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Modulation of Neurogenesis by Targeting Epigenetic Enzymes Using Small Molecules: An Overview

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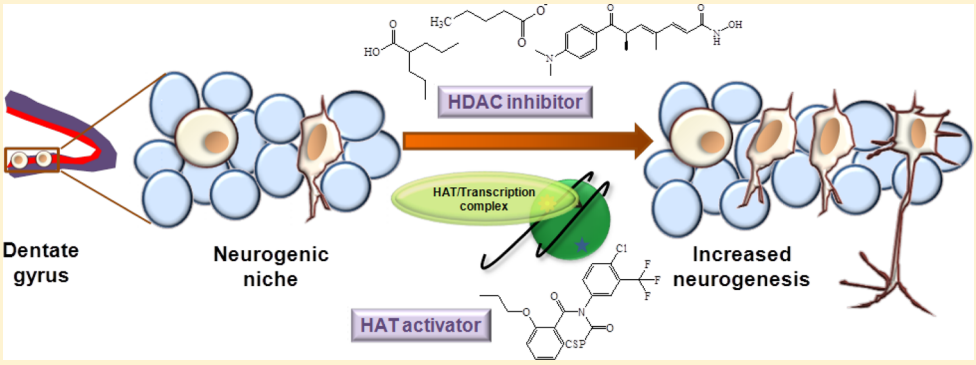

ABSTRACT: Neurogenesis consists of a plethora of complex cellular processes including neural stem cell (NSC) proliferation, migration, maturation or differentiation to neurons, and finally integration into the pre-existing neural circuits in the brain, which are temporally regulated and coordinated sequentially. Mammalian neurogenesis begins during embryonic development and continues in postnatal brain (adult neurogenesis). It is now evident that adult neurogenesis is driven by extracellular and intracellular signaling pathways, where epigenetic modifications like reversible histone acetylation, methylation, as well as DNA methylation play a vital role. Epigenetic regulation of gene expression during neural development is governed mainly by histone acetyltransferases (HATs), histone methyltransferase (HMTs), DNA methyltransferases (DNMTs), and also the enzymes for reversal, like histone deacetylases (HDACs), and many of these have also been shown to be involved in the regulation of adult neurogenesis. The contribution of these epigenetic marks to neurogenesis is increasingly being recognized, through knockout studies and small molecule modulator based studies. These small molecules are directly involved in regeneration and repair of neurons, and not only have applications from a therapeutic point of view, but also provide a tool to study the process of neurogenesis itself. In the present Review, we will focus on small molecules that act predominantly on epigenetic enzymes to enhance neurogenesis and neuroprotection and discuss the mechanism and recent advancements in their synthesis, targeting, and biology.

KEYWORDS: *Neurogenesis, histone modifications, acetyltransferase, DNA methylation, memory, neurodegeneration, neurotherapeutics*

Neural development remains one of the most complex processes in biology. Although the development, maintenance, and ultimate decay of the neural system have been studied for decades, novel concepts are still being uncovered. Like most other cellular phenomena, neurogenesis is governed by cell-intrinsic gene expression patterns, along with other physiological, pathological, chemical, and environmental factors.[1] Gene expression in the eukaryotic nucleus is modulated by the transcriptionally competent state of chromatin, which is a nucleoprotein complex consisting of DNA, RNA, histones, and several other nonhistone proteins. Of the multiple factors that help regulate the compaction state of chromatin structure, DNA methylation and histone modifications play a significant role through distinct mechanisms. With the advancement of mass spectrometry methods, novel and rare modifications of histone proteins continue to be discovered,[2] while previously characterized modifications are being assigned functional roles both in developmental and disease pathways. While some modifications act as positive regulators of transcription by facilitating the recruitment of transcriptional machinery, others recruit chromatin-compacting proteins that aid the formation of heterochromatin, making the environment unconductive for transcription.[3] Because gene expression patterns, which are controlled by epigenetic

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modifications, play an important role in the process of neurogenesis, it is logical to speculate that fine-tuning the cellular epigenetic state will ultimately affect neurogenesis itself. In this Review, we discuss the recent advancements in our understanding of how neurogenesis is driven by epigenetic modifications. The modulation of epigenetic enzymes using small-molecule modulators and their potential therapeutic uses will also be highlighted.

1. NEUROGENESIS: THE PROCESS

The extensive process of neurogenesis begins during embryonic development. After its completion, this process is maintained in the adult by a small but significant population of precursor cells that resides in specific regions. This section briefly describes the processes of both embryonic and adult neurogenesis.

1.1. Embryonic Neural Development. Most of the early studies in neural development were performed in embryos that were both easily available and transparent, such as *Xenopus*, while later studies involved mammalian systems such as mice. Neural induction (specification) in the embryo begins during gastrulation, when a part of the ectoderm gives rise to the neuroectoderm (neural tube epithelium). This neural induction process involves diffusible signaling molecules that originate from the notochord, which forms a part of the mesoderm. The first demonstration of this process in the Spemann organizer experiment, was performed in amphibian embryos.[4] Several of the molecules controlling this process have now been identified as activin, follistatin, noggin, and bone morphogenetic protein (BMP4), among others.[5−7] Following neural induction, the neuroectoderm undergoes a transformation into the neural plate, which gives rise to folds of neural precursor cells. The meeting of these folds forms a tube, thus transforming the initial neuroectoderm into the neural tube. Following specification, cells in the neural tube proliferate and undergo differentiation to produce the many different cell types of the nervous system. The neural tube thus gives rise to the entire nervous system, composed of multiple cell types such as neurons, astroglia, oligodendrocytes, and a small population of neural stem cells. The processes of proliferation and differentiation are modulated by both the environment and the genetic programming of the precursor cells (reviewed in ref 8). The newly formed cells of the nervous system migrate from the site of generation to various sites, depending on the site of their activity. They project processes, such as dendrites and spines, supported by neurotrophins (e.g., brain-derived neurotropic factor, BDNF) to form synaptic connections with other neurons for communication.[9] Another critical component of the development process is the programmed cell death (PCD) of surplus neurons, which is essential for fine-tuning the nervous system.[10]

1.2. Adult Neurogenesis. Neurogenesis was first thought to be restricted to the embryonic and perinatal developmental stages, and the adult nervous system was thought to be incapable of self-repair.[11] However, after the discovery of neural stem cells,[12,13] which have the potential to self-renew and to differentiate into various cell types including neurons and glia, there have been numerous studies on adult neurogenesis. Neurogenesis in the adult mammal occurs primarily in the subventricular zone (SVZ) of the lateral ventricles and in the subgranular zone (SGZ) of the dentate gyrus in the hippocampus.[1] While neurogenesis has also been observed to a minor extent in other regions, such as the amygdala and the hypothalamus, it remains to be studied in further detail[14] (Figure 1). Similar to the embryonic stage, adult neurogenesis involves cell proliferation, migration, and differentiation and is

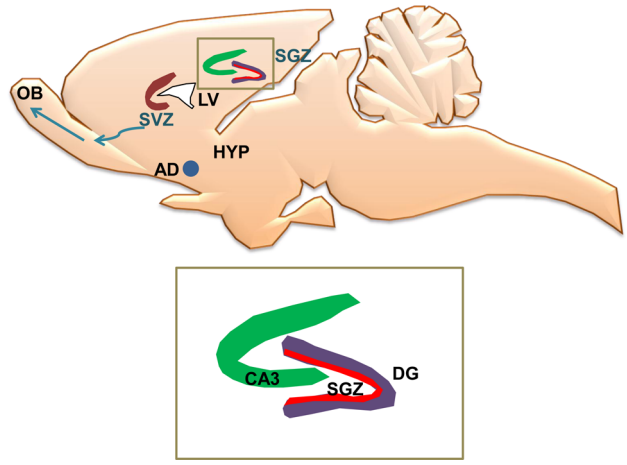

Figure 1. Adult neurogenesis in rodents occurs at small restricted zones. Neurogenesis occurs in the subgranular zone (SGZ) in the dentate gyrus (DG) of the hippocampus, which consists of the pyramidal neuron layer (CA) along with the DG. The SGZ has neural stem cells and proliferating neural precursor cells. Apart from the SGZ, neurogenesis also occurs in the subventricular zone (SVZ) of the lateral ventricle (LV). The neurons produced here ultimately migrate to the olfactory bulb (OB). The amygdala (AD) and hypothalamus (HYP) are minor sites of neurogenesis.

controlled by signals from the immediate environment as the newly differentiated neurons integrate into the existing circuitry. Toward this end, determining the role of new players (e.g., microglia) as well as the level of crosstalk between the precursor cells and their cellular environment during neurogenesis has gained importance in the past few years.[15] Although similar in mechanistic details to some extent, adult neurogenesis occurs at a relatively restricted rate and in small regions compared to the extensive neurogenesis that occurs at the embryonic stages.

While the majority of studies on adult neurogenesis have been performed in mammals such as mice and rats, there is also evidence for adult neurogenesis in humans[16] as well as in nonmammalian vertebrates and insects.[17] Although the physiological role of neurogenesis in behavior, learning, and memory, in particular, is still under debate, there is accumulating evidence that the perturbation of adult hippocampal neurogenesis leads to deficits in several forms of hippocampus-dependent memory in rodents.[18−20] Adult hippocampal neurogenesis has also been shown to play a significant role in situations where fine discrimination is required. It particularly provides a substrate for the dynamic aspects of behavior, such as pattern separation, flexibility of behavior, and memory resolution, indicating an important role in reversal of learning.[21−23] Of note, young neurons (2−4 weeks old) are thought to be more plastic than their older counterparts, and a recent theory postulates that the continuous addition of these neurons could promote forgetting by degrading the existing information stored in the hippocampus while simultaneously providing substrates for new learning.[24,25] Taken together, these studies strongly indicate the undisputable role of adult neurogenesis in plasticity. The presence of adult neural stem cells is also promising for applications in therapeutics because

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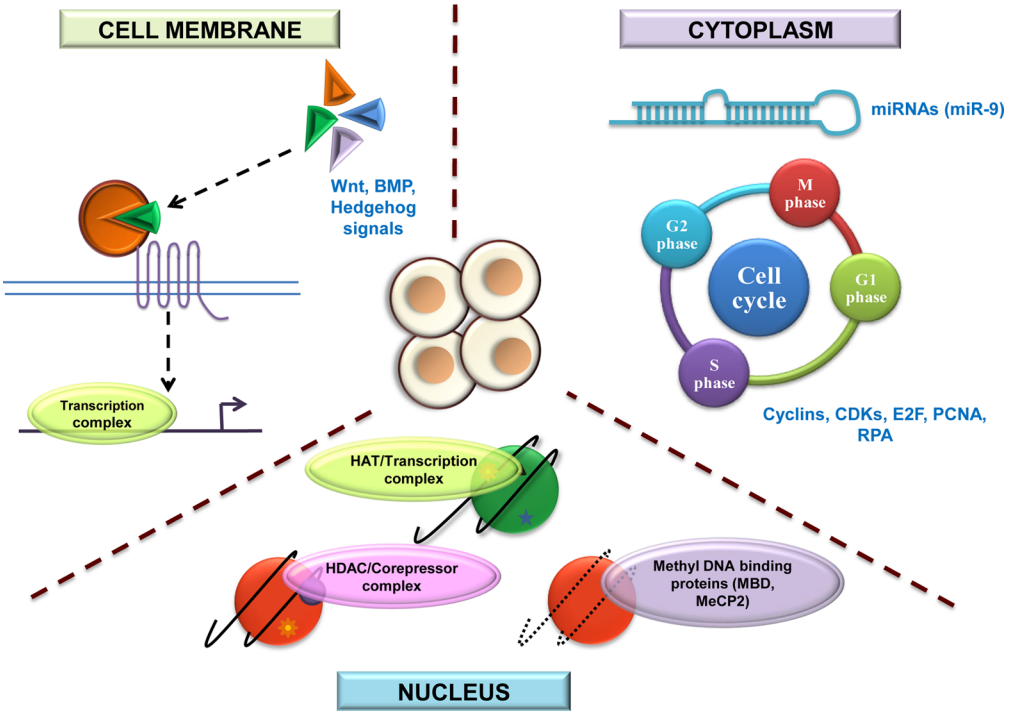


Figure 2. Factors influencing differentiation in neural stem cells (NSCs): Various factors control the stemness-differentiation balance in NSCs, and they might be signaling pathways through the membrane, small RNAs, and cell cycle related proteins in the cytoplasm or the epigenetic machinery in the nucleus. (CDK, Cyclin dependent kinase; PCNA, proliferating cell nuclear antigen; RPA, replication protein A; BMP, bone morphogenetic protein.)

the potential of these precursor cells is restricted, and the possibility of developing tumors is limited.

1.3. Molecular Mechanisms Governing Neurogenesis. Among the primary determinants of neural development in the embryo and neurogenesis in the adult, are signaling pathways, which function as morphogens. For instance, during early embryonic neural development, gradients of BMP and Wnt are generated across different axes in the presence of the Spemann organizer. In *Drosophila* and in mice, sonic hedgehog mediates the functions of the notochord and determines the functions across the dorso-ventral axis, soon after this initial specification.[26] The Notch signaling pathway also plays an important negative role by demarcating the cells that will ultimately differentiate into neurons, and preventing further insurgence into other areas by inhibiting neurogenesis; this has been demonstrated in various organisms including *Drosophila*, *Xenopus*, zebrafish, and mice.[27−30] Many of these pathways also come into play in the later stages of development (reviewed in ref 31).

Numerous signaling pathways act to bring about neurogenesis in the adult by controlling transcriptional programs, such as Wnt signaling in the SGZ and BMPs in the SVZ. The nonautonomous control of neurogenesis is also brought about by the influence of neurotransmitters, cytokines, growth factors, and hormones.

Other important factors for neurogenesis act within neurons. For example, the cell cycle related proteins ensure that postmitotic neurons no longer enter the cell cycle. In addition, cytoskeletal proteins maintain a neuron's distinct morphology; these factors are often disrupted in neurodegenerative disorders. The past decade has also seen emerging evidence supporting the role that miRNAs (small noncoding RNAs that regulate gene expression at the post-transcriptional level by binding to specific regions on target mRNAs) play in the nervous system, owing to fluctuations in their relative levels at different stages of development and in different cell types. Apart from the brain-specific miRNAs (e.g., miR-9), other miRNAs and miR clusters have also been demonstrated to play a role both in neural development and in the differentiation of specific cell types. The miRNA profile of the brain is altered in different pathophysiological states (reviewed in refs 32 and 33). Apart from the broad families of biomolecules described above, many individual factors and small molecules (e.g., GABA, presenilin etc.) have also been shown to be significant players in adult neurogenesis. A brief overview of such factors can be found in Figure 2.

2. EPIGENETIC REGULATION OF GENE EXPRESSION IN NEUROGENESIS

Apart from the factors briefly mentioned above, gene expression plays a significant role during the course of neural development and in adult neurogenesis. Transcription is, in turn, modulated by epigenetic changes on both the DNA and histones, which are controlled by different enzymes. Epigenetics may be broadly defined as the heritable phenomenon by which modifications of the DNA and underlying histones lead to changes in gene expression (and thus, cellular phenotype) without alterations in the primary DNA sequence of the genome.

While some epigenetic modifications, such as DNA methylation and histone acetylation, have been studied extensively over the past few decades, the potential role of other modifications in neural development remains to be explored. The role of epigenetic modifications as key regulators controlling neurogenesis will be described in detail in this section.

2.1. Epigenetic Modification of Histones. The core component of eukaryotic chromatin is the nucleosome, an octamer comprising two units each of the core histones, namely H2A, H2B, H3, and H4, with approximately 146 bp of DNA wrapped around it.[34] The loosely structured N-terminal tails of histones that protrude out from the nucleosome core undergo different post-translational modifications, such as acetylation, ubiquitination, methylation, and phosphorylation.[3,35] Several modifications of the globular domain have also been reported, the functions of which are currently under investigation.[36] The epigenetic modifications of histones alter the state of chromatin condensation by working in tandem and exerting a crosstalk that modulates transcription from the corresponding DNA segment. Different combinations of these modifications is commonly referred to as the "Histone Code".[37]

2.1.1. Histone Acetylation in Neural Development. One of the most well-studied histone modifications is histone acetylation. Histone acetylation occurs at lysine residues and is catalyzed by the nuclear histone/lysine acetyltransferases (HATs/KATs), leading to the relaxation of the underlying chromatin due to changes in the overall charge (reviewed in ref 38). Acetylation is reversed by the catalytic action of histone/lysine deacetylases (HDACs/KDACs).

The reversible acetylation of histone and nonhistone proteins in the process of neurogenesis and neural function has been studied extensively. The level of histone and nonhistone protein acetylation increases during the postnatal development of the brain.[39] The levels of H3 and H4 acetylation are considerably higher in developing neurons in the mouse cerebral cortex and chick spinal cord compared to their levels in the proliferating stem cell and progenitor populations, indicating that this modification plays a significant role during the course of neural development.[40]

Among HATs, CBP/p300 (CREB binding protein/E1A binding protein p300), which has a wide range of histone and nonhistone substrates, has been well-studied in the context of neural development. While deletion of either enzyme leads to neural tube closure defects and embryonic lethality in mice,[41,42] mutations or haploinsufficiency of CBP leads to mental disability, as observed in Rubinstein−Taybi Syndrome (RTS).[43] Moreover, it was recently demonstrated that CBP regulates the differentiation of interneurons from neuronal precursors in the ventral forebrain.[44] This phenomenon is further complicated by the observation that post-translational modifications of these enzymes, in turn, regulate their enzymatic activity and, thus, neuronal differentiation. For instance, the phosphorylation of CBP by protein kinase C ζ is required for CBP-mediated histone acetylation at a number of neuronal gene promoters.[45] However, because both p300 and CBP are potent transcriptional coactivators, their intrinsic acetyltransferase activity may not always be essential for their function. In this regard, HAT-specific inhibitors or activators would be useful in delineating the specific contribution of acetylation (of histone and nonhistone proteins).

Using $cbp^{+/-}$ mice, a potential role has been reported for CBP in driving adult neurogenesis during an adaptive response to certain environmental stimuli. Neurogenic genes such as neurogenin 1 and 3, Nestin, and double cortin (DCX) were all upregulated by an enriched environment (EE) in a CBP-dependent manner. This effect of CBP on adult neurogenesis has functional consequences as it impaired the EE-mediated enhancement of spatial navigation and pattern separation ability.[46]

Gcn5, a member of another family of HATs, has also been well-studied in the context of neural development. Similar to CBP/p300, the loss of Gcn5 leads to embryonic lethality, and its HAT activity is involved in neural tube closure.[47,48] Interestingly, knocking out Gcn5 in neural stem cells leads to effects that are quite similar to the phenotype observed upon knocking out Myc, a well-known cell cycle regulator and oncogene. This could be attributed to the cooperative regulation of transcriptional programs by Gcn5 and Myc, that help regulate neural stem cell proliferation and brain growth.[49]

In contrast to these two families, the role of the MYST family of HATs in neural development remains relatively unknown. However, it has been shown that mice lacking the MYST family member Querkopf (Qkf, Myst4, Morf) have several defects in adult neurogenesis, including fewer neural stem cells with a reduced capacity for both self-renewal and neuronal differentiation.[50]

Mammals have 18 HDACs, which are expressed in a cell type specific manner and are grouped into four classes.[51] These diverse HDACs play different roles during neural development; it is known that HDACs function in corepressor complexes and function as molecular brake pads in transcription related to memory.[52] A deficiency in HDAC2 of the Class I HDACs (which includes HDAC 1, 2, 3, and 8) leads to specific and cell autonomous defects in adult neural differentiation; surprisingly, these defects are not known to occur during embryonic neurogenesis.[53] Class II HDACs (HDACs 4, 5, 7, and 9 in IIa and 6, 10 in IIb) are also expressed in a cell type specific manner, and their levels increase during neuronal differentiation.[54] HDAC6, a known tubulin deacetylating enzyme, helps in the neuroprotection of the brain.[55]

Collectively, the homeostasis of histone and nonhistone protein acetylation, as regulated by HATs and HDACs, is a crucial component for adult neurogenesis and differentiation.

2.1.2. Histone Methylation in Neural Development. Lysine and arginine residues of histones are methylated by histone/lysine methyltransferases (HMT/KMT) and protein arginine methyltransferases (PRMTs), respectively, and represent another common epigenetic modification that controls gene expression. The outcome could be either gene silencing or activation, depending on the residue modified, the number of methyl groups added, and the coexistence of other modifications (crosstalk). This is exemplified by two antagonistic complexes, namely, the Polycomb (PcG) and trithorax (TrxG) group. While PcG catalyzes the trimethylation of lysine 27 on histone 3 (H3K27me3), leading to gene repression by heterochromatinization, TrxG methylates lysine 4 of histone 3 (H3K4me3), which is involved in target gene activation by RNA polymerase II recruitment.[56,57] These complexes also play a crucial role in neurogenesis in the mammalian brain. The PcG members, Bmi1 and PRC2, regulate the self-renewal of neural stem cells and are involved in the maintenance of neural progenitor cells.[58] In contrast, mixed-lineage leukemia (Mll1), a TrxG member, plays a role in postnatal neurogenesis in mice.[59] The role of several other methyltransferases, such as EZH2, in adult neurogenesis remains to be elucidated. However, several lines of evidence support a role for EZH2 similar to that of Bmi1 in the postnatal brain. EZH2 is highly expressed in proliferating cells but its expression progressively decreases during differentiation into neuronal cells.[60] Recently, it has also been shown that EZH2 is expressed in the SVZ of the infant brain and in hippocampus-localized neuronal stem cells

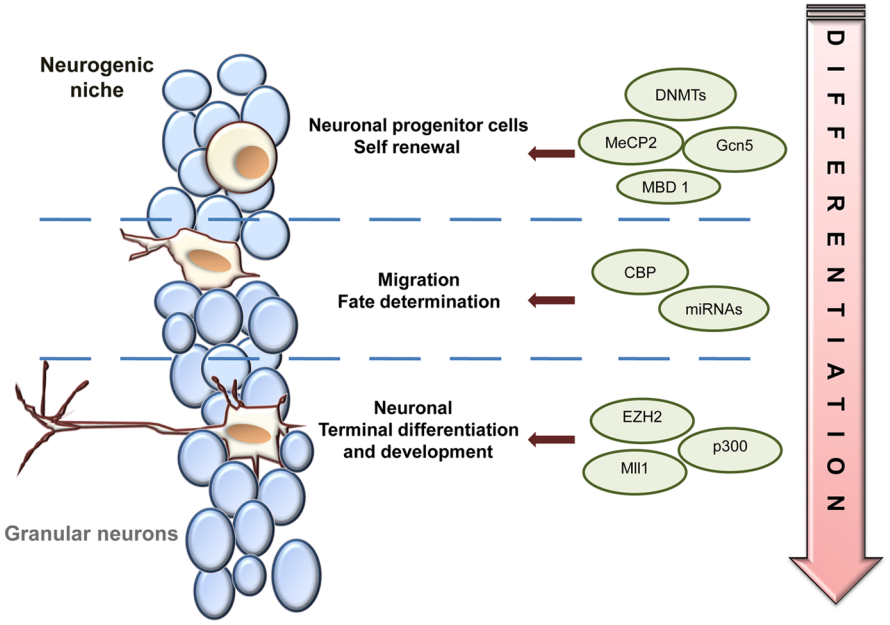


Figure 3. Epigenetic factors control differentiation: Different regulatory factors (indicated in circles on the right) are involved in different processes like self-renewal, fate determination, migration, and terminal differentiation. (DNMTs, DNA methyltransferases; MeCP2, methyl CpG binding protein 2; MBD 1, methyl-CpG-binding domain protein 1; CBP, CREB-binding protein; Mll1. the mixed-lineage leukemia-1.)

(NSCs), where it supports neuronal proliferation and differentiation.[61,62]

Along with histone methyltransferases, histone demethylases have also been shown to be involved in neuronal development. Recently, a genome-wide occupancy analysis of the jumonji-domain-containing gene JMJD3 using ChIP-sequencing has revealed that JMJD3 is present on the SMAD3 promoter and subsequently regulates neuronal development through the TGF-beta signaling pathway.[63] It has also been shown that JMJD3, a transcriptional target of SMRT, plays a vital role in neuronal differentiation through the retinoic acid receptor. The importance of JMJD3 has been reinforced by the finding that the deletion of its homologue in zebrafish resulted in decreased neuronal survival and defects in dendritic growth.[64,65]

Gene expression is also regulated by the chromatin signature of enhancer regions, and these have been shown to control expression of neurogenic factors.[66] This regulation is a relatively more recent aspect of study, and has not been studied as well as chromatin modifications on the promoter region. In a recent study, JMJD3 has been shown to activate neurogenic gene expression by activating poised chromatin elements at both transcriptional enhancers and promoters, along with its above-mentioned modes of action.[67]

Although arginine methylation has a specific and significant function in the transcriptional regulation of both coding and noncoding RNA and is involved in other differentiation pathways, its role in neural differentiation remains unknown.

2.2. DNA Methylation in Neural Development. DNA methylation, which is an extensively studied reversible epigenetic modification that regulates gene expression, predominantly occurs at cytosine residues of CpG dinucleotides to form 5-methylcytosine.[68,69] DNA methylation is catalyzed by two families of DNA methyltransferases: the de novo methyltransferases, DNMT3A and DNMT3B, which transfer a methyl group from the donor, *S*-adenosyl-L-methionine (SAM), to unmethylated DNA and DNMT1, which methylates hemimethylated DNA immediately after DNA replication.[70] Several studies have reported a crucial role for DNA methylation in neurogenesis and differentiation.[71,72] For example, DNMT1 is one of the methyltransferases that modulates the JAK-STAT signaling pathway, which is involved in regulating the critical switch between neurogenesis and gliogenesis.[73,74]

Three families of methyl-CpG binding proteins (MBPs) act as effectors of DNA methylation. These proteins regulate gene expression by binding to methylated DNA and subsequently recruiting chromatin remodeling complexes.[75] MBD1 and MeCP2, which belong to the first class of MBPs, have been extensively studied in relation to neural development and differentiation. Although MBD1 null mice appear to be healthy throughout life, they have defects in adult neurogenesis in the dentate gyrus,[76] likely mediated by MBD1's regulation of FGF2 expression, which is essential for the maintenance of neural progenitor cells.[77] MeCP2 is highly expressed in neurons and its absence or mutation is associated with Rett syndrome,[78−80] owing to its role in the alteration of gene expression programs that ensure timely neurogenesis.[81] MeCP2 also plays a role in promoting neurogenesis when overexpressed in vitro and in vivo.[82] The dynamics of methylation are also controlled by other proteins, such as GADD45b, which regulate adult neurogenesis in the dentate gyrus by promoting the demethylation of critical gene promoters (e.g., BDNF and FGF) to maintain progenitor cells.[77]

In summary, controlled reversible epigenetic modifications are among the crucial mechanisms that regulate gene expression during neural development and higher order brain functions such as learning and memory (Figure 3). An increasing body of evidence has established a connection between reversible acetylation and neuronal death, atrophy, age-related neurodegenerative diseases, and cognitive decline. As described below, the loss of chromatin acetylation is a common feature of neurodegenerative diseases. As such, therapeutic strategies using small-molecule modulators that

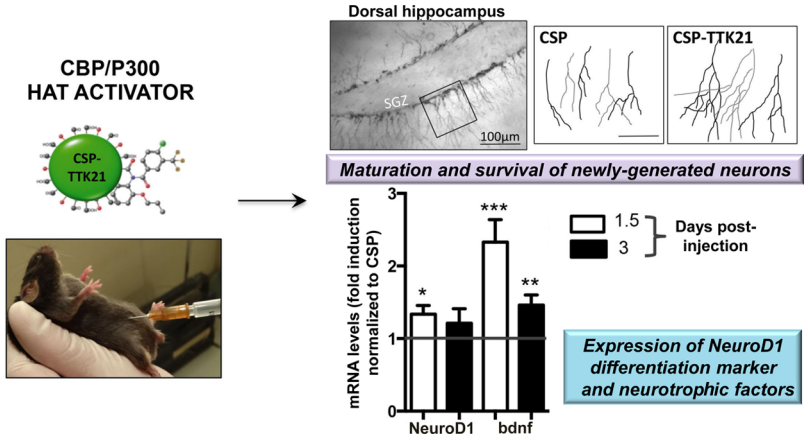


Figure 4. CBP/p300 HAT activation increases adult neurogenesis in C57BL6 mice: Upon intraperitoneal administration, CSP-coupled TTK21 molecule is able to increase the differentiation of adult-born neurons in the dorsal hippocampus on day 3 as highly branched double-cortin-labeled neurons are visible in the CSP-TTK21 versus CSP-treated mice, probably through a previous (1.5 day postinjection) induction of the differentation marker NeuroD1 and the neurotrophic factor BDNF (***$p < 0.0001$, **$p < 0.001$, and *$p < 0.005$). NeuroD1 and bdnf transcripts were measured in the dorsal hippocampus by RT-qPCR. SVG, subgranular zone.

can either inhibit HDACs or enhance HAT activity hold lot of promise.

Apart from chromatin modifying machinery, chromatin remodelling complexes have also been shown to modulate neurogenesis. For instance, it has recently been shown that a physical interaction between Pax6 and a Brg1-containing BAF complex activates a cross-regulatory transcriptional effector network that maintains high expression of genes regulating neuronal differentiation and downstream neuronal fate stabilization.[83]

The following sections will discuss these small molecules and their effects on neurogenesis, as well as their potential therapeutic applications.

2.3. Epigenetic Modulators Influence Neurogenesis. Several small molecules that can target different signaling pathways and gene networks involved in the various stages of neurogenesis have been identified. Some of these compounds directly target epigenetic enzymes, with a few off-targets. Among these, the histone deacetylase inhibitors have been studied to a large extent. HDAC inhibitors (HDACi) such as sodium butyrate (NaBu), valproic acid (VPA), and trichostatin A (TSA) induce neuronal differentiation in the hippocampus, most likely by inducing a large array of genes, including the neurogenic transcription factor NeuroD,[84] which is required for the survival and maturation of adult born neurons.[85] The chronic treatment of adult rats with VPA stimulates neuronal differentiation and hippocampal neurogenesis by increasing the expression of bHLH pro-neuronal transcriptional factors such as neurogenin1, Math1, p15, and so forth, as well as activating the ERK pathway.[86−88] Suberoylanilide hydroxamic acid (SAHA) and NaBu block cells in the G1 phase of the cell cycle, thereby suppressing the formation of neurospheres by NSCs of the SVZ. This is likely due to elevated H3K9 acetylation and the subsequent overexpression of p21 and p27, which results in a reduction of the stem cell/progenitor state.[89] Interestingly, although TSA is a broad spectrum HDACi, its use in developing mice has opposing effects on neurogenesis depending on the brain area; it reduces neurogenesis in the ganglionic eminences but increases cortical neurogenesis.[90] These data suggest that the above-mentioned HDACi may have unknown off-target effects and preferential areas of action.

HAT activation is a relatively new concept in the field and carries significant potential because most of the known HDACis either target a class of HDACs, or target HDACs nonspecifically, rather than targeting any one specific HDAC. Therefore, treatment with HDACi affects the acetylation of a wide spectrum of substrates; this results in a large amount of nonspecific acetylation in the process of achieving a specific level of acetylation. Direct activation of histone acetylation became possible with the discovery of a p300/CBP specific HAT activator, *N*-(4-chloro-3-trifluoromethyl-phenyl)-2-ethoxy-6-pentadecyl-benzamide (CTPB), which is a flutamide derivative of the first identified, natural HAT inhibitor, anacardic acid.[91] The major challenge of enabling CTPB to cross the cell membrane was overcome by utilizing another discovery by the same group: self-fluorescent cell permeable glucose-derived carbon nanospheres (CSP).[92] Upon adsorption of CTPB to the surface of CSP, it could be successfully delivered to the mouse brain and was found to activate histone acetylation.[92,93] Further derivatization of CTPB gave TTK21, which upon covalent conjugation with CSP (CSP-TTK21) was able to induce acetylation at H3K14, H3K9, and H2B in the dorsal hippocampus and prefrontal cortex of injected mice. Such a specific treatment resulted in an increase of neurogenesis in the dentate gyrus, which was characterized by an accelerated maturation of newly formed neurons together with the expression of NeuroD1 and an increase in BDNF levels[94] (Figure 4).

Though few in number, a few more HAT activators, such as nemorosone and pentadecylidenemalonate (LoCAM), have been reported.[95] Their effects on the process of neurogenesis are yet to be explored.

2.4. Epigenetic Modulators Influence Learning and Memory. Epigenetic modifications, particularly histone acetylation, have been shown to play a major role in memory formation and consolidation.[96−98] It has also been shown that mice lacking HDAC2 and HDAC3 show improved memory function in addition to increased H4K12 but not H3K14 acetylation.[99,100] There are several HDAC inhibitors, such as TSA, NaBu, phenyl butyrate, VPA, and SAHA, which have been shown to ameliorate the deficits in learning and memory associated with many neurodegenerative disorders, as described in the following subsections and summarized in Figure 5 and

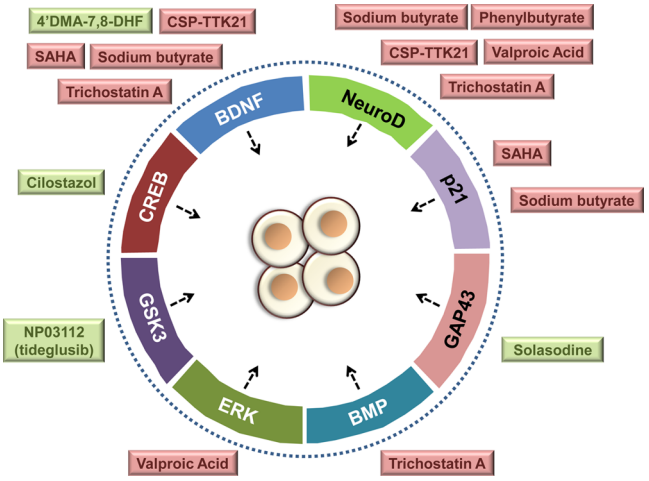


Figure 5. Small molecule modulators of neurogenesis. Different classes of small molecules exert their effect on NSCs through epigenetic (red boxes) or nonepigenetic (green boxes) means to modulate neurogenesis. For details of their mode of action, refer to the text and Table 1.

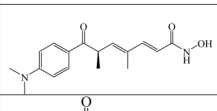
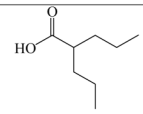
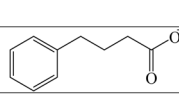
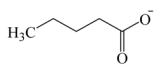
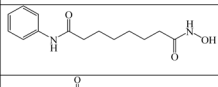
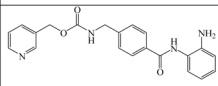
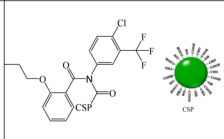
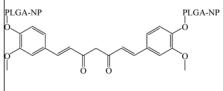
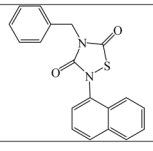
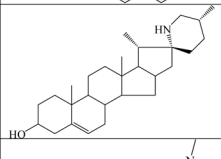
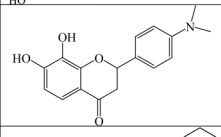
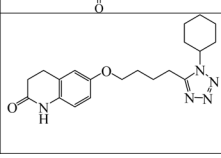
Table 1. Interestingly, mice treated with the HAT activator CSP-TTK21 show a significant increase in the persistence of spatial memory (>10 days), while long-term but recent memory (2 days) is not affected. Memories initially formed in the hippocampus require activity in other regions such as the cortex to become enduring memories (reviewed in ref 101). Therefore, the results obtained with CSP-TTK21 suggest that there is an improvement in the processes involved in systemic and synaptic consolidation, in which adult neurogenesis could also be a potential player as CSP-TTK21 also triggered increased maturation of newborn neurons.[94]

3. SMALL-MOLECULE EPIGENETIC MODULATORS AS NEUROTHERAPEUTICS

3.1. Epigenetic Changes in Neurodegenerative Disorders. Our knowledge of the epigenetic changes during memory consolidation dates back to 1979,[97] after which there have been various studies focusing on the role of histone acetylation in memory formation and memory loss. Diseases that follow different pathological courses, such as Alzheimer's, Parkinson's, and Huntington's disease, share a common feature of neurodegeneration that is generally associated with age (though there are other controlling factors), and impacts societies and economies worldwide.

Global histone acetylation levels are altered during various neurodegenerative disorders,[102] and many are characterized by a loss of CBP, due to multiple reasons such as proteasomal degradation,[103,104] caspase cleavage,[102] sequestration leading to nonavailability,[105] and so forth. The absence of HAT control leads to a preponderance of HDAC activity that also recruits corepressor complexes.[106] This results in a global decrease in acetylation and in the levels of prosurvival molecules that are controlled at the transcriptional level by histone acetylation.[107] These changes illustrate the importance of a delicately balanced HAT/HDAC equilibrium, which, when disturbed, results in abnormal transcriptional activity. While other lysine acetyltransferases, p300,[108] PCAF,[109] and Tip60[110] have all been implicated in neurodegeneration, the mechanistic details are not as well-characterized as in the case of CBP.

Table 1. Small Molecule Modulators of Neurogenesis

Modulator	Name	Structure	Enzyme Specificity	Effect on neural differentiation/ neurogenesis	Ref.
HDAC Inhibitor	Trichostatin A		Class I, II and IV HDACs	Induces neural differentiation *in vitro* through NeuroD1	84
	Valproic Acid		Class I and IIa	Induces neural differentiation *in vitro* by NeuroD1, bHLH induction; Induces proliferation and maturation in neurogenesis *in vivo* by activating ERK signaling	84, 86, 87
	Phenyl Butyrate		Class I and IIa	Induces neural differentiation *in vitro* by NeuroD1 induction	84
	Sodium Butyrate		Class I and IIa	Induces proliferation, migration and differentiation in neurogenesis *in vivo* by BDNF-TrkB signaling; Suppresses neurosphere formation *in vitro*	89, 132
	SAHA		Class I, II and IV HDACs	Suppresses neurosphere formation *in vitro*	89
	MS-275		HDAC1, HDAC2 and HDAC3	Effect on neurogenesis unknown; reduces amyloid plaque deposition in the hippocampus	156
HAT Activator	CSP-TTK21		P300/CBP	Induces differentiation (and likely survival) in adult neurogenesis *in vivo* by increasing acetylation on NeuroD1 and BDNF promoters. Reduces proliferation of BrdU positive cells	94
Non-Epigenetic targeting molecules	Cur-PLGA-NPs			Induces proliferation and differentiation in neurogenesis *in vivo* by increasing β-catenin translocation and GSK3 phosphorylation	173
	NP03112 (tideglusib)			Induces proliferation, differentiation *in vitro* and neurogenesis *in vivo* by the inhibition of GSK-3 and Wnt signaling	139
	Solasodine			Induces proliferation and differentiation in neurogenesis *in vivo* and differentiation *in vitro* by GAP43/HuD pathway	160
	4'-DMA-7,8-DHF			Induces neurogenesis *in vivo* by BDNF-TrkB pathway; exhibits anti-apoptotic activity	169
	Cilostazol			Induces proliferation and migration in neurogenesis *in vivo* by cAMP-responsive element binding protein (CREB) signaling	170

As expected, HDAC expression profiles exhibit the reverse pattern, with many HDACs being increased in neurodegeneration such as HDAC2,[111] HDAC3,[112] and HDAC4.[113] The role of DNA methyltransferases in neurodegeneration has been explored to a limited extent; DNMT1 and DNMT3A are involved in neuronal apoptosis and neurodegeneration.[114,115] In contrast to CBP mediated histone acetylation, both DNA and

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histone methylation have not been studied in relation to neurodegeneration to a large extent.

3.2. Targeting Neurodegenerative Disorders Using Small Molecules. Neurogenesis is affected by various physiological, pathological, and pharmacological conditions, and can be increased or decreased (reviewed in ref 116). For instance, pathological conditions like infections influence neurogenesis, which also decreases with stress,[117] depression, and age.[118] The correlation between aging and the development of multiple memory-associated neurodegenerative disorders such as Alzheimer's and Parkinson's disease is quite conspicuous.[119−121] Most neurodegenerative disorders show an alteration in adult neurogenesis.[122] The decreased neurogenesis observed in these conditions can be reversed to some extent by exercise.[123] Apart from exercise, pharmacological agents, such as antidepressants,[124] and inducing neural activity by learning and environmental enrichment positively affect neurogenesis.[125] In other conditions, such as epilepsy,[126] stroke,[127] and multiple sclerosis, there is an increase in neurogenesis, but the molecular mechanisms remain unclear. Varied effects on neurogenesis have been observed in Huntington's disease.[128] The extent to which different disease conditions display perturbed neurogenesis is variable; in some conditions, downstream processes are affected, rather than neurogenesis itself. The following sections describe recent advances in the application of epigenetic modulators to ameliorate various neurodegenerative disorders. It is important to note, however, that whether the positive effects of these molecules occur through effects on neurogenesis has not been definitely proven.

3.2.1. Stroke. Stroke is characterized by cerebral ischemia, a rapid loss of neurons and reduced acetylation levels.[129] However, in the case of focal cerebral ischemia, an induction of neurogenesis has been observed, with migration of SVZ neuroblasts to the damaged brain regions. This interesting self-repair mechanism has been observed even in advance-aged patients, making it a possible target for stroke treatment.[130]

In a middle cerebral artery occlusion (MCAO) stroke model, it has been shown that postinsult treatment with VPA, NaBu, or TSA can improve behavior,[131−133] and the long-term behavioral benefits in NaBu-treated MCAO rats are associated with enhanced neurogenesis in the ischemic brain. This enhanced neurogenesis is abolished by blocking the BDNF-TrkB pathway,[132] indicating that the neurogenesis process is regulated by BDNF. In contrast, other studies have described the use of small molecules with no effect on neurogenesis. The administration of 4-phenylbutyrate in mice subjected to hypoxia-ischemia protects them against endoplasmic reticulum (ER) stress, as evidenced by decreased eIF2a phosphorylation and the expression of the eIF2a-regulated proapoptotic protein, CHOP.[134] Treatment with HDACi also markedly inhibits ischemia-induced p53 overexpression and heat shock protein 70 (HSP70) superinduction in the ischemic brain.[129,131,133]

3.2.2. Huntington's Disease. Huntington's disease (HD) occurs due to a large number of CAG repeats within the coding region of the *htt* gene, encoding the Huntingtin protein (HTT). This protein was recently shown to affect adult hippocampal neurogenesis, thus relating polyglutamine (polyQ) expansion to the mood disorders (such as anxiety and depression) observed in Huntington's patients.[135,136] Deficits in adult neurogenesis related to cellular proliferation, differentiation, and the survival of newborn DG neurons have also been observed in HD mouse models. Conversely, an increase in SVZ neurogenesis has been described in postmortem HD brain tissue.[137]

The pathology of Huntington's disease is also intimately coupled to BDNF and Hsp70 deficiency in the affected brain regions,[138−140] and the use of HDACi restores normal levels of BDNF and Hsp70. For instance, the HDACi vorinostat and TSA increase vesicular transport of BDNF by inhibiting HDAC6 specifically, the consequence of which is an increase in tubulin acetylation that compensates for the transport deficit of BDNF in Huntington's disease.[141]

3.2.3. Parkinson's Disease. Parkinson's disease (PD) is a highly prevalent neurodegenerative disease of sporadic occurrence characterized by a relatively selective loss of dopaminergic neurons, mainly in the substantia nigra. Decreased adult neurogenesis has been observed in several wild-type and mutated α-synuclein overexpressing mouse models,[142,143] and in patients with PD.[144]

The death of dopaminergic neurons induced by a dopaminergic toxin 1-methyl-4-phenylpyridinium (MPP+) (related to the classical dopaminergic toxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)) can be rescued by treatment with VPA, NaBu, or TSA. Furthermore, there is a marked increase in dopamine uptake and in the number of tyrosine hydroxylase positive neurons upon HDACi treatment in rat cells in culture.[145,146] These treatments also induce BDNF and GDNF gene transcription. Notably, the use of GDNF gene delivery has been considered as a potential therapy for neurodegenerative diseases including PD.[147]

3.2.4. Alzheimer's Disease. Alzheimer's disease (AD) is characterized by progressive memory loss and personality changes, ultimately leading to dementia. Its neuropathological hallmarks include the accumulation of extracellular β-amyloid (Aβ) and neurofibrillary tangles that results from hyperphosphorylation of the tau protein. Hippocampal neurogenesis has been studied in a number of mouse models of AD that exhibit amyloid deposition.[148,149] Hippocampal neurogenesis is altered to varied extents depending on the transgenic cell line used and the stage of AD at the time of the study. For example, Krezymon et al. identified severe alterations of adult hippocampal neurogenesis as an early event in the etiology of AD in Tg2576 mice. Despite the high proliferative activity of progenitors observed in these mice, few new neurons survived, and importantly, these neurons exhibited an impaired maturation. The cognitive deficit observed in the Tg2576 mice could thus be due to the compromised integration of new neurons into the hippocampal circuitry.[150] Strikingly, increased adult neurogenesis has been associated with abnormal tau phosphorylation and tau aggregation in a tau transgenic mouse line, but the long-term viability and functionality of these newborn neurons have not been explored.[151] Overall, strategies designed to stimulate neurogenesis in vivo may be suitable for the AD brain.[152]

In the Tg2576 AD mouse model, daily injections of 4-phenylbutyrate can reverse spatial memory deficits by normalizing tau hyperphosphorylation in the hippocampus without affecting Aβ levels; deficits in hippocampal H4 acetylation and dendritic spine density were also rescued.[153] In APP23 transgenic AD mice, daily injections with a relatively low dose of VPA significantly reduced the number of Aβ plaques and improved memory deficits if treatment was started early (at 7 months).[154] This beneficial effect of VPA is most likely due to the inhibition of GSK-3β-mediated γ-secretase cleavage of APP. TSA treatment rescues the decrease in H4 acetylation, resulting

in an increase of memory formation in APP/PS1 mice.[155] NaBu also helps to restore learning and associated memory in Ck-p25 mice with AD pathology. Treatment with MS-275 (Entinostat), a class I HDACi, reduces amyloid plaque deposition in the hippocampus and cortical regions of APP/PS1-21 mice.[156] The direct injection of SAHA into the hippocampus of aged C57BL/6 mice can rescue the reduced H4K12 acetylation, which could be considered a biomarker of nuclear environment changes, and help in the recovery from age-associated memory impairment.[157]

The HAT activator CSP-TTK21 improves adult neurogenesis in healthy mice by favoring maturation and differentiation processes, and due to the reasons of specificity cited earlier, the application of HAT activators could surpass HDAC inhibitors as the preferred therapeutic in the treatment of neurodegenerative diseases. The possibility of employing CSP-TTK21 to ameliorate the neurodegeneration occurring in Alzheimer's disease is currently being explored, and it would be worthwhile to determine its effect in other neurodegenerative diseases.

Taken together, though diverse in nature, these studies uniformly indicate the promise that the modulation of histone acetylation in the brain holds, to target the damaging pathological and personality changes observed in AD.

3.3. Epigenetic Changes in Brain Tumors and Therapeutic Targets. Changes in the epigenetic language are not restricted to the neurodegenerative disorders described above but are commonly observed in brain-related tumors as well. DNA hypermethylation and aberrant histone modifications are often observed in glioma, a common brain tumor. A mutation screening analysis revealed that various epigenetic enzymes, including histone deacetylases, HDAC2 and HDAC9, histone demethylase, JMJD3, and histone methyltransferases, MLL and SET7, are frequently mutated in glioblastoma patients.[158] These mutations often result in changes in expression profiles and enzymatic activity. As such, HDACi and DNMT inhibitors are currently being tested in clinical trials; some, such as SAHA and panobinostat, show reduced proliferation rates in glioma cell lines.

■ CONCLUSION AND PERSPECTIVE

As the operating gene network behind the process of neurogenesis is not fully understood, the modulation of the epigenetic landscape that regulates these genes is a far-reaching goal. However, a concerted effort has begun to unravel this unique phenomenon by employing epigenetic enzyme targeting molecules and knocking out genes. The pharmacological inhibition of the GSK3 pathway is capable of inducing neurogenesis in the adult rat brain. Among the various thiadiazolidinediones (TDZDs) that inhibit GSK3, NP03112 (tideglusib) is an effective inducer of proliferation and differentiation in the SGZ of adult rats.[159] Solasodine, a naturally occurring compound from the *Solanaceae* family, induces neurogenesis in vitro and in vivo,[160] likely acting through the GAP43/HuD pathway that regulates neuronal differentiation and neurite out-growth.[161−164] Emerging evidence supports the concept that BDNF and the tropomyosin receptor kinase B (TrkB) receptor are implicated in both the development of mood disorders and the positive action of monoamine antidepressants on neurogenesis.[165−168] Similarly, the catechol group in hydroxyl flavone derivatives might be indispensible for their activity through TrkB activation, and 4′DMA-7,8-DHF is a potent synthetic TrkB agonist.[169] Cilostazol reduces infarct volume and induces the regeneration of neural progenitor cells through the activation of the CREB signaling pathway in various pathological conditions such as stroke and neurodegenerative diseases.[170] These small molecules may also affect the overall epigenetic landscape, directly or indirectly, and need to be further investigated. For instance, curcumin and its derivative, CTK7A, are known to inhibit HATs.[171,172] It has recently been found that curcumin that is encapsulated by biodegradable poly(lactic-*co*-glycolic acid) (Cur-PLGA-NPs) nanoparticles exhibits a potent reversal of the amyloid-beta-mediated inhibitory effects on hippocampal neurogenesis in an Alzheimer's disease rat model. Curcumin has also been found to enhance the expression of proneurogenic genes through the nuclear translocation of β-catenin and an increased phosphorylation of GSK-3β;[173] however, the role of histone modifications in this system remain to be explored since the effect of curcumin could be broad-spectrum.

In conclusion, a combined effort of chemical biologists and neurobiologists is essential to thoroughly understand the process of neurogenesis and the related epigenetic network and may lead to the discovery of therapeutically important molecules.

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Author Contributions

T.K.K. put forth the concept. A.S. and T.K.K. developed the outline and designed the figures. A.S. wrote major part of the review, and organized the final review. M.K. contributed in the area of epigenetics and neurogenesis. S.H.S. contributed to the chemistry aspect of the review. A.S.A. and A.L.B. contributed in the area of fundamental process of neurogenesis.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

HAT: histone acetyltransferase; HDAC: histone deacetylase; DNMT: DNA methyltransferase; CBP: CREB binding protein; HMT: histone methyltransferase; NSC: neural stem cell; HDACi: HDAC inhibitor; AD: Alzheimer's disease

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