Hippocampus development and function: role of epigenetic factors and implications for cognitive disease


The hippocampus is a primary region of the brain controlling the formation of memories and learned behaviours. The ability to learn or form a memory requires a neuron to translate a transient signal into gene expression changes that have a long-lasting effect on synapse activity and connectivity. Numerous studies over the past decade have detailed changes in epigenetic modifications under various learning paradigms to support a role for chromatin remodelling in these processes. Moreover, the identification of mutations in epigenetic regulators as the cause of mental retardation or intellectual disability (MR/ID) disorders further strengthens their importance to learning and memory. Animal models for many of these disorders are emerging and advancing our understanding of the molecular mechanisms linking epigenetic regulation and cognitive function. Here, we review how chromatin remodelling proteins implicated in MR/ID contribute to the development of the hippocampus and memory formation.

Conflict of interest

The authors declare no competing conflicts, financial or otherwise.

Epigenetic modification of the genome is a major point of regulation governing many developmental processes. In the central nervous system (CNS), epigenetic regulators play crucial roles during development in the transition of a multipotent neuroprogenitor to a committed neuron, in the generation of the vast number of specialized cell types and their specific gene expression profiles, and for cell survival and neuronal plasticity in response to external and intrinsic signals (1–3). Epigenetic processes primarily impinge on the basic subunit of chromatin, the nucleosome, which is comprised of 146 base pairs of DNA wrapped around an octamer of two copies each of histones H2A, H2B, H3, and H4. Alteration in chromatin compaction is a dynamic process regulating gene expression and it can be modified by several mechanisms including DNA methylation, the post-translational alteration of the histones (acetylation, methylation, phosphorylation, ADP-ribosylation, sumoylation, and ubiquitination), or by ATP-dependent nucleosome remodelling machines (Fig. 1). The covalent
Fig. 1. Mechanisms involved in chromatin modification. Three categories of epigenetic modification are shown: DNA methylation, histone modification and chromatin remodeling. Left panel: Methyl groups are added to cytosine residues within CpG dinucleotides by DNA methyltransferases (DNMTs). The methylated DNA is recognized and bound by methyl-binding domain (MBD) proteins, which then typically recruit other remodeling factors for repression. Histone tails can be modified by methylation, phosphorylation, acetylation (middle panel) or by ubiquitination, sumoylation, or ribosylation (not shown). Acetyl groups are transferred to the residues of histone tails by histone acetyltransferases (HATs) and are removed by histone deacetylases (HDACs), whereas methyl groups are transferred by histone methyltransferases (HMTs) and removed by histone demethylases. Acetylated histones are associated with transcriptionally active regions, whereas methylation of histones can be associated with either active or repressed genes depending on the residue modified. Right panel: Chromatin remodeling complexes use energy from ATP hydrolysis to slide, evict, or reposition nucleosomes and are typically recruited to genes via subunits that recognize and bind to modified histones.

modification of histone tails can directly affect DNA/histone interactions to modulate compaction or serve as a scaffold for the recruitment and binding of other chromatin-modifying factors. Collectively, these dynamic processes regulate changes in gene expression and form the basis of the histone code hypothesis, which has been reviewed elsewhere (4, 5).

As such, it comes as no surprise that dysfunction of the proteins that remodel chromatin results in a wide range of human developmental disorders with cognitive deficits. Mental retardation (MR) or intellectual disability (ID) is a common clinical problem defined by an intelligent quotient (IQ) score <70 and a broad range of learning, memory and adaptive behaviour deficits. Genetic defects are the most common causes of severe MR/ID and more than 300 genes are associated with its etiology, including >90 X-linked genes that contribute to the preponderance of affected males (6–8). Strikingly, a high number of MR/ID genes encode epigenetic regulators (Table 1) and the syndromes and phenotypes associated with such mutations are highlighted in several recent reviews (3, 9).

Despite the growing number of chromatin remodelling proteins implicated in neurodevelopmental disorders, our understanding of their function in CNS development remains sparse at best. Here, we focus our review on insights derived from studies of mice ablated for different epigenetic regulators within the context of hippocampal development and the processes of learning and memory.

Hippocampal development

The hippocampus is located in the medial temporal lobe of the brain and originates from the dorsomedial telencephalon adjacent to the cortical hem (Fig. 2a). The hippocampus has two main histological divisions: Ammon’s horn or cornu ammonis (CA) and the dentate gyrus. The primary neuronal cell layer of Ammon’s horn is composed of glutamatergic excitatory pyramidal neurons. While the pyramidal cell layer (PCL; Fig. 2c) is present throughout the Ammon’s horn, the pyramidal neurons have different morphological and genetic properties, which divide it into the regions of CA1 and CA3. CA2 refers to a transitory region between CA1 and CA3 (10). Pyramidal cell precursors arise from the neuroepithelium and, guided by radial glia, migrate in an inside-out fashion to the ammonic plate over the course of several days following their maturation (11–13). Pyramidal cells are born primarily prenatally with the peak of neurogenesis in the last
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CBP, CREB-binding protein; HDAC, histone deacetylase; LTP, long-term potentiation.
Hippocampus development and function

Fig. 2. Anatomy of the developing hippocampus. (a) Nissl-stained coronal section of an embryonic day 15.5 murine brain showing the location of the ganglionic eminence (GE) and cortical hem (CH). The epithelial precursors of the hippocampus (H) reside adjacent to the CH. (b) Nissl-stained coronal section of an adult murine brain showing the location of the hippocampus in the dorsomedial forebrain. The box corresponds to the magnified image shown in (c). The dark staining nuclei of the pyramidal cell layer (PCL) are evident and can be subdivided into the CA1 and CA3 fields. The dentate gyrus contains the granule cell layer (GCL) and subgranular zone (SGZ), whose cells are derived from the first (DM1) and second (DM2) dentate migration. The DM1 and DM2 migratory streams are shown as large arrows. Schematically depicted onto the image are the Schaffer collateral (SC) axons of CA3 pyramidal neurons that synapse onto CA1 pyramidal neuron dendrites. Also shown are the axons from the GCL that synapse onto CA3 pyramidal neuron axons via mossy fibres (MF).

week of gestation in rodents (14, 15). GABAergic interneurons migrate into the hippocampus tangentially from the ganglionic eminences and develop functional synapses prior to the excitatory neurons (16, 17). CA3 pyramidal neurons extend afferent axons that synapse with CA1 pyramidal neurons; these are termed Schaffer collaterals (SC; Fig. 2c). The dendrites of CA3 pyramidal cells continue to mature postnatally with the formation of spines (18). These spines receive synaptic input from the axons of dentate gyrus granule neurons, termed mossy fibres (MF; Fig. 2c) (19). The granule cells are the primary cell layer of the dentate gyrus and 85% are formed postnatally (15). There are two cellular migrations of granule cell precursors, originating from the secondary dentate matrix.
close to the neuroepithelium, that contribute to the development of the granular cell layer (GCL; Fig. 2c) (20). The first dentate migration (DM1; Fig. 2c), completed prenatally, follows a subpial route and directly contributes cells to the growing GCL. The second dentate migration stream (DM2; Fig. 2c) is between the PCL and the forming GCL. It gives rise to late-born granule cells, which migrate radially to the inner portion of the GCL, and the subgranular zone (SGZ; Fig. 2c) (20). Granule cells continue to be generated from the SGZ in the adult hippocampus and are a source of adult neural stem cells (NSCs), a potential therapeutic for neurodegenerative and neuropsychiatric diseases (21, 22).

**Hippocampal function**

While historically there has been debate over the precise role of the hippocampus in various functions of the limbic system, it is now widely accepted that its major contribution lies in the formation of long-term memories and the process of learning. The cellular mechanism believed to underlie memory and learning is known as long-term potentiation (LTP) (23, 24). LTP is a form of synaptic plasticity that refers to the enhancement in signal transmission of excitatory synapses that persists for long periods of time following its induction (24). In the hippocampus, LTP at CA3–CA1 pyramidal neuron synapses is the most widely studied and is commonly used as an experimental system for assessing learning and memory in animal models. Three sequential phases of LTP are typically recognized: short-term potentiation (STP) and early LTP (E-LTP), both transient phenomena independent of gene transcription and protein synthesis, followed by late LTP (L-LTP), which lasts from several hours in vitro to weeks in vivo and requires gene expression changes and de novo protein synthesis (24, 25). These changes in gene expression contribute to increases in dendritic spine number, synaptic surface area, pre-synaptic neurotransmitter release, and post-synaptic sensitivity to neurotransmitter that underlie L-LTP expression and maintenance (24, 26). A growing collection of studies document epigenetic changes that mediate the process of memory consolidation and cognitive function attributed to the hippocampus [reviewed in (27, 28)]. In the following sections, we review studies of transgenic mice ablated for epigenetic regulators, many of which are implicated in MR/ID, to highlight their contributions to our understanding of hippocampal development and memory formation.

**Involvement of DNA methyltransferases and methyl-binding proteins in hippocampal development and function**

DNA methylation is catalysed by DNA methyltransferases (DNMTs) that covalently add a methyl group to cytosine residues within Cytosine-phosphate-Guanine (CpG) dinucleotides (Fig. 1). The DNMT1 protein is required for maintenance of methylation, whereas DNMT3a and DNMT3b are involved in de novo methylation. Typically, DNA methylation is associated with repression of gene expression and it can occur directly, whereby methylated cytosines sterically interfere with transcription factor binding, or indirectly, through the binding of methyl-CpG-binding domain (MBD) proteins to methylated DNA that subsequently recruit repressive complexes [Fig 1; reviewed in (29)]. Various methylated DNA-binding factors are expressed in the hippocampus including MBD1, MBD2, MeCP2, and ZBTB4 (30, 31), and two of these proteins, MBD1 and MeCP2, have been linked to hippocampal development and function.

Specific roles for the DNMT family in hippocampal development are emerging through the use of conditional mouse mutants, as complete ablation of any Dnmt gene leads to early embryonic lethality (32, 33). Initial studies with neuron-specific inactivation of Dnmt1 or Dnmt3a showed that all brain structures were intact but that the double knockout animals had 10% volume reductions in the hippocampus and dentate gyrus. Further analysis showed that the brain structures had equivalent cell numbers but that the neurons were significantly smaller in size (34). Other studies have indicated that Dnmt1 mutants also have defects in neuronal maturation and synaptic plasticity (35, 36). Mutation of Dnmt3b in humans causes Immunodeficiency, Centromere instability, Facial anomalies (ICF) syndrome and murine Dnmt3b knockouts exhibit neural tube defects and early lethality (33, 37). Our understanding of the role of Dnmt3b in hippocampal development and function awaits the use of conditional Dnmt3b mutants.

These models have also shown important roles for DNA methylation in several aspects of hippocampal function including synaptic plasticity and memory formation. Mice lacking both Dnmt1 and Dnmt3a in mature forebrain neurons were impaired in long-term plasticity and learning and memory tasks that were attributable in part to deregulated gene expression (34). Other studies have shown that activation of the signalling pathways that induce LTP and contextual fear
conditioning increases the expression of DNMTs in the CA1 region (38, 39). DNMT inhibition causes defective excitatory synaptic transmission in hippocampal neurons, implying that DNA methylation changes lead to alterations in neuronal function at a cellular level (40). In addition, when the hippocampus is treated with DNMT inhibitors, changes in DNA methylation and transcription are observed for several genes involved in synaptic plasticity and memory including reelin, brain-derived neurotrophic factor (BDNF), and protein phosphatase 1 (38, 39, 41). These inhibitors can also block LTP at SC synapses, as well as memory consolidation in vivo, suggesting a critical role for DNA methylation in both plasticity and memory in the hippocampus.

Mouse mutants for Mbd1 and Mecp2 have also been described and show the importance of methyl-binding proteins in the biogenesis of hippocampal structures. Mice lacking Mbd1 exhibit significantly lower cell density in the dentate gyrus due to reduced newborn cell survival and impaired neurogenesis (42). Mecp2 has been extensively studied in a variety of mutant mice that represent good models of Rett syndrome (43–46). Rett syndrome is the most widely studied MR/ID disorder arising from mutations in an epigenetic regulator, and the various murine models recapitulate many of the morphological abnormalities of hippocampal neurons that are observed in Rett patients (47–49). Mecp2−/− neurons in the CA2 region of mutant mouse brains are reduced in cell size and neurons in the dentate gyrus of Mecp2 knockout mice have fewer dendritic spines and an abnormal orientation of neuronal processes compared to wild-type animals (43, 50). CA1 pyramidal neurons additionally exhibit abnormal morphological features including decreased density and size of dentritic spine heads, elongation of spine necks, reduced number and disorganization of axons, and dendritic swelling (51). Reduced dendritic complexity is also observed upon shRNA-mediated knockdown of endogenous Mecp2 in pyramidal neurons within rat hippocampal slice cultures, further highlighting the importance of Mecp2 in establishing proper synaptic connectivity and function in the hippocampus (49, 52).

The involvement of MeCP2 in Rett syndrome has fuelled research to determine the underlying molecular mechanisms of this disease. Mecp2 disruption causes alterations in hippocampal gene expression, resulting in both the up- and down-regulation of synaptic proteins within the granule neurons of the dentate gyrus and a reduction in NMDA receptor levels (50, 53). In addition, changes in the size of post-synaptic densities and glutamatergic synapse numbers have been observed in the CA1 region in vivo (54, 55). These diverse morphological and genetic alterations impinge on neurotransmission and consequently hippocampus-dependent spatial learning and memory, contextual fear memory, and long-term social memory in Mecp2 mutant mice (53, 54, 56). Similarly, studies with Mbd1−/− mice showed deficits in LTP and hippocampus-dependent learning (57). Continued work in this area will help identify specific pathways that may provide targets for therapeutic intervention of the cognitive deficits observed in Rett and related MR/ID syndromes.

**Hippocampus development and function**

Post-translational histone modifications represent a second basic molecular epigenetic mechanism that regulates chromatin structure and influences changes in gene expression. Covalent chemical modification of histone proteins, namely acetylation, methylation, phosphorylation, ubiquitination, sumoylation, and ribosylation, results in alterations in the degree of compaction of chromatin and changes in the transcriptional state of genes. There are an increasing number of enzymes that catalyse these changes and these have been reviewed elsewhere (58). Importantly for this review, gene mutations in histone acetyltransferases (HATs) (CBP, P300), histone methyltransferases (EHMT-1, NSD1), and a histone ubiquitin ligase (HUWE1) are the cause of ID disorders (Table 1) and will be discussed in more detail below. Nonetheless, it should be noted that there is an expanding collection of studies suggesting a role for histone phosphorylation (59–61), ribosylation (62), and methylation (63) in the regulation of hippocampal chromatin structure, gene expression, and memory formation.

Ablation of the HATs Gcn5, p300, or Cbp in mice causes neural tube defects, exencephaly, and death at mid-gestation in most cases (64–67). As such, it is difficult to assess their role in hippocampal development. Studies with Pcaf mutant mice showed subtle modifications in hippocampal formation that specifically reduced CA1 and CA3 pyramidal neuronal cell numbers (68). Other studies with Cbp heterozygous mice suggested that there were no changes in brain anatomy despite deficits in learning and memory (69, 70). Similarly, deletion of the HMTs Ehmt-1 (Glp), G9a, or Nsd1 all results in embryonic lethality, supporting the idea that conditional mutants are required to assess a possible role in hippocampus development (71, 72). Analysis of Ehmt-1 conditional
knockout or heterozygous mice showed that they had autistic-like features that appeared to recapitulate the behavioural characteristics of human patients (73, 74). EHMT-1 regulates H3K9 methylation and its mutation is the cause of the 9q34 subtelomeric deletion syndrome (75). In addition, conditional inactivation of the Huwel gene, a histone ubiquitin ligase mutated in non-syndromic MR, resulted in lamination defects to the cortex, a poorly developed dentate gyrus and neonatal lethality (76).

While a role in hippocampal development must await the generation of conditional mutants, many more studies have addressed the role of histone-modifying enzymes in learning and memory. Indeed, acetylation is the most widely studied chromatin modification in the context of hippocampal function. Animal models of Rubinstein–Taybi syndrome, arising from mutations in genes encoding the HAT enzymes CREB-binding protein (CBP) and p300 (77, 78), show impairments in hippocampal synaptic plasticity and memory consolidation (27). Transgenic mice expressing a mutant form of p300 exhibited long-term memory and learning deficits (79, 80). Conversely, Pcaf knockout animals have impaired short-term memory associated with hippocampal alterations in PCL organization and neuronal activation (68).

As these studies establish a link between histone acetylation and hippocampal function, it is logical to expect that histone deacetylase (HDAC) inhibition might improve the deficits observed in HAT-deficient mutant mice. Indeed, memory deficits caused by Cbp mutations are rescued by administration of HDAC inhibitors (69, 70), indicating the importance of the HAT component of CBP in memory formation and also suggesting potential therapeutic applications of HDAC inhibitors in treating cognitive impairment. HDAC inhibitors were also shown to improve memory and learning capabilities of mice with hippocampal neurodegeneration, and this improvement coincided with increases in the sprouting of dendrites and the number of synapses in the hippocampus (81). In addition, increased excitatory neurotransmission was observed for HDAC inhibitor-treated dissociated hippocampal cultures (82). In line with the transcriptional repression mediated by HDACs, memory-associated neuronal gene expression is suppressed by Hdac2 and increased in Hdac2 knockout mice (83). These studies show the reciprocal and dynamic effects of HAT and HDAC activities on hippocampal gene expression, synapse formation and function, and behavioural consequences for learning and memory. It is anticipated that future studies of other histone-modifying enzymes will elucidate additional regulatory effects.

**Proper hippocampal development requires ATP-dependent nucleosome remodelling factors**

The modifications added to histone tails serve as marks that are recognized by ATP-dependent chromatin remodelling protein complexes (Fig. 1). ATP-dependent chromatin remodelling complexes are important for regulating nucleosome mobility and chromatin accessibility to transcriptional regulatory proteins [reviewed in (84)]. Such complexes are characterized by a subunit that has a Switching/Sucrose non-fermenting-2 (SWI/SNF2)-like helicase motif that functions as an ATPase, utilizing the energy to slide, exchange, assemble, or unwrap nucleosomes (85). Their role in CNS development was established by the identification of mutations in ATRX as a cause of the alpha-thalassemia MR syndrome and the subsequent identification of ERCC6 and CHD7 as the cause of Cerebro-Oculo-Facio-Skeletal (COFS) syndrome and Coloboma, Heart defects, Atresia, Retardation Genital defects, Ear anomalies (CHARGE) syndrome, respectively (Table 1). Studies are slowly emerging that garner a role for these proteins in hippocampal development and function.

Mice that lack Atrx expression in the forebrain showed reduced cell numbers and smaller cortices due to enhanced apoptosis (86). Most striking was the absence of the dentate gyrus granule neurons due to defects in differentiation and incomplete migration of precursors. Atrx null mice also had reduced numbers of GABAergic interneurons in the hippocampus (87). The complete loss of Atrx in the transgenic mouse is more severe than the human mutations, which are thought to be functional hypomorphs, but these studies imply that ATRX likely also contributes to hippocampal function. Mouse mutants of Chad7 are embryonic lethal at E10.5 and analysis of heterozygotes shows size reductions in numerous organs and olfactory development problems; however, no specific hippocampal defects have been analysed (88, 89). Ercc6 knockout mice are viable, display a slight reduction in body weight, develop a circling neurobehaviour defect and have a predisposition to skin cancer (90). Double mutants also lacking the Xpa gene have a severe cerebellar defect suggesting that compensation by other DNA repair proteins could potentially modulate a role for this protein in the hippocampus (91).
Multiple studies examining the role of Swi/Snf complexes have suggested that Brg1-containing complexes are required for both the maintenance of NSCs and for neuronal differentiation of NSCs through interactions with neurogenic transcription factors (92–94). Further work has shown that cell cycle exit and differentiation is dependent on subunit switching of the Brg1-associated factors (BAFs) within Brg1 remodelling complexes (95). Indeed, inactivation of the Baf53b gene in mice results in defects in synapse formation and activity-dependent dendritic outgrowth and arborization in cultured hippocampal neurons (96). Taken together, these studies suggest that Swi/Snf complexes are important for hippocampal neuronal function and NSC fate determination, the latter of which has important implications for adult neurogenesis and the potential use of these cells to treat neurodegenerative disorders.

Conclusions and perspectives

Transgenic mice deficient for genes encoding epigenetic regulators are emerging and beginning to shed light on MR/ID disease pathology. In some instances, these mutants are associated with severe developmental defects that highlight their importance in hippocampal development. In other mutants, the gross anatomy is preserved but there are subtle defects in neuronal number or dendritic spine complexity that impinge significantly on hippocampal function. As additional animal models with hippocampal defects are characterized, and as novel MR/ID disease genes are identified, we will continue to unveil specific functions for epigenetic regulators and bridge the gap between disease pathology and mechanism. As such, we anticipate that the list of genes and disorders given in Table 1 will expand in the coming years. In this regard, some of the BAFs and other histone-modifying enzymes represent good candidates for autosomal MR/ID diseases.

The dynamic nature of chromatin and the ability to modulate the transition between transcriptionally active and inactive chromatin states allow the possibility of pharmacological intervention of disease mechanisms linked to chromatin regulation. The therapeutic potential of DNA and histone chemical modification inhibitors has been described in the treatment of neuropsychiatric disorders (97) and has shown promise in animal models of memory and learning deficits (81, 83). Therefore, a knowledge of how epigenetic events orchestrate hippocampal neuron and circuit formation and activity holds the potential of modulating these processes for therapeutic intervention in cases of neurological disease involving cognitive impairment.

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References


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