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REVIEW ARTICLE
Epigenetic dysregulation in cognitive disorders

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Abstract

Epigenetic mechanisms are not only essential for biological functions requiring stable molecular changes such as the establishment of cell identity and tissue formation, they also constitute dynamic intracellular processes for translating environmental stimuli into modifications in gene expression. Over the past decade it has become increasingly clear that both aspects of epigenetic mechanisms play a pivotal role in complex brain functions. Evidence from patients with neurodegenerative and neurodevelopmental disorders such as Alzheimer's disease and Rett syndrome indicated that epigenetic mechanisms and chromatin remodeling need to be tightly controlled for proper cognitive functions, and their dysregulation can have devastating consequences. However, because they are dynamic, epigenetic mechanisms are also potentially reversible and may provide powerful means for pharmacological intervention. This review outlines major cognitive disorders known to be associated with epigenetic dysregulation, and discusses the potential of 'epigenetic medicine' as a promising cure.

Introduction

Brain functions such as learning and memory are biological processes with extremely complex modes of regulation. Because they recruit multiple molecular mechanisms that are intimately linked, a dysregulation in one or the other of these mechanisms can have devastating consequences and induce neurodevelopmental or neurodegenerative disorders. Accumulating evidence suggests that several epigenetic mechanisms also contribute to these disorders. The term 'epigenetic mechanisms' refers to the processes that modify gene expression without altering the genetic code itself, and include covalent modifications on histone proteins and the DNA, two core components of the chromatin. Depending on their chemical properties, epigenetic modifications such as histone acetylation and phosphorylation can open the chromatin structure and favor gene transcription. Other modifications such as DNA methylation are most often associated with increased condensation of the chromatin and gene silencing. Additional mechanisms such as histone methylation can lead to either the activation or the silencing of gene transcription (for a recent review see Klose & Bird, 2006; Kouzarides, 2007; Li *et al.*, 2007). Epigenetic mechanisms were originally thought to be stable and irreversible; however, several studies have revealed that they are dynamic and can be reversed even in fully differentiated brain cells (Guan *et al.*, 2002; Alarcon *et al.*, 2004; Korzus *et al.*, 2004; Levenson *et al.*, 2004, 2006; Tsankova *et al.*, 2004, 2006; Kumar *et al.*, 2005; Chwang *et al.*, 2006, 2007; Bredy *et al.*, 2007; Fischer *et al.*, 2007; Miller & Sweatt, 2007; Miller *et al.*, 2008; Oliveira *et al.*, 2007; Renthal *et al.*, 2007; Vecsey *et al.*, 2007). This reversibility confers on epigenetic mechanisms the potential of being targeted by pharmacological intervention to alleviate or reverse the symptoms resulting from their dysfunctions. The following sections describe the best-studied neurodevelopmental and neurodegenerative disorders involving epigenetic dysregulation, and summarize the current standing for their potential treatment based on epigenetic drugs.

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Neurodegenerative disorders

Two degenerative disorders of the central nervous system have been convincingly shown to depend on epigenetic mechanisms; Alzheimer's and Huntington's disease (Table 1).

Alzheimer's disease (AD)

AD is a common neurodegenerative disease (~1–2% prevalence in the US) which affects essentially the elderly. This late-onset disorder is characterized by cognitive alterations and dementia, and by the accumulation of neurotoxic amyloid plaques and neurofibrillary tangles in different regions of the brain (for a review see Cummings, 2004). Recent evidence has suggested that histone acetylation and DNA methylation are implicated in the etiology of AD. Amyloid plaques are formed by the deposition of β-amyloid peptides, which are produced by cleavage of the amyloid precursor protein (APP) by β- and γ-secretase. The same cleavage also generates an APP intracellular domain which, *in vitro*, can interact with the histone acetyltransferase (HAT) TIP60 and co-act as a transcriptional activator (Cao & Sudhof, 2001). AD is therefore thought to be associated with an overall increase in histone acetylation. This assumption is supported by findings in neuronal culture showing that AD-related mutations in *presenilin 1 (PS1)*, a gene coding for a member of the γ-secretase complex, inhibit proteasomal degradation of the HAT CREB-binding protein (CBP) and result in increased CREB-mediated gene expression (Marambaud *et al.*, 2003). A recent study *in vivo* further showed that lentivirus-mediated overexpression of the histone

TABLE 1. Epigenetic mechanisms in neurodegenerative disorders and potential epigenetic treatment

Disorder	Epigenetic alteration	Gene involved	Model organism	Epigenetic-related treatment	References
Alzheimer's disease	Histone acetylation ↑	*APP*	Human cell culture	None	Cao & Sudhof, 2001
		PS1	Human cell/murine neuronal culture	Substitution of PS1-mediated enzymatic activity	Marambaud *et al.*, 2003
		None specific	*p25*/Cdk5 mouse model	HDAC SIRT1	Kim *et al.*, 2007
	Histone acetylation ↓	*APP*	Murine neuronal culture	None	Rouaux *et al.*, 2003
		PS1	*PS1* mouse model	None	Saura *et al.*, 2004
		None specific	*p25*/Cdk5 mouse model	HDACi sodium butyrate	Fischer *et al.*, 2007
	DNA methylation ↓	*APP*	Aged monkey	None	Wu *et al.*, 2008
		PS1	Human cell culture	Methyl-donor SAM	Scarpa *et al.*, 2003
			Human *post mortem* tissue	None	Wang *et al.*, 2008
Huntington's disease	Histone acetylation ↓	*Htt*	Human cell culture/ *Drosophila* model	HDACi SAHA and sodium butyrate	Steffan *et al.*, 2001
		Htt	Human cell culture	None	Sugars *et al.*, 2004
		Htt	R6/2 and 82Q mouse models	HDACi sodium butyrate, SAHA, phenylbutyrate, anthracycline	Ferrante *et al.*, 2003; Hockly *et al.*, 2003; Gardian *et al.*, 2005; Stack *et al.*, 2007
	Histone methylation H3K9 ↑	*Htt*	R6/2 and 82Q mouse models	Anthracycline	Stack *et al.*, 2007

APP, amyloid precursor protein; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; Htt, huntingtin; PS1, presenilin 1; SAHA, suberoylanilide hydroxamic acid; SAM, S-adenosylmethionine; SIRT1, silent information regulator homologue 1.

deacetylase silent mating type information regulation 2 homolog (SIRT1) confers substantial protection against neurodegeneration in a mouse model of AD (Kim *et al.*, 2007). However, it remains unknown whether, in this case, SIRT1 acts through the epigenetic machinery and/or through other targets.

Conversely, however, several studies have also reported that a decrease in histone acetylation is causally linked to AD. Thus, APP overexpression in cultured cortical neurons was shown to result in an overall decrease in histone 3 (H3) and H4 acetylation, and was accompanied by decreased CBP levels (Rouaux *et al.*, 2003). Similarly, loss-of-function mutations in *PS1* and *PS2* genes in mice were found to reduce the expression of CBP and CBP/CREB target genes such as *c-fos* and *brain-derived neurotrophic factor (BDNF)*, and were accompanied by impaired synaptic plasticity and impaired spatial and contextual memory (Saura *et al.*, 2004). Moreover, in a mouse model of neurodegeneration and memory loss due to p25 overexpression and cyclin-dependent kinase 5 hyperactivation, intracerebroventricular injection of sodium butyrate, a potent inhibitor of histone deacetylases (HDACs), rescued memory and synaptic connectivity (Fischer *et al.*, 2007). Notably, a comparable cognitive improvement can be obtained in wild-type mice by long-term exposure (4 weeks) to an enriched environment. Such stimulation is accompanied by increased histone acetylation and methylation [on H3 lysine (K) 4] in the hippocampus and cortex, indicating that it engages epigenetic mechanisms. Taken together, these results establish that histone acetylation is involved in AD, but further studies are needed to determine whether decreased or increased acetylation is causally linked to the disease. It is conceivable that both types of change in histone acetylation co-occur and may be different depending on the brain area, cell type and gene.

DNA methylation is another epigenetic mechanism implicated in the etiology of AD, and hypomethylation has been most generally reported. In cell culture, hypomethylation of the promoter region of *PS1* was found to increase presenilin expression, and enhance β-amyloid formation (Scarpa *et al.*, 2003). This effect could be reversed by application of the methyl donor S-adenosylmethionine (SAM) which, by rescuing methylation, increases presenilin expression and reduces β-amyloid formation. These observations have suggested that methyl donors or drugs targeting the methyl metabolism may be potential therapeutic agents for treating AD (Scarpa *et al.*, 2006). The idea that DNA hypomethylation underlies some aspects of AD etiology was further confirmed in a primate model of AD. In this model, the enzymatic activity of DNA methyl transferase 1 is decreased in cortex and is associated with increased APP mRNA expression (Wu *et al.*, 2008). A recent post-mortem study in human further reported hypomethylation of the *PS1* promoter region in late-onset AD patients when compared to age-matched controls (Wang *et al.*, 2008). However, other AD-related susceptibility genes were hypermethylated in their promoter region, suggesting that both hypo- and hypermethylation can occur in AD, most likely in a gene-specific manner. Further investigations are therefore required to identify these genes, and how and to what extent their DNA methylation is altered.

Huntington's disease (HD)

HD is a rare progressive neurodegenerative disorder (prevalence of 3–7 in 100 000 in the US) characterized by cognitive impairment, mood disturbance and uncoordinated body movements. HD results from a mutation in the *huntingtin* gene that causes a high number of CAG repeats at its 5′-end, and produces a polyglutamine extension on the N-terminus of the protein huntingtin (for a review, see Bates, 2005). Several studies have suggested that both acetylation and methylation of histones are altered in HD. One mechanism demonstrated in cell culture involves the binding of polyglutamine extension to the acetyltransferase domain of the HATs, CBP and p300/CBP-associated factor, which reduces HAT activity and the level of acetylated H3 and H4 (Steffan *et al.*, 2001). This also impairs the transcription of CRE-containing genes, a defect that can be reversed by CREB overexpression (Sugars *et al.*, 2004). Interestingly, in a *Drosophila* model of polyglutamine disease, reduced HDAC activity by partial loss-of-function mutation or pharmacological inhibition by sodium butyrate or suberoylanilide hydroxamic acid (SAHA) alleviated pathological symptoms induced by polyglutamine (Steffan *et al.*, 2001). Further, broad HDAC inhibitors such as sodium butyrate, SAHA, phenylbutyrate and the HDAC inhibitor 4b could also improve motor deficits and neuronal atrophy in several mouse

models of HD (Ferrante *et al.*, 2003; Hockly *et al.*, 2003; Gardian *et al.*, 2005; Sadri-Vakili *et al.*, 2007; Thomas *et al.*, 2008). In most cases, the improvement was accompanied by increased histone acetylation, suggesting that HD is indeed associated with an overall decrease in histone acetylation (Ferrante *et al.*, 2003; Hockly *et al.*, 2003; Gardian *et al.*, 2005; Sadri-Vakili *et al.*, 2007).

Remarkably, one study reported that the beneficial effect of HDAC inhibitors might result from a reversion of the hypoacetylation of the cytoplasmic protein α-tubulin (Dompierre *et al.*, 2007). When mouse striatal cells with or without HD pathology were treated with the HDAC6-specific inhibitor tubacin, α-tubulin acetylation was increased and some signs of HD pathology were reversed. These findings suggest that acetylation of cytoplasmic proteins is affected in HD pathology and that broad HDAC inhibitors might be beneficial because they act through cytoplasmic HDACs such as HDAC6 and cytoplasmic substrates. Further studies are, however, needed to determine the precise contribution of histone and α-tubulin hypoacetylation in HD pathology (for a review see Butler & Bates, 2006), and to evaluate the specificity of HDAC inhibitors (Haggarty *et al.*, 2004).

Further to acetylation, histone methylation is also altered in mouse models of HD and is increased on dimethyl H3K9 (Ferrante *et al.*, 2004), a mark for transcriptional repression (Kouzarides, 2007). Thus, a combined effect of altered histone acetylation and methylation is thought to underlie reduced gene transcription in HD. This possibility was recently confirmed in another mouse model of the disease in which H3 and H4 acetylation was found to be downregulated, and methylation was upregulated (Stack *et al.*, 2007). Interestingly, a normal pattern of histone acetylation and methylation and an attenuation of locomotor deficits could be obtained by intraperitoneal injection of DNA/RNA-binding anthracyclines, potent anticancer drugs. This supports the hypothesis that histone acetylation and methylation interact in HD although this interaction remains poorly understood, despite preliminary findings showing that phenylbutyrate can reduce histone methylation on H3K9 (Gardian *et al.*, 2005). Taken together, these results indicate that drugs targeting histone-modifying enzymes directly or indirectly might constitute potent means of HD treatment. However, their precise mechanisms of action will need to be better understood to alleviate their undesired side effects and lack of specificity.

Neurodevelopmental disorders

A substantial body of evidence suggests that epigenetic dysregulation of gene expression is involved in several neurodevelopmental disorders. Four prevalent disorders, Rett syndrome, Rubinstein–Taybi syndrome, Fragile X syndrome and schizophrenia, are well-documented examples for potential pharmacological interventions targeting the epigenetic machinery (Table 2).

Rett Syndrome (RS)

RS is a relatively common neurodevelopmental disorder (1 : 10 000 to 1 : 15 000 prevalence in the US) manifested in early to mid-childhood by an arrest of neurological development resulting in microcephaly and mental retardation. RS involves a dysregulation of gene silencing by DNA methylation due to mutations in the X-linked *methyl-CpG-Binding Protein 2* (*MeCP2*) gene (Amir *et al.*, 1999). MeCP2 is a member of the transcriptional repressors methyl-binding proteins (MBP) (for a review see Bird, 2002) and has a dual role in transcriptional silencing and activation (Chahrour *et al.*, 2008). In mice, brain-specific deletions of *MeCP2* recapitulate some of the phenotypes of RS patients. *MeCP2*-deficient mice have reduced brain weight and smaller neurons, and have an overall decrease in exploratory activity (Chen *et al.*, 2001; Guy *et al.*, 2001), cognitive deficits and reduced synaptic plasticity (Collins *et al.*, 2004). Consistent with an effect linked to MeCP2 deficiency, these cognitive impairments can be reversed by MeCP2 overexpression in MeCP2-deficient animals (Collins *et al.*, 2004), suggesting that MeCP2 regulates genes which are important for cognitive processes and synaptic plasticity. *Bdnf* was shown to be one of these genes. Its expression is increased by a mechanism involving calcium-dependent phosphorylation of MeCP2 induced by synaptic activity, followed by release of MeCP2 from the BDNF promoter and decreased promoter methylation (Chen *et al.*, 2003; Martinowich *et al.*, 2003). However, MeCP2 phosphorylation also leads to dendritic growth and spine maturation (Zhou *et al.*, 2006), presumably through alteration of the expression of genes involved in development processes (Smrt *et al.*, 2007; Chahrour *et al.*, 2008), which highlights the dual role of MeCP2.

Interestingly, dysregulation in DNA methylation induced by MeCP2 deficiency also influences histone acetylation and methylation. Upon binding to methylated DNA, MeCP2 forms a complex with HDAC1 (Martinowich *et al.*, 2003) which triggers histone hyperacetylation on both H3 and H4. This is paralleled by decreased H3K9 and increased H3K4 methylation, two post-translational histone modifications that inhibit and promote gene transcription respectively (Kouzarides, 2007). These results suggest a cooperation of epigenetic modifications that increase gene expression and are consistent with the observation that mice with truncated MeCP2 have hyperacetylated H3 (Shahbazian *et al.*, 2002). Together, these results strongly argue for an overall increase in gene transcription in RS. Such increase may be pharmacologically attenuated by drugs targeting either one of the three epigenetic mechanisms involved or by directly reversing the enhanced rate of transcription. So far, however, such potential treatment has not been investigated.

Rubinstein–Taybi syndrome (RTS)

RTS is a rare developmental disorder (1 : 100 000 to 1 : 125 000 prevalence in the US) characterized by a short stature, abnormalities in skeletal extremities, and varying degree of mental retardation. RTS is caused by mutations in the *CBP* gene (Petrij *et al.*, 1995) which result in a deficiency in CBP and altered HAT activity (Murata *et al.*, 2001; Kalkhoven *et al.*, 2003; Roelfsema *et al.*, 2005). Recent evidence also suggests the implication of another HAT, p300, because mutations in the gene *E1A binding protein p300* (*EP300*), which codes for p300, causes RTS symptoms (Roelfsema *et al.*, 2005; Bartholdi *et al.*, 2007). The disease has been modeled in mice, and several knock-out lines partially lacking *CBP* have been generated. These models have memory impairments reminiscent of human RTS cognitive deficits, which confirms the critical importance of CBP in the etiology of the disease (Oike *et al.*, 1999; Bourtchouladze *et al.*, 2003; Alarcon *et al.*, 2004; Korzus *et al.*, 2004). At the molecular level, these mice have reduced HAT activity, decreased acetylation of several histone proteins and impaired CBP-dependent gene expression, which can be reversed by the HDAC inhibitors trichostatin A (TSA) and SAHA (Alarcon *et al.*, 2004; Korzus *et al.*, 2004). It was further suggested that these inhibitors act specifically on CBP-dependent genes (Vecsey *et al.*, 2007), suggesting a targeted mode of action for some HDAC inhibitors. As HDAC inhibitors can also restore the cognitive deficits and plasticity impairments in these mice (Alarcon *et al.*, 2004; Korzus *et al.*, 2004), they might constitute a promising treatment for RTS.

TABLE 2. Epigenetic mechanisms in neurodevelopmental disorders and potential epigenetic treatment

Disorder, epigenetic alteration and gene involved	Model organism	Epigenetic-related treatment	References
Rett syndrome			
DNA methylation ↓			
MeCP2	Human patients	None	Amir *et al.*, 1999; Chen *et al.*, 2001; Guy *et al.*, 2001
MeCP2	*MeCP2* mouse models	None	Chen *et al.*, 2001; Guy *et al.*, 2001; Shahbazian *et al.*, 2002
DNA methylation ↓/Histone acetylation ↑			
MeCP2	*MeCP2* mouse models	None	Shahbazian *et al.*, 2002
DNA methylation ↓/Histone acetylation ↑/Histone methylation H3K9 ↓/H3K4 ↑			
MeCP2	Murine cell culture	None	Martinowich *et al.*, 2003
Rubinstein–Taybi syndrome			
Histone acetylation ↓			
CBP	*CBP* mouse models	HDACi SAHA and TSA	Alarcon *et al.*, 2004; Korzus *et al.*, 2004; Roelfsema *et al.*, 2005
EP300	Human patients	None	Roelfsema *et al.*, 2005; Bartholdi *et al.*, 2007
Fragile X syndrome			
DNA methylation ↑/Histone acetylation ↓			
FMR1	Human patient-derived cell lines	5-aza, HDACi sodium butyrate, SAHA and TSA	Chiurazzi *et al.*, 1998, 1999
DNA methylation ↑/Histone acetylation ↓/Histone methylation H3K9 ↑/H3K4 ↓			
FMR1	Human patient-derived cell lines	None	Tabolacci *et al.*, 2005, 2008
Schizophrenia			
DNA methylation ↑			
RELN	Human patients; reeler mouse model; cell culture	5-aza, HDACi sodium butyrate, and valproic acid	Chen *et al.*, 2002; Costa *et al.*, 2002
Histone methylation H3K27 ↑/H3K4 ↓			
GAD1	Human patients; neural stem cells	Antipsychotic clozapine	Huang & Akbarian, 2007; Huang *et al.*, 2007

CBP, Creb-binding protein; EP300, E1A binding protein p300; FMR, fragile X mental retardation; H, histone; HAT, histone acetyltransferase; HDACi, histone deacetylase inhibitor; K, lysine; MeCP2, methyl-CpG binding protein 2; SAHA, suberoylanilide hydroxamic acid; TSA, trichostatin A; 5-aza, 5-aza-2-deoxycytidine.

Fragile X syndrome (FXS)

FXS is a common form of inherited mental impairment (1 : 4000 to 1 : 8000 prevalence in the US), characterized by learning disabilities and autistic-like behaviors. FXS is caused by CGG and CCG trinucleotide expansions at the 5′-end of the *fragile X mental retardation* genes *FMR1* and *FMR2*, respectively (Ashley *et al.*, 1993; Gecz *et al.*, 1996; Gu *et al.*, 1996). DNA methylation and both acetylation and methylation of histone have been implicated in the molecular mechanisms of the disease. The trinucleotide expansions of *FMR* genes result in increased DNA methylation of the gene promoter, which silences gene transcription and decreases mRNA and protein level (Ashley *et al.*, 1993; Gecz *et al.*, 1996; Gu *et al.*, 1996). Treatment of lymphoblastoid cells from FXS-patients with the demethylating drug 5-aza-2-deoxycytidine (5-aza) efficiently reverses *FMR1* promoter hypermethylation and restores mRNA and protein levels to baseline (Chiurazzi *et al.*, 1998). Interestingly, mRNA expression is restored to even above baseline level when 5-aza is combined with the HDAC inhibitors 4-phenylbutyrate, sodium butyrate and TSA (Chiurazzi *et al.*, 1999). This suggests a combined effect of histone deacetylation and DNA hypermethylation as causative mechanisms of FXS and, oppositely, a potential synergistic effect of histone hyperacetylation and DNA demethylation as a possible treatment for FXS. Two recent studies further reported that 5-aza treatment of fragile X cell lines shifts the epigenetic pattern of histone methylation (Tabolacci *et al.*, 2005, 2008). Chromatin immunoprecipitation assays at the *FMR1* promoter showed that 5-aza treatment decreases H3K9 methylation, a mark for transcriptional silencing (Kouzarides, 2007), and simultaneously increases H3K4 methylation, a mark for transcriptional activation (Kouzarides, 2007), consistent with the increase in *FMR1* gene expression (Tabolacci *et al.*, 2005). Intriguingly, histone methylation seems to outcompete histone acetylation with respect to its influence on *FMR1* expression. In lymphoblastoid and fibroblast cell lines derived from FXS patients carrying a full CGG extension of the *FMR1* gene (> 200 triplets) but lacking the typical DNA methylation pattern associated with normal gene expression, only histone methylation but not acetylation was similar to healthy control samples (Tabolacci *et al.*, 2008). Histone acetylation was reduced similarly to that in fragile X cell lines, suggesting that this epigenetic mark alone is not sufficient to regulate *FMR1* expression. However, it should be noted that these findings are based on only a few case studies, and therefore require further confirmation. Taken together, these studies demonstrate that FXS is characterized by alterations in three prominent epigenetic marks, DNA methylation, histone acetylation and histone methylation, and that this diversity might allow for synergistic and efficient epigenetic treatment of this disease in the future.

Schizophrenia (SZ)

SZ is a common mental illness (1 : 100 prevalence in the US in people ≥ 18 years old) characterized by two main types of psychotic symptoms. Positive symptoms include delusions, hallucinations and disordered thoughts, and occur in schizophrenic patients but not in nonschizophrenic controls. Negative symptoms include social withdrawal, lack of motivation and general apathy, and reflect a loss of these behavioral abilities that are normally present in nonschizophrenic controls. The causes of SZ are not well understood, but are likely to result from a complex interplay between a genetic predisposition and environmental conditions during pre- and postnatal development. At least two lines of evidence suggest the involvement of epigenetic mechanisms, in particular DNA and histone methylation. In brain tissue from patients diagnosed with SZ, the mRNA level of reelin, an extracellular matrix protein implicated in neuronal migration and in SZ pathology, was found to be significantly decreased (Chen *et al.*, 2002; Costa *et al.*, 2002) and this correlated with an increased level of DNA methyl transferase 1. This suggested that DNA hypermethylation in the promoter region of *RELN*, the gene coding for reelin, may be responsible for lower reelin expression in SZ patients. Consistently in cell and neuronal culture, both *in vitro* and *in vivo* methylation of *RELN* suppressed its expression (Chen *et al.*, 2002; Costa *et al.*, 2002; Tremolizzo *et al.*, 2002), an effect that *in vitro* could be reversed by 5-aza treatment (Chen *et al.*, 2002; Costa *et al.*, 2002). Strikingly, treatment of cell cultures with TSA and valproic acid also increase DNA methylation at the *RELN* promoter (Chen *et al.*, 2002; Costa *et al.*, 2002), an effect also observed *in vivo* (Tremolizzo *et al.*, 2002). Likewise, in mice heterozygous for *RELN*, valproic acid injection enhances *RELN* expression (Costa *et al.*, 2002). These findings thus suggest an interplay between DNA demethylation and histone acetylation for reinstatement of reelin expression (Chen *et al.*, 2002) which may also contribute to the regulation of other genes involved in SZ. Notably, it has been suggested that DNA methyl transferase inhibitors are potential therapeutic agents in SZ (Chen *et al.*, 2002; Costa *et al.*, 2002; Levenson & Sweatt, 2005); in combination with HDAC inhibitors they may look even more promising.

Further to reelin, components of glutamatergic signaling pathways have been implicated in the etiology of SZ. Post-mortem brain samples from SZ patients show reduced glutamate decarboxylase 67 (GAD_{67}) mRNA and protein (Chen *et al.*, 2002). This correlates with hypermethylation of H3K27, a mark for transcriptional repression, and hypomethylation of H3K4, a mark for transcriptional activation (Kouzarides, 2007) in the promoter region of *GAD1*, which codes for GAD_{67}. This suggests a dual mechanism of transcriptional downregulation (Huang & Akbarian, 2007; Huang *et al.*, 2007). Of note, DNA methylation did not seem to play a role in *GAD1* transcriptional regulation as methylation of its promoter was not changed in SZ patients (Siegmund *et al.*, 2007). Finally, several other genes such as genes coding for ionotropic glutamate receptors may also be epigenetically dysregulated in SZ, as they were shown to have altered histone methylation with age (Stadler *et al.*, 2005). A complete analysis of DNA and histone methylation, and of other epigenetic changes such as histone acetylation and phosphorylation, will be required to better understand the full contribution of epigenetic mechanisms to the etiology of SZ.

Conclusions and outlook

It has become increasingly clear that epigenetic mechanisms play a central role in higher-order brain functions. Their dysregulation can lead to several neurodevelopmental and neurodegenerative cognitive diseases as discussed here but also to emotional disorders in psychiatric diseases (Tsankova *et al.*, 2007), disturbed stress resistance (Seckl & Meaney, 2006) and addictive behaviors (Renthal & Nestler, 2008). Epigenetic mechanisms were further shown to be dynamically regulated and can be modulated by learning and memory (for recent reviews see Levenson & Sweatt, 2005, 2006; Gräff & Mansuy, 2008). They might therefore also constitute potential strategies for treating cognitive disorders. In this respect, HDAC inhibitors have received particular attention over the past years (Abel & Zukin, 2008) because histone acetylation is not only upregulated during memory formation (Levenson *et al.*, 2004; Chwang *et al.*, 2007; Fischer *et al.*, 2007; Miller *et al.*, 2008) but is also downregulated in several examples of cognitive decline such as in AD, HD and RTS (Ferrante *et al.*, 2003, 2004; Hockly *et al.*, 2003; Rouaux *et al.*, 2003; Alarcon *et al.*, 2004; Korzus *et al.*, 2004; Gardian *et al.*, 2005; Sadri-Vakili *et al.*, 2007; Thomas *et al.*, 2008). Several HDAC inhibitors are currently in preclinical phase I/II trials for the treatment of HD and AD. Although most HDAC inhibitors still act nonspecifically and target not only histone proteins but also cytoplasmic proteins, recent effort was gladly made to identify structural features that confer both potency and specificity (Haggarty *et al.*, 2004). This is expected to allow the development of HDAC-type or subclass-specific HDAC inhibitors with a more specific range of action (for a review see Kazantsev & Thompson, 2008). In combination with methods for cell type-specific delivery, this constitutes a promising avenue for the development of epigenetic drugs to treat cognitive diseases. As HDAC inhibitors are also widely used in cancer therapy (Carew *et al.*, 2008), it is tempting to speculate that diseases caused by transcriptional alterations due to aberrant histone acetylation share common molecular pathways and might therefore be targeted by similar pharmacological intervention.

An alternative to generic epigenetic inhibitors would be the development of drugs that target the epigenetic machinery in a gene-specific manner. For DNA methylation, this has recently been achieved in two groundbreaking studies using specific zinc finger peptides that confer *de novo* methylation to targeted loci both *in vitro* and *in vivo* (Smith & Ford, 2007; Smith *et al.*, 2008). However, such targeted approach requires that the genes and the epigenetic events engaged in the disease under study are known and understood. High-throughput genetic and biochemical analyses are therefore needed to identify these mechanisms and understand the enzymatic pathways engaged in the epigenetic machinery. Importantly, although this review has focused on DNA methylation and histone acetylation and methylation, many other epigenetic mechanisms exist and may also be involved in brain diseases. Thus histone phosphorylation, ubiquitination and sumoylation play important regulatory roles in the epigenetic machinery which have not been thoroughly investigated, except for phosphorylation (Chwang *et al.*, 2006, 2007; Stipanovich *et al.*, 2008). Similarly, RNA interference or prion proteins might also be involved in the epigenetic regulation of cognitive functions (Levenson & Sweatt, 2005) and merit further attention. Finally, as epigenetic modifications on histones show a high degree of *cis* and *trans* crosstalk (Latham & Dent, 2007), manipulating one epigenetic mark is likely to influence other marks as well as multiple genes and pathways. A better understanding of such histone crosstalk is therefore another prerequisite to the refinement of 'epigenetic medicine' against cognitive diseases and other brain disorders.

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Abbreviations

5-aza, 5-aza-2-deoxycytidine; AD, Alzheimer's disease; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; CBP, CREB-binding protein; EP300, E1A binding protein p300; FMR, Fragile X mental retardation; FXS, Fragile X syndrome; H3, histone 3; HAT, histone acetyl transferase; HD, Huntington's disease; HDAC, histone deacetylase; K, lysine; MBP, methyl-binding protein; MeCP2, methyl-CpG-binding protein 2; PS1, presenilin 1; RELN, reelin; RS, Rett syndrome; RTS, Rubinstein–Taybi syndrome; SAHA, suberoylanilide hydroxamic acid; SAM, S-adenosylmethionine; SIRT1, silent mating type information regulation 2 homolog; SZ, schizophrenia; TSA, trichostatin A.

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