulate chromatin structure are the histone deacetylases (HDACs). HDACs can deacetylate the N-terminal tails of the core H3 and H4 histones enhancing their interaction with DNA resulting in the compacting of chromatin. The compressed chromatin prevents access to

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transcriptional machinery rendering it into a transcriptionally repressed state [2,3]. In addition to regulating their access to DNA, HDACs can control the function of transcription factors by regulating their subcellular localization, their DNA-binding activity and their interaction with other proteins [4,5]. HDACs can also affect transcription through deacetylation of other components within the multiprotein complexes that include transcription factors or RNA polymerase, which can promote assembly or disassembly of the complexes [4,5]. The action of HDACs on histones and non-histone proteins is opposed by histone acetyltransferases (HATs) [6,7]. Based on the realization that the substrate repertoire of HDACs and HATs include large numbers of non-histone nuclear and cytoplasmic proteins, these enzymes also referred to as lysine deacetylases (KDACs) and lysine acetylases (KATs).

Neurons are postmitotic and long-lived cells, but yet possess a high level of malleability with respect to morphology and gene expression patterns. Dynamic epigenetic mechanisms, such as histone acetylation and deacetylation, play a critical role in the ability of neurons to respond and adapt to diverse sensory and experience-based stimuli during development and into adulthood by making short and long-lasting changes in gene expression [8]. Failure to do this can lead to aberrant functioning of the brain. Indeed, it is now recognized that disruption in the balance between histone acetylation and deacetylation can directly cause or contribute to neurodevelopmental and psychiatric disorders [9–13].

The histone deacetylases

Eighteen different HDACs are expressed in mammals [4,5]. These are sub-divided into four families – Class I, II, II and IV. Whereas Class I, II and IV HDACs are zinc-dependent enzymes, often referred to as classical HDACs, Class III HDACs, also referred to as sirtuins, are structurally different and are activated by nicotinamide adenine dinucleotide (NAD). Class I include HDACs 1, 2, 3 and 8, which are widely expressed. Whereas HDAC3 can localize to both the cytoplasm and nucleus, the other Class I HDACs are generally nuclear proteins. Class II HDACs display a restricted pattern of expression further divided into two sub-families. Class IIa includes HDACs 4, 5, 7 and 9, which are proteins with extended N-terminal regulatory domains and that can translocate between the nucleus and the cytoplasm in a stimulus-dependent manner [4,5]. Class IIa HDACs have little or no deacetylase activity because of the presence of a histidine residue rather than a tyrosine residue in the active site of these HDACs [14]. HDAC6 and HDAC10 are Class IIb HDACs possessing distinct C-terminal domains. Whereas HDAC6 is cytoplasmic, HDAC10 can be in both the nucleus and cytoplasm. A well-established substrate of HDAC6 is tubulin, the building block of microtubules [15,16]. HDAC11, the only Class IV HDAC, structurally resembles both Class I and Class II HDACs.

A large amount of evidence supports the involvement of both classical HDACs and sirtuins in injury and age-related neurodegenerative processes and diseases [17–20]. While some HDACs promote neurodegeneration others protect against it and in some cases, such as for HDAC1, both neuroprotective and neurotoxic actions have been described [19]. This review covers the role of the classical HDACs in the development of the CNS. Focus is placed primarily on members of the Class I group - HDAC1, HDAC2 HDAC3 and HDAC8.

Germline deletion of either *Hdac1* or *Hdac3* causes severe developmental abnormalities and embryonic lethality indicating critical functions of these two HDACs during embryogenesis that cannot be compensated for by other HDACs (Hagelkruys et al., 2014; R. L. Montgomery, Hsieh, Barbosa, Richardson, & Olson, 2009). In comparison, germline deletion of *Hdac2* causes death perinatally or after a few months depending on the ablation strategy used (HDAC2) [22–24]. In one study a portion of *Hdac2* knockout mice even had a normal lifespan albeit with reduced body size, weight, and female fertility (Guan et al., 2009; R. L. Montgomery et al., 2009; Trivedi et al., 2007). Although much valuable information on the role of HDACs in physiological and pathophysiological processes has been derived from studies using chemical inhibitors of HDACs, these inhibitors are not selective with regard to their effects on the different members of the HDAC family, particularly the Class I HDACs. Moreover, it is now clear that some of members of the HDAC family have related and opposing functions rendering the results obtained from the use of chemical inhibitors difficult to interpret [21,26]. An additional complication is that, as described in this review, HDAC3 and likely also HDACs1 and 2 have functions that are independent of deacetylase activity [27,28]. For these reasons we have restricted this review only to studies that have employed molecular biological and genetic approaches to dissect the functions of Class I HDACs in CNS development. Although not covered in this review, it should be noted that deregulation or mutations of HATs, which counteract the activity of HDACs, also cause or are associated with brain abnormalities and severe neurodevelopmental disorders. The involvement of HATs in brain function and disease has been reviewed elsewhere [6,7,13,29–31].

Class I HDACS

Based on phylogenetic analyses, mammalian *Hdac1* and *Hdac2* likely originated the duplication of a common ancestral gene that occurred relatively lately (Oger et al., 2008). Consistent with this is that while many vertebrates and all mammals analyzed so far possess both *Hdac1* and *Hdac2* genes, some vertebrates such as zebrafish and frogs possess a single *Hdac1/Hdac2*-like gene. Also consistent with the duplication being recent, human HDAC1 and HDAC2 exhibit 84% amino acid sequence identity [33–35]. Both proteins are targets of various posttranslational modifications and many of the modified sites are conserved in the two proteins. It is therefore believed that HDAC1 and HDAC2 play largely redundant roles. In mammalian cells, HDAC1 and HDAC2 can homo- and heterodimerize, and are part of co-repressor multiprotein complexes which are recruited to chromatin primarily via DNA-binding transcription factors. Since HDAC1 and HDAC2 don't bind DNA directly, the complex in which they exist dictates the functional roles that they play. Three of the best studied HDAC1/2-containing multiprotein complexes are Co-REST (co-repressor for element-1-silencing transcription factor), NuRD (nucleosome remodeling and deactylation) and Sin3 [32]. It is not clear how HDAC1/HDAC2 are recruited to these functionally-distinct complexes. Furthermore, the CoREST, NuRD and Sin3 complexes are themselves heterogenous in their composition even within the same cell type which adds further complexity to the functions of HDAC1/HDAC2 [32,36,37]. Based on their histone deacetylase activity and association with co-repressors, it was expected that HDAC1/HDAC2 act to repress gene transcription. But based analyses of knockout mice as well as

molecular and biochemical studies it is now known that HDAC1/HDAC2 are more enriched at transcriptionally active regions of chromatin [22,38–42]. It is thought that epigenetic modifications made by HDAC1/HDAC2 may at least promote and are possibly critical for the activation of transcription by HATs [43].

HDAC3, which shares only about 50% amino acid identity with HDAC1 and HDAC2, is part of two protein complexes distinct from those containing HDAC1 and HDAC2. The two complexes contain either NCOR1 (Nuclear Receptor Corepressor-1) or NCOR2 (also known as silencing mediator of retinoid and thyroid receptors, or SMRT) [44–47] along with TBL1, a WD40 protein and GPS2, a signaling regulator [44,45,48].

An HDAC8 ortholog has been identified in protosomia but has been lost subsequently during evolution in some species, including *Drosophila* and *C. Elegans* [35,49]. However, all vertebrates express HDAC8.

Development of the neocortex

Studies on the molecular and cellular mechanisms regulating brain development have focused predominantly on the neocortex, the seat of higher cognitive functions. Neuroepithelial cells (NECs) along the wall of the neural tube rapidly proliferate generating the ventricular zone (VZ) that lines the walls of the lateral ventricle [50–52]. The NECs transform to the highly polarized radial glial progenitors (RGPs), henceforth referred to as neural progenitor cells (NPCs), which have their cell bodies in the VZ. NPCs undergo either symmetrical to self-renew, or asymmetrical divisions to produce neurons and intermediate progenitors (IPs). While differentiating neurons migrate out of the VZ and towards the pial surface on the fibers of NPCs, IPs migrate to form the subventricular zone another proliferative zone in which the IPs divide symmetrically to produce neurons. It deserves mention that while the overall design in humans is similar to brain development in rodents, human neocortical development is more complex involving the generation of additional subtypes of NPCs and IPs [53–55]. Whereas the early-born NPC-derived neurons produced in the VZ migrate radially to predominantly form the deep layers of the 6-layer cortex, the neurons produced subsequently from the IPs localized to the SVZ are more enriched in the upper layers [56]. While excitatory projection neurons, which account for about 80% of all neurons in the neocortex, migrate in such a radial pattern from the VZ/SVZ to the 6-layered cortex, inhibitory GABAergic interneurons migrate tangentially to the neocortex from the ganglionic eminences. These two broad neuronal classes include a multitude of subtypes that reside in specific layers and locations within the neocortex. A large number of neurons in the neocortex, estimated at 20% - 70% in rodents, are eliminated by programmed cell death both prenatally and in the first few weeks after birth, a process regulated by neuronal activity and neurotrophic factors [57].

Following migration and maturation, excitatory projection neurons and inhibitory interneurons form local and long-range synaptic connections to generate functional neural circuitry, a highly complex process that is built through genetic control but refined by sensory stimulation, experience and learning [58]. Proper functioning of neural circuitry depends on maintaining a proper balance of excitatory and inhibitory inputs onto projection neurons [59]. Synaptic input is plastic permitting adaptation of neural circuity to diverse

environmental cues, sensations and experiences. Disruption in synaptic transmission or plasticity in the neocortex or brain parts, such as the hippocampus and cerebellum, is a consistent feature of various neurodevelopmental and psychiatric disorders, including Down syndrome, epilepsy, autism, bipolar disorder, and schizophrenia [59–63].

Roles of HDAC1 and HDAC2 in the developing CNS

Role in neurogenesis and neuronal migration: During early CNS development HDAC1 and HDAC2 display an overlapping pattern of expression [64,65]. At the earliest stages of cortical development both proteins are highly expressed in neuroepithelial cells and subsequently in neural progenitor cells (NPCs) [66]. Postnatally however, HDAC1 and HDAC2 show relatively contrasting patterns of expression in the cortex and the rest of the CNS. Furthermore, HDAC1 is expressed primarily glial cells whereas HDAC2 is expressed predominantly in mature neurons in the neocortex and in other brain regions [65].

It was first reported that mice with germline deletion of either *Hdac1* or *Hdac2* display no obvious abnormalities in the brain, no overt phenotype and a normal lifespan [22]. However, deletion of both proteins using *GFAP-Cre*, which is active in most NPCs and astrocytes, results in major brain abnormalities and lethality at around postnatal day 7. Brain regions, including the cortex, hippocampus and cerebellum, are severely affected [22]. This study described that a single allele of *Hdac1* or *Hdac2* was sufficient for normal brain development and viability [22]. These findings suggested redundant roles of HDAC1 and HDAC2 during brain development where the function of one of these proteins could be compensated for by the other. Further analyses revealed increased proliferation of neuronal progenitors but an impairment in differentiation leading to aberrant cell death during a narrow time window spanning E15.5. It was concluded that HDAC1 and HDAC2 promote the differentiation of NSCs to neurons, failure of which resulted in excessive cell death. Whether HDAC1 and/or HDAC2 directly regulate cell death is not clear, but possible.

Using *Nestin-Cre* to delete *Hdac1* and *Hdac2* either individually or in combination in mice, Hagelkruys confirmed the findings of Montgomery et al. that deletion of either *Hdac1* or *Hdac2* has no discernible effect on brain development but mice lacking both proteins display loss of much of the brain by E18.5 [64]. In contrast to the study by Montgomery et al., however, who reported a defect in the ability of proliferating NPCs to differentiate, these authors described reduced proliferation and premature differentiation of NPCs prior to abnormal cell death in *Hdac1/Hdac2* deficient mice [64]. The difference between the two studies likely is due to the different patterns of expressions of the *Nestin* and *GFAP* promoters in the NPC pools. Also noteworthy, is that there are different *GFAP-Cre* lines displaying different patterns of Cre recombination. A separate study performed using zebrafish also described that *Hdac1* is necessary to maintain proliferation in the NSC pool of the embryonic brain by preventing premature cell cycle exit and differentiation [67]. Deletion of *hdac1* in zebrafish led to reduced proliferation of NSC cells lining the ventricle and consequently reduced brain size. While *hdac1* promotes proliferation in the developing zebrafish brain, it has the opposite effect in the developing zebrafish retina where loss of *hdac1* results in enhanced proliferation due to the failure of cells to exit the cell cycle. The abnormal proliferation in the retina is due to a failure to downregulate cyclin D and cyclin E

expression. Despite the enhanced proliferation, the retina in *hdac1* mutants is smaller because of widespread apoptosis. Retinal ganglion cells were missing, and the inner and outer plexiform layers were severely reduced in in the *hdac1* mutant zebrafish. Based on the findings from mice and zebrafish it can be concluded that the role of HDAC1 in the brain is complex with either positive or negative regulation of cell cycle depending on the NSC population and region of the CNS, as well as perhaps the developmental stage.

Interestingly, in mice lacking HDAC1, HDAC2 (which is normally expressed predominantly in neurons) was also expressed in astrocytes whereas mice lacking HDAC2 displayed expression of HDAC1 in neurons (although it is normally expressed predominantly in astrocytes and oligodendrocytes) providing an explanation for the lack of brain abnormalities in single mutants [64]. The level of HDAC1 was upregulated in brain extracts from *Hdac2* conditional knockout mice, although HDAC2 was not discernibly upregulated in HDAC1 cKO mice. Also, interestingly, whereas a single allele of HDAC2 in the absence of HDAC1 was sufficient for normal brain development, mice with a single allele of HDAC1 in the absence of HDAC2 displayed abnormal brain development and perinatal lethality [64]. This points to a particularly important role for HDAC2 in brain development. The finding that a single allele of HDAC1 was unable to protect against brain abnormalities is also at odds with the observation of Montgomery et al. These differences are likely due to the different *Cre* lines used for deletion or the genetic background of the mice. A study by Jin et al. using cultured embryonic NSCs described that neuronal nitric oxide synthase activity, which increases nitric oxide production, promotes neuronal differentiation, an action that is mediated by decreased HDAC2 expression and enzymatic activity [68]. This study found that forced knockdown of *Hdac2* results in NSCs exiting the cell cycle and differentiating into neurons. On the other hand, forced upregulation of HDAC2 had no effect on NSC proliferation, but reduced neuronal differentiation [68]. Interestingly, particularly given that it is highly expressed in astrocytes, differentiation to astrocytes was not affected by *Hdac2* knockdown or overexpression. Whether HDAC1 had effects similar to those of HDAC2 was not analyzed in this study. The requirement for HDAC1 in promoting the proliferation of NSCs during CNS development has also been described in *Xenopus* laevis. Basal NPC proliferation as well as visual deprivation-induced increase of NPC proliferation is reduced in the optic tectum of frog embryos when *hdac1* is knocked down using morpholinos [69].

The role of HDAC1 and HDAC2 is regulating neurogenesis has also been studied in *Drosophila*, which has a single gene for *HDAC1* and *HDAC2* called *dHdac1*. In the fly larval brain, dHDAC1 keeps neuroblasts in a cell-renewing state (Schultz et al., 2018). During neurogenesis, these stems divide asymmetrically to produce intermediate neural progenitor (INP) cells that rapidly differentiate to neurons. The rapid differentiation of the INPs requires the inactivation of *dHdac1* immediately after the INP is produced from the neuroblast.

The critical involvement of HDAC1 in neurogenesis in mice continues through adulthood. One site of active neurogenesis in the adult brain is the hippocampus, where NSCs exist either in a quiescent or an active state [71,72]. New neurons are generated from NSCs that are activated. However, excessive activation of NSCs leads to their depletion over time. Indeed, it is believed that age-related decline in hippocampal neurogenesis results from

depletion of the NPC pool [73–75]. Such a depletion of the NSC pool also occurs in fragile X-syndrome, a neurodevelopmental disorder resulting from loss of fragile X mental retardation protein (FMRP). FMRP plays a critical role in learning and memory [76,77]. Although the neurological symptoms and cognitive impairment is seen early in life, the deficits in fragile X-syndrome continue into adulthood. FMRP deficiency leads to excessive adult NSC activation in the hippocampus, an effect resulting from reduced levels of HDAC1 through ubiquitin-mediated degradation [78,79]. At the same time, loss of FMRP causes an increase in the histone acetylase, EP300, which along with reduced HDAC1 results in abnormally elevated levels of histone acetylation in hippocampal NSCs. Reducing EP300 levels or increasing HDAC1 activity in fragile X syndrome mice normalize histone acetylation rescuing both the neurogenic and cognitive deficits in fragile-X syndrome mice [79].

An interesting study by Hagelkruys et al. examined whether the deacetylase activities of HDAC1 and HDAC2 are required for their critical developmental functions by generating knock-in mice that expressed deacetylase-dead forms of either HDAC1 or HDAC2. Although lacking enzymatic activity, the mutant HDAC1 and HDAC2 proteins retained their scaffolding and other potential functions that are independent of their deacetylase activity [28]. Interestingly, heterozygous mice with a normal *Hdac2* allele and deacetylase-dead *Hdac2* allele had a more severe phenotype than mice lacking HDAC2 altogether [28]. The mice with a single mutant *Hdac2* allele mice died within several hours after birth with reduced body and brain weights. As described above, *Hdac2*-null mice live for between 1 day and 3 weeks, with one study reporting long-term viability of some *Hdac2*-null mice. While the heart and a few other parts in the mice with a single mutant *Hdac2* allele were normal, the brains of these mice were smaller with markedly reduced cerebellar and cortex sizes [28]. In comparison with heterozygous mutant *Hdac2* mice, heterozygous mice with normal and one deacetylase-dead *Hdac1* allele were indistinguishable from wildtype littermates. This is somewhat surprising given that HDAC1 is necessary for embryonic development and *Hdac1* null mice have a much more severe phenotype than *Hdac2* null mice. As described for homozygous *Hdac1* knockout mice, homozygous expression of catalytically-dead *Hdac1* results in embryonic lethality [28].

A recent study by Tang et al. reported that that HDAC1 and HDAC2 play a critical role in neocortical development by regulating the localization of IPs [66]. These scientists found that deletion of both *Hdac1* and *Hdac2* in NPCs using *Emx-Cre* resulted in the reduction of NPCs due to their apoptotic death and consequently, the thickness of the cortex was reduced. Additionally, IP cells were positioned in the VZ rather than migrating out of it to localize in the SVZ [66]. These ectopic IPs produced differentiated neurons in the VZ ultimately leading to a disruption of the integrity of the VZ. Analyses of the neurons in the abnormally laminated cortex showed that only early-born neurons were produced in the *Hdac1/Hdac2* double cKO mice. Thus, besides confirming earlier findings that *Hdac1/Hdac2* play a critical role in regulating the NPC population [22,64], this study showed that HDAC1 and HDAC2 are also critical for the proper positioning of progenitor cells in the developing cortex, as well as the differentiation and migration of neurons.

Like the neocortex, the cerebellum also displays a laminated pattern. Development of the cerebellar cortex involves the rapid proliferation of granule neuron progenitor cells within the external granule layer (EGL), which in rodents, occurs during the first postnatal week [80,81]. This is followed by the differentiation and migration of the newly formed granule neurons on the fibers of Bergmann glial cells past the Purkinje cell monolayer to form the internal granule layer (IGL). An analysis of HDAC1 and HDAC2 expression in the developing mouse cerebellum revealed that progenitor cells in the EGL express high levels of HDAC1 and low levels of HDAC2 suggesting that HDAC1 is promotes the robust proliferation of these cells [82]. In migrating granule neurons however, the expression of HDAC1 is low, but that of HDAC2 is high. Other neuronal types in the cerebellum, including Purkinje cells, unipolar brush cells, and GABAergic interneurons, also express high levels of HDAC2 and low levels of HDAC1 [82]. It is therefore likely that both HDAC1 and HDAC2 are required for proper neurogenesis in the cerebellum with HDAC1 being more important for the proliferation of NPCs and HDAC2 acting subsequently to ensure proper their differentiation and maturation. This is consistent with the previous observations of severe cerebellar abnormalities in cKO mice lacking HDAC1/2 in the brain, including reduced cerebellar size with reduced folia and fissure formation [22,64]. A similar cerebellar phenotype is observed in mice lacking Rack1 (receptor for activated C kinase) in proliferating progenitor cells [83]. Rack1 is a multifaceted signaling adaptor protein highly expressed in the external granule layer of the immature cerebellum [83,84]. A recent study described that Rack1 regulates proper cerebellar morphogenesis through the stabilization of HDAC1/HDAC2, which then suppresses Wnt/β-catenin signaling while activating Shh signaling [83].

Role in development of glial cell types: HDAC1/HDAC2 activity is necessary for progression of both the oligodendrocyte and Schwann cell lineages, the myelinating cells of the CNS and PNS, respectively [65,85,86]. Schwann cells are derived from neural crest cells that migrate from the dorsal neural tube. However, neural crest cells generate several other cell types, including neurons and non-neuronal cell types. Specification of neural crest cells to the Schwann cell lineage, as opposed to other cell fates, requires the expression of the Pax3 transcription factor, which then maintains high expression of Sox10, a key regulator of Schwann cell development [87,88]. HDAC1/2 are highly expressed in neural crest cells at the time of glial specification [86]. Deletion of *Hdac1/Hdac2* in neural crest cells of mice using *Wnt1-Cre* for ablation resulted in the failure of Schwann cells to be specified [86]. This was due to a failure in the induction of Pax3 and Sox10 expression which was found to be under HDAC1/HDAC2 control [86]. Additionally, HDAC1/HDAC2, in a complex with induced Sox10, promote myelination and survival of Schwann cells by stimulating expression of the myelin protein zero (P0) as well as several survival-promoting genes [85,86]. In a separate study, the deletion of *Hdac1/Hdac2* in Schwann cells using *Dhh-Cre*, which expresses Cre in PNS glia cells but not in neural crest cells or neurons, resulted in a massive loss of Schwann cells. The mutant mice displayed tremor and reduced hind limb mobility, and died around P17. Results from additional in vitro studies using overexpression and knockdown of either HDAC1 or HDAC2 indicated that it was HDAC2 that was required for Sox10 upregulation and Schwann cell myelination,while HDAC1 promoted the survival of the Schwann cells by inhibiting Wnt/β-catenin apoptotic signaling [85]. Interestingly,

deletion of either the HDAC1 or HDAC2 allele had no effect on the viability, appearance or behavior of mice [85]. A robust effect on Schwann cells development was also described in another study which examined the effect of conditional *Hdac1/Hdac2* ablation, also using *Dhh-Cre*. In this study HDAC1/HDAC2 was found to promote Schwann cells development not through inhibiting Wnt/β-catenin signaling, but by direct deactylation of the NF-κB subunit p65/RelA [89]. These authors described that although proliferation of Schwann cell progenitors was normal in mice lacking HDAC1/HDAC2, their development was blocked in an immature state because of reduced binding of p65 to the *Sox10* gene promoter. In contrast to their requirement during development, HDAC1/2 are not required in adult Schwann cells for promoting myelination or for survival, although integrity of peripheral nerves is affected when *Hdac1/Hdac2* are deleted during adulthood, an effect resulting from reduced expression of P0, which is also a component of paranodal and nodal adhesion complexes [90]. Thus, besides playing a crucial role in the specification, myelination and survival of Schwann cells during development, HDAC1/HDAC2 maintains Schwann cell-axon interaction in the adult PNS.

Oligodendrocytes are specified from NPCs of the ventral neural tube. In zebrafish, oligodendrocyte specification begins in neuroepithelial cells in rhombomeres 5 and 6 of the neural tube with the expression of *olig2*, a transcription factor essential for oligodendrocyte generation in zebrafish as well as mammals [91–93]. In contrast to most vertebrate organisms, zebrafish do not have a separate *hdac2* gene and the functions of *hdac1* and *hdac2* are represented by a single *hdac1* gene. In mutant zebrafish lacking *hdac1*, there is a complete loss of *olig2* expression in the neural tube and oligodendrocytes fail to develop [94]. Similarly, in mice, *hdac*1/2 double-knockout in early oligodendrocyte lineage progenitors resulted in a loss of PDGFR-positive oligodendrocyte precursor cells (OPCs) and oligodendrocytes in the postnatal spinal cord and brain [95]. The mice develop severe tremor because of myelin-deficiency and die around postnatal week 2. As observed in fish, *olig2* expression was repressed. This repression was found to be mediated by β-catenin, which is stabilized in the absence of *hdac1/hdac2.* Ablation of either *hdac1* or *hdac2* by itself had no effect of oligodendrocyte specification or differentiation. A more recent study used cultured mouse cortical OPCs to examine the role of HDAC1 and HDAC2 individually, and in combination [96]. Both HDAC1 and HDAC2 are abundantly expressed in cultured OPCs compared with other glial cell types. Whereas knockdown both HDAC1 and HDAC2 using shRNA resulted in decreased differentiation, knockdown of HDAC1 also was sufficient to inhibit OPC differentiation into oligodendrocytes [96]. Surprisingly, knockdown of *Hdac2* promoted oligodendrocyte differentiation indicating previously unappreciated complexity in the role of these two HDACs in oligodendrocyte generation. When both *Hdac1* and *Hdac2* were ablated, oligodendrocyte differentiation was inhibited [96]. Another study conducted using neural stem cells (NSCs) cultured examined the effect of HDAC2 knockdown on thryroid hormone (T3)-induced regulation of oligodendrocyte differentiation [97]. In this paradigm HDAC2 was found to inhibit oligodendrocyte differentiation by repression of Sox10 and other oligodendrocyte-associated genes. Knockdown of *Hdac2* using siRNA derepresses oligodendrocyte differentiation of NPCs in the presence of T3 [97].

HDAC1 and HDAC2 also play a critical role in the maturation and function of microglia, the sole immune cells in the brain. Unlike neurons and other glial cell types that are derived from NPCs, microglia originate from primitive macrophages of the yolk sac which localize to the CNS early during development and prior to the formation of the blood brain barrier [98]. Despite its distinct origins, the maturation of microglia is coordinated with the generation and maturation of other brain cell types playing an essential role in the appropriate formation, pruning, and modulation of synapses both during development and subsequently in the mature brain [99]. In the adult brain microglia regulate inflammation serving to clear cellular debris, while continuing to modulate synapses [99]. A growing body of evidence indicates that inappropriate activation of microglia contributes to a variety of psychiatric and neurodegenerative diseases [100–102]. Deletion of both *Hdac1* and *Hdac2* from primitive yolk sack macrophage in mice using CX3C chemokine receptor *(Cx3cr1)*-Cre results in the generation of microglia that lack HDAC1 and 2 [103]. Microglial numbers in these mice are reduced prenatally and perinatally and display shorter and fewer processes. The morphological abnormalities continue as the mice mature although the number of microglia normalize at around 6 weeks of age [103]. Surprisingly, the effects on microglial proliferation and morphology were not seen when *Hdac1*and *Hdac2* were deleted during adulthood indicating a special role for these HDACs for microglial development in the embryonic brain [103].

HDAC1 and HDAC2 in synaptic transmission, plasticity, and cognition.— Following neurogenesis, migration and maturation of neurons, HDAC1 plays a role in the formation of neural circuitry. Refining of diverse neural circuits during development is a plastic process regulated by sensory experience and learning. In the rodent somatosensory cortex, intracortical plasticity (between and within different cortical layers) is regulated by the maturation of inhibitory parvalbumin-positive (PV) interneurons, which is promoted by brain-derived neurotrophic factor (BDNF). Sensory deprivation, such as whisker-derivation, during specific developmental stages, reduces BDNF expression and hence the maturation of PV interneurons. This sensory deprivation-induced reduction in maturation is mediated by HDAC1, which associates with, and repressing the promoters of both *Bdnf* and *Parvalbumin (Pvalb)* genes. Knockdown of *Hdac1* de-represses the *Bdnf* and *Pvalb* genes enhancing maturation of PV interneurons thus regulating inhibitory connections with projection neurons. Surprisingly, although HDAC2 is also expressed in PV interneurons and associates with the *Bdnf* and *Pvalb* promoters, its knockdown has no effect on expression or maturation, at least in the somatosensory cortex. Somewhat different results were observed in the developing optic tectum of frogs, which express both *Hdac1* and *Hdac2.* In *Xenopus laevis*, mopholino-mediated knockdown of *Hdac1* in the optic tectum sharply reduced the frequency of AMPA receptor-mediated synaptic currents while increasing the frequency of GABA receptor-mediated currents [104]. On the other hand, the frequency of GABA receptor-mediated synaptic currents was reduced when HDAC1 was overexpressed in the optic tectum. Although the difference in the effect of HDAC1 on synaptic transmission could be attributed to the different species used in the two studies, it is also possible that HDAC1 is part of distinct protein complexes in the two CNS regions, which produces different effects. As described above, HDAC1 can exist in at least three multiprotein complexes and within each of these complexes the precise components can differ. Knockdown of *Hdac1* in the frog

optic tectum impairs visually-guided behavior due to a reduction in BDNF expression. Support for this conclusion came from the finding that acute infusion of BDNF in the tectum rescues the impairment resulting from *Hdac1* knockdown.

HDAC2 also modulates synaptic transmission in the brain [105]. However, in contrast to HDAC1 which reduces inhibitory transmission in some brain parts, HDAC2 enhances inhibitory synaptic transmission in the hippocampus. Specifically, knockdown of *Hdac2* in hippocampal slice cultures reduced inhibitory synaptic transmission whereas its overexpression enhanced it [105]. The reduced inhibitory synaptic transmission resulting from *Hdac2* knockdown was caused by reduced expression of the GABA receptor ($GABA_AR$) and its synaptic abundance [105]. In addition, *Hdac2* knockdown enhanced excitatory neurotransmission, Although the molecular basis for the enhancement of excitatory synaptic transmission is unclear, an increase in surface expression of the AMPA subunit, GluA2, has been described in two studies following *Hdac2 k*nockdown [21,105]. Surprisingly, another study conducted using mice in which *CaMK-Cre* was used to delete *Hdac2* in forebrain neurons described that HDAC2 enhanced excitatory neurotransmission [106]. It is possible that the effects of *Hdac2* deletion in this *in vivo* study reflects a combination of cell autonomous and non-cell autonomous effects. Regardless of these unexplained differences it is certain that HDAC2 regulates the balance of excitatory versus inhibitory synaptic transmission.

HDAC2 represses synaptic plasticity and memory formation in the fully developed brain [21,107]. The repressive action of HDAC2 is mediated, at least in part through its association with and repression of the transcriptional activity promoters of genes involved in promoting synaptic plasticity and cognitive function [107,108]. This in turn leads to long-lasting changes in neural circuity negatively regulating learning and memory. Neuron-specific overexpression of HDAC2 in mice reduces synaptic morphology, synaptic plasticity, and memory, whereas its ablation in neurons enhances these aspects of brain function [21]. Interestingly, the overexpression of HDAC1 in mice did not have the same effects. Another study described enhanced working memory and performance in certain cognitive tests in mice lacking *Hdac2* in forebrain neurons generated using *CaMK-Cre*, but not in mice lacking *Hdac1* [106]. *Hdac2* cKO mice were found to have a reduced number of active synapses although dendritic spine density was normal. HDAC2 expression, but not the expression of HDACs1, 3 and 8, is elevated in the prefrontal cortex (PFC) of mice deficient in the *Shank3*-deficient mouse model of autism [109]. Reducing HDAC2 activity in these mutant mice reduces synapse dysfunction and atypical social behavior [109]. HDAC2 promotes an autistic phenotype in *Shank1*-deficient mice by increasing β-catenin expression. Indeed, HDAC2 expression is higher in Alzheimer's disease and reducing HDAC2 activity has been suggested as a therapeutic approach for this progressive neurodegenerative disease [21,110]. Together, these results suggest the reducing HDAC2 activity has beneficial effects on brain function both in the developing and mature brain.

HDAC1 expression is high in the human and mouse brain embryonically, but its expression decreases perinatally and is undetectable in the adult brain (Večeřa et al., 2018). However, HDAC1 expression remains elevated in the prefrontal cortex (PFC) and other brain regions in mouse models of schizophrenia [111,112]. Three separate groups have described that

HDAC1 expression is also elevated in the PFC and hippocampus of patients with schizophrenia [111,113,114]. Dysfunction of synaptic transmission between the hippocampus and the PFC due to neurodevelopmental abnormalities has been considered a central deficit in schizophrenia and other psychiatric disorders [115,116]. Overexpression of HDAC1 in the PFC by stereotaxic injection of an adeno-associated virus (AAV) expressing it recapitulates schizophrenia-like phenotypes induced by early life stress [111]. ChIP analysis showed increased HDAC1 association with the promoters of genes linked to schizophrenia, such *Gad1, Pvalb1* and *Kcnv1*, along with a reduction in their expression in HDAC1-overexpressing mice [111]. Increased association of HDAC1 with the promoters of the *Gad1, Pvalb1* and *Kcnv1* genes has also been found the PFC of schizophrenia patients [111]. Virally-mediated overexpression of HDAC1 in the hippocampus resulted in the impairment of fear extinction while not affecting explorative, spatial or working memory [117]. Another study overexpressing HDAC1 in the PFC by AAV injection described robust impairments in working memory, increased repetitive behaviors and other behavioral abnormalities [118]. Interesting, different studies have described that HDAC1 expression is increased in the PFC and other brain regions in patients with schizophrenia [113,114,119]. Although these results point to a role of elevated HDAC1 in neurodevelopmental disorders such as schizophrenia, it deserves mention that mice overexpressing HDAC1 in the forebrain show no defects in synaptic transmission or cognitive function [21]. The possibility that mental impairments in mice when HDAC1 is acutely overexpressed in the PFC and/or the higher than pathophysiological expression levels resulting from AAV-mediated delivery. Other studies have shown that elevated HDAC1 activity in the adult brain contributes to abnormal neuronal death and neurodegenerative disease [120–122].

HDAC3 in brain development

HDAC3 plays a critical role in brain development and is the only member of the HDAC family the individual deletion of which has a severe effect on brain development and function. Norwood et al, described that mice in which *Hdac3* was ablated in the CNS using *Nes-Cre* for ablation displayed major abnormalities in the cytoarchitecture of the brain died within 24 hours of birth [123]. In the cortex, production of late-born neurons was reduced, and the lamination pattern was disrupted. Localization of Purkinje neurons in the cerebellum was also affected and the cerebellum of *Hdac3* cKO mice lacked the rudimentary folia that normal mice display at birth. Norwood et al also generated mice lacking *Hdac3* in neurons of the forebrain using *CaMK2a-Cre* and *Thy-1-Cre* for ablation [123]. These mice displayed severe neurological deficits and died within 5–6 weeks. Surprising, another study by Nott et al, described that HDAC3 cKO mice generated using the same HDAC3$^{loxP/LoxP}$ line as Norwood et al. but with a different *CaMK2a-Cre* displayed social behavior deficits but were otherwise not obviously abnormal [124]. The striking difference in phenotype of the HDAC cKO mice in these two studies could be due to different Cre recombinase expression patterns or the genetic background of the mice. Different constructs of the *CaMK2a* promoter could produce different spatial and temporal patterns of Cre recombinase expression. For example, a *CaM2a-Cre* mouse line generated by Tonegawa lab expresses Cre restricted largely to the CA1 region of the hippocampus with expression starting during the third to fourth postnatal week [125]. A recently published study of mice in which *Hdac3* was deleted in the cerebrum using *Emx-Cre* described abnormal behavior and death of the mice at around 3 weeks of age

[126]. Premature cell cycle exit and differentiation into neurons was found in the developing neocortex. Neuronal migration was also abnormal in *Hdac3*-mutant mice. The hippocampus was poorly formed and dentate gyrus barely visible in the mutant mice [126]. Within the embryonic neocortex extensive DNA damage and apoptosis was described.

Using NPCs cultured from the adult mouse hippocampus Jiang and Hiesh found that HDAC3 is required for cell cycle progression through the stabilization of the cell cycle protein cyclin-dependent kinase 1 (CDK1) [127]. This finding was confirmed in young *Hdac3* cKO mice in which ablation was achieved in an inducible manner using *Nestin-CRE-ERT2.* Following *Hdac3* ablation, reduced proliferation of neural progenitor cells and consequently, reduced numbers of differentiated neurons was observed in the hippocampus [127]. Li et al described that NPCs from the neocortex of mice in which Hdac3 was deleted from the cerebrum (using Emx-Cre) are impaired in their ability to form neurospheres *in vitro* [126]. While there was no difference in the size of neurospheres between wild-type and hemizygous mutant, neurospheres generated from the neocortex of homozygous mutants were smaller with significant apoptotic cell death. Another study using NPCs cultured from the normal embryonic mouse cortex described that siRNA-mediated knockdown of HDAC3 with siRNA increased neuronal differentiation through stimulation of expression of *Bdnf* and neuronal genes including *Tubb3* and *Neurog2* [97]. Whether the enhanced differentiation was related to repression of NPC proliferation was not directly examined. A stimulatory role for *hdac3* in the proliferation of NPCs has also been described in the zebrafish visual system [128]. In the developing zebrafish, axons of the retinal ganglion cells connect in a topographic manner to the optic tectum which possesses progenitor cells which subsequently differentiate to generate neurons. Visual activity negatively regulates progenitor cell proliferation whereas visual deprivation increases the proliferation rate of the progenitors. Analysis using morpholinos to knockdown *hdac3* in the zebrafish optic tectum has shown that both normal and visual deprivation-induced proliferation of progenitor cells is dependent on HDAC3 [128]. Although *hdac2* is also expressed in the progenitor cells of the optic tectum, its knockdown had no effect on cell proliferation [128].

Within NCOR1 and SMRT complexes, HDAC3 interacts with the deacetylase activation domain (DAD) on the amino-terminal region of the two corepressor proteins [129,130]. The deacetylase activity of HDAC3 is critically-dependent on this interaction, as DAD point-mutations disrupting HDAC3 - NCOR1/SMRT binding lead to a complete loss of HDAC3 activity [129,130]. Knock-in mice have been generated bearing point-mutations in the DAD of both NCOR1 and SMRT (NS-DADm). Despite having normal levels of HDAC3 protein, these mice have no HDAC3 enzymatic activity [130]. Surprisingly, and in striking contrast to the embryonic lethality of *Hdac3* knockout mice, NS-DADm mice are born at normal Mendelian ratio, appear normal, and live to adulthood demonstrating that the life-supporting functions of HDAC3 during embryonic development do not require its enzymatic activity [130,131]. Indeed, while interaction with NCOR1/SMRT is necessary, catalytically-dead forms of HDAC3 are able to mediate key roles of HDAC3 on transcription and metabolism in the liver [27,132]. Therefore, although deactylation is reduced in the brain tissue of mice in which *Hdac3* is deleted [126,133], whether HDAC3 enzymatic activity is actually required for its critical roles during brain development deserves investigation. Although whether HDAC3 complexes with NCoR1 could have different functional roles from those

containing SMRT has not been meaningfully explored, such a possibility is likely. For example, knockdown of *Hdac3* has been shown to specify human pluripotent stem cells to NPCs. This cell specification role of HDAC3 depends on SMRT, but not NCOR1 [134].

HDAC3 in synaptic plasticity and memory.—HDAC3 has complex roles in learning and memory. Focal ablation of *Hdac3* in the CA1 region of the hippocampus achieved by stereotaxic AAV-*CaMK-Cre* injection *Hdac3*$^{loxP/loxP}$ caused an enhancement of cocaine-context-associated memory formation [135]. Focal deletion of HDAC3 in the CA1 region also rescued impairment of long-term object location memory resulting from mutation of BAF53b, a chromatin remodeling protein necessary for long-term memory and synaptic plasticity [136–138]. Rather than injection into the CA1 region, another group ablated *Hdac3* in the CA3 region using a similar approach and found no effect on learning behaviors or memory [131]. Other studies have also described distinct properties of CA1 and CA3 pyramidal neurons [139]. However, focal ablation of *Hdac3* in neurons of the lateral hypothalamus, another region involved in motivated behaviors, caused substantial learning and memory impairment indicating that HDAC3 can also facilitate memory formation [131]. The promotion of recognition memory by HDAC3 requires interaction with NCOR1/SMRT because NS-DADm mice, which lack HDAC3 enzymatic activity because of the mutation in the DAD sequence that disrupts interaction with NCOR1/2, also display marked memory deficits although these mice express normal levels of HDAC3 protein [131]. This demonstrates that unlike many of the developmental functions of HDAC3, its role in promoting memory requires its deacetylase activity. Although HDAC3-NCOR1/2 are better known for transcriptional repression, the positive effects of HDAC3 and NCORs on recognition memory results from direct association and stimulation of the $GABA_A$ receptor gene promoter by HDAC3-NCOR [131]. Indeed, is $GABA_A$ receptor expression reduced in NS-DADm mice. Furthermore, pharmacological stimulation of $GABA_A$ receptor rescued the recognition memory deficit of NS-DADm mice. Moreover, depletion of NCOR1 and NCOR2 specifically in GABAergic neurons of the lateral hypothalamus using NCOR1$^{loxP/loxP}$ /NCOR2$^{loxP/loxP}$ mice and a *Vgat-Cre* line for ablation, resulted in mice that were overtly normal but that displayed impaired memory [131]. The memory impairment was shown to result from the hyperexcitability of lateral hypothalamic GABAergic neurons projecting to the CA3 region of the hippocampus likely causing an excitation/inhibition imbalance in the hippocampus [131]. A recent study described that deterioration of long-term memory formation during aging is negatively regulated by HDAC3. This action of HDAC3 on memory is mediated through its repression of the Nrf4 proteins, a group of CREB-dependent nuclear orphan receptors [140]. Whether the effects of HDAC3 on memory in other contexts and stages of life also requires repression of Nrf4 proteins remains to be determined. Together, these findings indicate that Hdac3 can both promote and inhibit memory by acting differentially in distinct brain regions to regulate different types of memory.

Emerging evidence indicates that some of the functions of HDAC3 in the brain are mediated through interaction with MeCP2, a protein the dysfunction of which causes neurodevelopmental disorders. Reduced expression or loss of function mutations of MeCP2 causes Rett syndrome, a severe neurological disorder in which cognitive and motor abilities

are impaired. Duplication of the *MeCP2* gene is responsible for an even more severe neurological disorder called MeCP2 duplication disorder. Although the molecular and cellular mechanisms underlying MeCP2 duplication syndrome are poorly understood, results of a recent study performed using a transgenic mouse model of the disorder described neuronal loss in the cortex and hippocampus resulting from glial dysfunction and excitotoxicity [141]. MeCP2 associates with the NCOR1/HDAC3 complex [124,142]. Nott et al described that the association between HDAC3 and MeCP2 facilitates cognitive and social behavior [124]. This action of HDAC3-MeCP2 involves interaction with FOXO3, a member of the *Forkhead* family of transcription factors, resulting in FOXO3 deacetylation and activation [124]. HDAC3-MeCP2 regulate social behavior through recruitment of FOXO3 to promoters of neurodevelopmentally-significant genes, such as those encoding Bdnf and Nrf4a1 [124].

Decision making and behavior are regulated controlled by a balance between two approaches, a cognitive, goal-directed approach and as a result of habit. These approaches are regulated by the dorsomedial striatum and the dorsolateral striatum, respectively. Decreasing HDAC3 function by expression of dominant-negative mutated HDAC3, in either the dorsolateral striatum or the dorsomedial striatum accelerated habit formation, while HDAC3 overexpression in either region prevented habit [143].

HDAC3 in gliogenesis.—Besides affecting the production and migration of neurons in the cortex, mice lacking *Hdac3* in the brain display disrupted gliogenesis with astrocytes being overproduced at the cost of oligodendrocyte progenitors [123]. A critical role for Hdac3 in regulating glial cell fate was also described by Zhang et al. who found that Hdac3 associates with the p300 acetyl transferase to antagonize astrogliogenesis while activating the oligodendrocyte lineage [133]. The suppression of astrogliogenesis was due to the inhibition of Stat3 acetylation by HDAC3 thereby antagonizing JAK-STAT signaling, which is required for development of astrocytes [144–146]. On the other hand, HDAC3 promoted the development of oligodendrocytes through the direct stimulation of *Olig2* expression [133]. When Hdac3 was ablated in the oligodendrocyte lineage using *Olig1*-Cre the mice displayed severe myelin deficiency, reduced oligodendrocyte numbers, and suffered tremors although these mice did survive to adulthood [133]. Thus, HDAC3 plays a crucial role in the switch between astrocyte-oligodendrocyte fate switch, a function that is apparently not shared by HDAC1 or HDAC2.

Myelination of Schwan cell axons is necessary for efficient conduction of action potentials in the peripheral nervous system. Hdac3 negatively regulated myelination [147]. Knockdown of *Hdac3* in cultured Schwann cells using siRNA resulted in hypermyelination. The antagonistic effect of HDAC3 on myelination was confirmed in mice in which *Hdac3* was selectively ablated in Schwann cells using *Cnp-Cre* [147]. The hypermyelinating effect was also observed in another line of mice in which *Hdac3* was deleted in Schwann cell progenitors using *Dhh-Cre*. Following damage, remyelination of peripheral axons is a slow and inefficient process which often results in permanent impairment of nerve function. HDAC3 also inhibits remyelination of injured Schwann cells [147]. The antagonistic effect of HDAC3 on myelination was found to be due to an inhibition of PI-3 kinase-Akt signaling resulting from an upregulation of PTEN expression. Furthermore, HDAC3 recruited p300

histone acetyltransferase to activate myelination-inhibitory programs in Schwann cells [147].

HDAC8

Little is known about the role of HDAC8 in brain development or function. An analysis of HDAC8 expression in chicks and mice during embryonic development revealed that in mice HDAC8 is exclusively expressed in forebrain and midbrain regions whereas the chick ortholog displayed a broader pattern of expression suggesting species-specific roles of HDAC8 [148]. One study used P19 embryonic carcinoma cells, a cell line that differentiates into neuron-like cells when treated with retinoic acid (RA), to examine whether HDAC8 regulated neuronal differentiation. It was found that HDAC8 promoted cell cycle progression and its knockdown permitted the formation of embryoid bodies, a step towards neural differentiation [149]. Whether this inhibitory effect on neurodifferentiation is true for genuine neural progenitor cells *in vitro* or *in vivo* remains to be investigated. One study has linked an HDAC8 mutation with a Rett-like disorder with facial abnormalities, hyperthyroidism and epilepsy [150]. Loss-of-function mutations of HDAC8 is also one of the causes of Cornelia de Lange syndrome, a clinically-variable X-linked neurodevelopmental disorder with varied symptoms including intellectual disability, microcephaly, craniofacial abnormalities, limb malformations, growth retardation, and intellectual disability [151–153]. Cornelia de Lange syndrome, also referred to as cohesinopathies, result from defects in the functioning of cohesion, a ring-like multiprotein complex. Although most often described in its function of keeping sister chromatids together in mitotic cells, recent investigations have shown that cohesion rings also organize genomic DNA into topologically associating domains (TADs) within the nucleus of cells, including NSCs and mature neurons [154]. HDAC8 plays a key role in regulating cohesion function by deacetylating one of the core cohesion proteins within the complex which could affect mitosis as well as transcription through loss of TAD function [151,154,155]. Recent findings describe transcriptional dysfunctions in Cornelia de Lange Syndrome and other cohesinopathies [156,157]. A characteristic abnormality in HDAC8-linked Cornelia de Lange syndrome is abnormal skull formation, a feature also seen in HDAC8 knockout mice [158]. Whether HDAC8-deficient mice suffer cognitive or behavioral impairment has not been specifically investigated. However, based on human studies it seems likely that HDAC8 plays important functions in the developing nervous system that are non-redundant with other Class I HDACs.

Other HDACs

While most investigation on the role of HDACs in the development and functioning of the nervous system has focused on Class I HDACs, there is solid evidence that other members of the HDAC family also make important contributions. One of these is the Class IIa HDAC, HDAC4. Majdzadeh et al described that germline ablation of HDAC4 leads abnormal development of the cerebellum, including a progressive loss of Purkinje neurons postnatally in posterior lobes [159]. Surviving Purkinje neurons in these lobes were found to have duplicated soma suggesting abortive cell-cycle reentry. Supporting such a possibility was the observation that large numbers of cells within these affected lobes incorporated BrdU and

that HDAC4 inhibited CDK1. Surprisingly, immunobiological analysis of mice lacking HDAC4 in forebrain neurons generated using CaMK-Cre or Thy1-Cre showed no abnormalities, suggesting that the effects observed in the total knockout mice were the consequence of mechanisms activated early during embryonic development or involved the contributions of cell types other than excitatory projection neurons [160]. More detailed analyses of HDAC4 cKO mice generated using CaMK-Cre described normal overall behavior and normal basal synaptic transmission but impaired long-term plasticity [161]. In contrast, HDAC5 cKO mice, which were also analyzed, showed no impairment. It is noteworthy that haplosufficiency of HDAC4 is primary genetic contributor to brachydactyly-mental retardation syndrome, a neurodevelopmental disorder in which patients display developmental delays, cognitive impairment, behavioral abnormalities [162,163]. Overexpression of HDAC4 in cerebellar granule neurons cultured from rat pups is strongly neuroprotective an effect likely mediated through its inhibition of CDK1, which would prevent abortive cell cycle entry, a well-described mechanism to explain neuronal cell death [159]. A more recent study found that HDAC4 overexpression in glial cell lines inhibited the expression of the CDK inhibitors, p21 and p27, and increased expression of CDK1 and CDK2 [164] leading to increased cell cycle progression. Thus, the effect of HDAC4 on cell cycle progression could be cell-dependent.

Mice lacking another class IIa HDAC, HDAC9, display no overt behavioral deficits [165]. However, detailed analyses of HDAC9 revealed that it regulates the branching of thalamocortical axons an activity-dependent manner [166]. This function of HDAC9 requires its translocation from the nucleus to the cytoplasm and its release from Mef2, a transcription factor with which HDAC9 interacts in the nucleus.

HDAC6, a Class IIb HDAC, enhances the elongation of axons in cultured hippocampal neurons [167]. This effect is mediated by the localization of HDAC6 at the distal end of axons where it positively regulates microtubule polymerization by influencing attachment of tubulin. HDAC6 also promotes the formation of the axonal initial segment, a structure that is important for neuronal function [167]. However, a recent study described that HDAC6 inhibits regeneration of axons [1]. This inhibitory effect of HDAC6 was mediated by deacetylating Miro, a calcium-binding outer mitochondrial membrane protein, which resulted in reduced mitochondrial transport in axons and growth cone function [1]. Neurogenesis also occurs normally in the adult brain within the SVZ and the hippocampus and this is stimulated following ischemic stroke [168,169]. Although generally regarded as positive, there is some evidence that neurites of the newly produced neurons do not mature properly resulting in an impairment of functional recovery [170,171]. A recent study described that abnormal dendritic morphology following stroke-induced neurogenesis was due to the nuclear translocation of HDAC6, which is normally exclusively cytoplasmic, leading to hyperacetylation of tubulin disrupting microtubule dynamics [172]. Knockdown of HDAC6 by shRNA infusion resulted in partial recovery of the dendritic phenotype [172].

Conclusions

Although most studied in the context of neurodegeneration, a compelling body of evidence indicates that Class I HDACs play a central role in the regulation of several different events

during CNS development, including the regulation of NPC proliferation, differentiation into neurons and glia, neuronal lamination, cell fate determination, the formation of neural networks and synaptic transmission. Although long assumed to exert their functions through their deacetylase activity, emerging evidence indicates that HDAC1, 2 and 3 can also act independent of enzymatic activity. Further investigation is needed to determine the precise mechanisms by which Class I HDACs regulate neurodevelopment. Understanding this will have significant impact on the understanding of many neurodevelopmental and psychiatric disorders paving the way for effective treatment strategies.

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