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Epigenetic Treatments for Cognitive Impairments

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Epigenetic mechanisms integrate signals from diverse intracellular transduction cascades and in turn regulate genetic readout. Accumulating evidence has revealed that these mechanisms are critical components of ongoing physiology and function in the adult nervous system, and are essential for many cognitive processes, including learning and memory. Moreover, a number of psychiatric disorders and syndromes that involve cognitive impairments are associated with altered epigenetic function. In this review, we will examine how epigenetic mechanisms contribute to cognition, consider how changes in these mechanisms may lead to cognitive impairments in a range of disorders and discuss the potential utility of therapeutic treatments that target epigenetic machinery. Finally, we will comment on a number of caveats associated with interpreting epigenetic changes and using epigenetic treatments, and suggest future directions for research in this area that will expand our understanding of the epigenetic changes underlying cognitive disorders.

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INTRODUCTION

Changes to the epigenome are a key mechanism by which cells initiate, maintain, and terminate gene expression programs, making them potent modulators of cell function and activity. Recent evidence suggests that epigenetic modifications within the CNS are critical for short and long-term behavioral adaptation to a wide range of environmental stimuli. As such, epigenetic modifications represent candidate mechanisms for the creation and maintenance of behavioral memories at multiple levels. These and other studies have generated interest in the therapeutic potential of drugs capable of enhancing or impairing these reactions in cognitive disorders. Recent advances in our understanding of the role of epigenetic molecular mechanisms in CNS development and function have allowed the conceptualization of epigenetically based CNS disorders. It is now clear that mutations to epigenetic machinery are the root cause of a number of clinical syndromes, including Rett syndrome, Rubenstein–Taybi syndrome, Fragile X mental retardation, and Angelman syndrome (Driscoll *et al*, 1992; Petrij *et al*, 1995; Amir *et al*, 1999; Alarcon *et al*, 2004; Penagarikano *et al*, 2007; Urdinguio *et al*, 2009). Moreover, a number of psychiatric disorders, such as drug addiction, schizophrenia, and Alzheimer's disease, are associated with aberrant epigenetic changes, suggesting that epigenetic modifications may hold promise as potential therapeutic targets in these disorders (Tsankova *et al*, 2007; Renthal and Nestler, 2008; Graff and Mansuy, 2009; Bredy *et al*, 2010; Penner *et al*, 2010a, b).

Epigenetic mechanisms are broadly defined as a set of regulatory modifications that influence gene expression above the level of the genome itself, that is, without changes in gene sequence. Within a cell nucleus, DNA is condensed within a three-dimensional structure called chromatin that regulates the ability of transcriptional machinery to access a specific gene site and initiate transcription (Russo *et al*, 1996). Thus, this complex forms a general template for the activation and repression of genetic material. The basic structural unit of chromatin is the nucleosome, which is made up ~147 bp of DNA wrapped around four pairs of basic histone proteins (H2A, H2B, H3, and H4). These histone proteins contain amino terminal 'tails' that protrude from the nucleosomal complex and contain multiple sites for potential modification (Kouzarides, 2007). Canonically, epigenetic mechanisms would include post-translational modification at the tails of these histone proteins, as well as direct chemical modification of DNA itself in which a methyl group is added to cytosine nucleotides (Russo *et al*, 1996). In mammals, DNA methylation can occur at CpG

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sites in the genome, which are vastly underrepresented in general but which are found in clusters (termed CpG islands) near ~60% of gene promoters (Weber *et al*, 2005, 2007).

Although both histone modifications and DNA methylation were once viewed as inherently stable mechanisms incapable of rapid change, a wealth of recent data suggests that this is not the case, even for putatively irreversible modifications such as DNA methylation (Swank and Sweatt, 2001; Weaver *et al*, 2004; Miller and Sweatt, 2007; Kangaspeska *et al*, 2008; Lubin *et al*, 2008; Metivier *et al*, 2008; Koshibu *et al*, 2009; Gupta *et al*, 2010; Miller *et al*, 2010). These findings build upon the long appreciated role for these mechanisms and their upstream regulators in transcriptional output and suggest that epigenetic mechanisms in non-mitotic and terminally differentiated neurons may represent a final common pathway for the alterations in neuronal function that produce long-term behavioral change.

This manuscript will review how epigenetic modifications occur and how drugs that target these modifications may be useful in the treatment of cognitive disorders. We will start by examining histone modifications, then turn to DNA methylation, and finally mention non-canonical mechanisms like proteins with prion-like activity and microRNAs. Finally, we will suggest some future directions and potential challenges for the study of epigenetics in cognitive disorders.

HISTONE MODIFICATIONS

Histone Acetylation

Perhaps the most well-understood epigenetic modification is the acetylation of lysine residues on histone *N*-terminal tails. This modification is typically associated with transcriptional activation, as it can physically relax the positive charge between the histone tail and the DNA backbone, enabling chromatin to unravel and transcriptional machinery to gain access to DNA (Russo *et al*, 1996; Clayton *et al*, 2006; Kouzarides, 2007). Additionally, the acetylation of lysine residues can lead to binding of bromodomain-containing proteins, which can recruit transcriptional activators (Dyson *et al*, 2001). Histone acetylation occurs via the activity of histone acetyltransferases (HATs), which include CREB-binding protein (CBP) and p300 (see Figure 1) (Ogryzko *et al*, 1996; McManus and Hendzel, 2003). Acetyl groups are removed from lysine residues by histone deacetylases (HDACs), a large family of proteins, which are organized into four different classes that differ in expression profiles across brain regions (Kouzarides, 2007; Renthal *et al*, 2007).

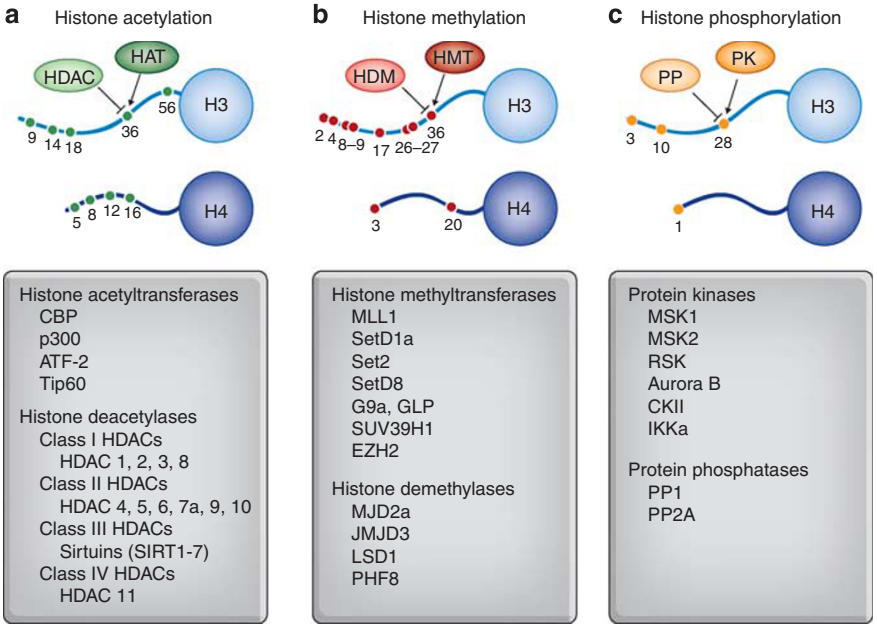

Figure 1. Summary of well-understood histone modifications and histone-modifying enzymes. (a) Histone acetylation at numerous lysine residues on histone tails is catalyzed by histone acetyltransferases (HATs) and removed by histone deacetlyases (HDACs). Histone acetylation is generally a transcriptionally permissive mark. Different HAT and HDAC enzymes are listed below. Importantly, specific HDACs isoforms are differentially expressed across brain structures and appear to uniquely regulate different aspects of cognition. (b) Histone methylation at lysine and arginine residues on histone tails is catalyzed by histone methyltransferases (HMTs) and removed by histone demethylases (HDMs). Histone methylation at different amino acid residues has been linked to both transcriptional activation and transcriptional repression. Methylation can occur in mono-, di-, or even tri-methylated states. Many HDMs and HMTs are specific for modifications at individual amino acids on histone tails or even a specific number of methyl groups. (c) Histone phosphorylation at serine residues is catalyzed by protein kinases (PKs) such as mitogen- and stress-activated protein kinase 1 (MSK1), whereas phosphorylation marks are removed by protein phosphatases such as protein phosphatase 1 (PP1). Histone phosphorylation is generally linked to transcriptional activation.

A wealth of research suggests that histone acetylation has a critical role in cognitive abilities such as learning and memory. Thus, behavioral paradigms that induce learning increase histone acetylation in the brain areas that regulate those specific types of learning. For example, exposing rodents to a contextual fear conditioning paradigm induces a significant increase in histone acetylation of multiple lysine residues on H3 and H4 within the hippocampus (Levenson *et al*, 2004; Chwang *et al*, 2006; Peleg *et al*, 2010). Impairing histone acetylation by knocking out the HAT CBP produces an impairment in memory formation as well as its cellular correlate, long-term potentiation (LTP) (Alarcon *et al*, 2004). Likewise, increasing histone acetylation by blocking the activity of HDACs improves memory formation and enhances the development of LTP in hippocampal slices (Levenson *et al*, 2004; Vecsey *et al*, 2007; Stefanko *et al*, 2009; McQuown *et al*, 2011). Importantly, these changes occur in concert with signal transduction mechanisms and transcription factors that are known to regulate learning and memory. Thus, blocking extracellular signal-regulated kinase (ERK) prevents increases in histone acetylation following contextual fear learning, whereas activation of NMDA receptors increases histone acetylation in an ERK-dependent manner (Levenson *et al*, 2004). Likewise, the CREB-binding protein CBP possesses HAT activity, and proper CREB function is required for the HDAC inhibitor trichostatin-A (TSA) to enhance fear memory and hippocampal LTP (Vecsey *et al*, 2007).

Since these discoveries, a key challenge has been to understand how HDAC inhibitors like trichostatin-A, sodium butyrate, and suberoylanilide hydroxamic acid (SAHA) enhance memory and whether they globally increase expression of all genes or are limited in action to specific genes. Given that both long-lasting hippocampal LTP and long-term memory require gene transcription and new protein synthesis (Frey *et al*, 1988, 1996; Alberini, 2008), it is not surprising that HDAC inhibitors require gene transcription to be an effective enhancer of LTP in the hippocampus (Levenson *et al*, 2004; Vecsey *et al*, 2007). Although it may be expected that treatment with HDAC inhibitors before behavioral conditioning would indiscriminately enhance all gene products (or at least boost a number of memory-associated genes), this does not appear to occur *in vivo*. Rather, treatment with TSA increases expression of a limited set of memory-induced genes, including the inducible nerve growth factor-B (Vecsey *et al*, 2007).

Importantly, the efficacy of HDAC inhibitors may also be caused by action at specific HDAC isoforms. Thus, compared with HDAC1, HDAC2 binding is enhanced at multiple memory and plasticity-associated genes such as *BDNF*, *Egr1*, and *CREB*, and *CaMKII*. Accordingly, overexpression of HDAC2 (but not HDAC1) in mice impairs hippocampal LTP and memory formation (Guan *et al*, 2009). Likewise, genetic deletion of *Hdac2* increases dendritic spine density, enhances hippocampal LTP, and improves fear memory formation (Guan *et al*, 2009). Nevertheless, additional studies have shown that focal deletion or pharmacological inhibition of HDAC3 (a class 1 HDAC) in the dorsal hippocampus results in increased expression of *Nr4a2* and *c-Fos* genes, and improves long-term memory retention on an objection location memory task (McQuown *et al*, 2011). In contrast, other reports have indicated that the sirtuins, a separate family of NAD^+-dependent HDACs, may positively regulate learning and memory. Thus, mice lacking SIRT1 activity in the brain exhibit impaired performance on a number of learning and memory tasks, as well as impaired hippocampal LTP (Gao *et al*, 2010). This deficit occurs because SIRT1 normally represses expression of a microRNA, miR-134, that when expressed leads to downregulation of the memory-related genes *CREB* and *BDNF* (Gao *et al*, 2010). Together, these data reveal that multiple HDAC isoforms contribute to memory formation and do so in unique ways.

A number of learning and memory disorders and syndromes are associated with impaired histone acetylation. For example, Rubenstein–Taybi syndrome, a disorder characterized by numerous physical defects and behavioral deficits, is caused by mutations in the gene for CBP (Petrij *et al*, 1995). Moreover, the results discussed above indicate that HDAC inhibitors enhance memory formation and could therefore potentially form the basis of pharmacotherapies for disorders of learning and memory, including age-associated cognitive decline and Alzheimer's disease (Abel and Zukin, 2008; Chuang *et al*, 2009; Penner *et al*, 2010a). Although this latter possibility is only beginning to be explored in human patients, the validity of this idea has already been confirmed in animal models. Thus, in a rodent model of spatially restricted neurodegeneration, the HDAC inhibitor sodium butyrate (as well as an enriched environment) boosted associative and spatial learning and memory, and even improves access to memories formed before neurodegeneration (Fischer *et al*, 2007). Similarly, the aging process induces a significant learning impairment in mice, which is associated with a decrease in acetylation at lysine 12 on H4 in the hippocampus and an inability to generate learning-related increases in expression of memory-related genes. However, intrahippocampal infusions of the HDAC inhibitor SAHA restored H4K12 acetylation and significantly improved memory function (Peleg *et al*, 2010). Moreover, a variety of HDAC inhibitors have also been shown to reverse learning deficits in a mouse model of Alzheimer's disease (Kilgore *et al*, 2010). In contrast, activation of the HDAC SIRT1 by resveratrol prevents learning deficits and signs of neurodegeneration and tauopathy in a separate Alzheimer's mouse model (Kim *et al*, 2007). This result is consistent with findings that SIRT1 boosts (rather than impairs) memory formation (Gao *et al*, 2010), and reveals a distinct pathway for therapeutic manipulation in the context of learning and memory disorders (Bonda *et al*, 2011).

Histone acetylation has also been implicated in drug addiction, a disorder characterized by chronic and persistent relapse in drug taking despite adverse consequences.

Repeated exposure to addictive drugs like cocaine is associated with long-term changes in brain reward circuits, specifically the nucleus accumbens (NAc). Specifically, cocaine produces an increase in histone acetylation at the promoter regions of plasticity genes within the NAc (Kumar *et al*, 2005), and treatment with HDAC inhibitors concurrent with drug experience enhances the development of conditioned place preferences for cocaine and morphine (Kumar *et al*, 2005; Sanchis-Segura *et al*, 2009). Likewise, overexpression of HDAC isoforms (specifically the striatally enriched isoforms HDAC5) impairs the development of drug place preference (Renthal *et al*, 2007). In contrast, cocaine place preference learning and cocaine self-administration are reduced by intra-NAc infusions of a sirtuin antagonist, indicating that this distinct class of HDACs regulates cocaine reward in a manner distinct from other HDAC classes (Renthal *et al*, 2009). Although these studies reveal that histone acetylation is potentially important for the development of drug addictions, the goal of treatment would be to reverse drug-related behavioral preferences. Consistent with this idea, a recent study found that HDAC inhibition during extinction of cocaine place preference significantly facilitated behavioral extinction and reduced subsequent cocaine reinstatement of a place preference (Malvaez *et al*, 2010). Therefore, this result indicates that treatment with HDAC inhibitors, in combination with behavioral therapy, may be useful in preventing drug relapse.

Beyond learning and memory, HDAC inhibitors have also been investigated for a number of other disorders that include cognitive components of psychiatric disorders, including depression, schizophrenia, Parkinson's disease, and anxiety disorders (Tsankova *et al*, 2007; Chuang *et al*, 2009; Bredy *et al*, 2010). However, there are also several potential issues concerning the use of HDAC inhibitors for cognitive disorders. First and foremost, the systemic use of these drugs can produce considerable side effects (Bruserud *et al*, 2007). This may be due to the fact that most available HDAC inhibitors are not isoform-selective, but bind with roughly equal affinity to distinct HDAC proteins in the same family (Kilgore *et al*, 2010). As discussed above, the memory-enhancing effects of HDAC inhibition is likely isoform-specific, as HDAC2 and HDAC3 have larger roles in the regulating memory formation than HDAC1 (Guan *et al*, 2009; McQuown *et al*, 2011). Additionally, side effects may occur as a result of off-target effects, as HDAC inhibitors (in addition to inhibiting acetylation of histones) also act to reduce acetylation at a host of other non-histone proteins (Drummond *et al*, 2005). Going forward, it will be important to develop new isoform-specific HDAC inhibitors, which will allow for specific functions to be targeted while others remain unperturbed. This is presently an area of intense focus in pharmaceutical drug discovery.

Histone Methylation

Unlike histone acetylation, lysine, and arginine methylation on histone tails has been associated with both transcriptional activation and transcriptional repression, depending largely on the specific lysine residue and the histone protein (ie, H3 or H4). Histone methyltransferases (HMTs), such as G9a and SUV39H1, catalyze histone methylation, but not in a global manner as appears to be the case for HATs (Greiner *et al*, 2005). Thus, G9a methylates lysine 9 on H3 (H3K9), which is generally a mark of repressed transcription (Tachibana *et al*, 2001, 2008). Likewise, MLL1 methylates H3K4, which is associated with transcriptional activation (Akbarian and Huang, 2009). Similarly, enzymes that remove methyl groups from lysine residues, called histone demethylases (HDMs) also exhibit substrate specificity, with JHDM1 removing methyl groups from H3K36 and LSD1 demethylating H3K9 (Shi *et al*, 2004; Tsukada *et al*, 2006; Shi and Whetstine, 2007). Indeed, part of the promise for using HMTs and HDMs as a therapeutic treatment is that the writers and erasers of this mark are exceptionally specific.

Unlike other histone modifications, histone methylation is not distinctly an either/or modification. In fact, lysine residues can be mono-, di-, or even tri-methylated, with each distinct methyl group addition producing unique results (Scharf and Imhof, 2010). These differential states are produced by tight regulation of histone methylation machinery, as HMTs and HDMs are known to catalyze the addition or removal of different numbers of methyl groups. For example, the HDM LSD1 (also known as KDM1) requires a protonated lysine to function, and therefore cannot remove methyl groups from a trimethylated lysine (Stavropoulos *et al*, 2006). In addition, it is clear that proteins which contain chromodomains (and therefore bind to methylated lysine) can possess different affinities for methylation levels at a specific histone target, thereby conferring unique methylation states with unique functional consequences (Shi and Whetstine, 2007; Scharf and Imhof, 2010).

A role for histone methylation in cognition is increasingly being appreciated. Within the hippocampus, trimethylation of H3K4 and dimethylation of H3K9 are both increased immediately after contextual fear conditioning (Gupta *et al*, 2010). This is interesting given that, as stated above, these marks are associated with opposite transcriptional regulation. Thus, this finding likely indicates that these modifications occur at gene-specific targets, whereby they can differentially control expression of memory associated genes. Importantly, histone methylation also appears to be functionally relevant for memory formation, as mice that lack Mll (an H3K4 specific methyltransferase) exhibit impaired contextual fear conditioning (Gupta *et al*, 2010). Likewise, mice with neuronal deletion of the HMT G9a/GLP (an H3K9 specific methyltransferase) exhibit impaired motor behavior, decreased motivation to consume palatable sucrose, and severe learning and memory deficits (Schaefer *et al*, 2009). Additionally, this methyltransferase also regulates cocaine reward and cocaine-induced neuronal plasticity in the striatum (Maze *et al*, 2010). Together, these emerging results indicate that treatments that increase

histone methylation at specific sites may be useful candidates for a range of learning and memory disorders. However, aberrant HDM signaling also appears to be relevant for human disorders, as mutations in the *JARID1c* gene (a lysine demethylase) have been associated with autism and X-linked mental retardation (Tzschach *et al*, 2006; Iwase *et al*, 2007; Adegbola *et al*, 2008). Currently, our understanding of these modifications and their role in cognitive disorders remains in its infancy. Thus, future research will be required to elucidate the complex functional consequences of altered histone methylation and determine which sites and which histone methylation enzymes are good candidates for therapeutic intervention.

Histone Phosphorylation

A third histone modification that has been shown to regulate cognitive processes is phosphorylation of serine residues on histone tails (Figure 1c). This mark, normally associated with transcriptional activation, is catalyzed by a range of protein kinases (Berger, 2007; Deng *et al*, 2008). This group includes the mitogen- and stress-activated protein kinase 1 (MSK1), which is activated downstream of the ERK/MAP kinase pathway. Conversely, histone phosphorylation is reversed by protein phosphatases PP1 and PP2a, which are known to be inhibited by other molecular cascades including dopamine and cyclic-AMP regulated phosphoprotein 32 (DARPP32). Perhaps the most well-characterized phosphorylation mark occurs at serine 10 on H3. This modification recruits GCN5, which contains HAT activity and therefore increases acetylation at neighboring lysine residues K9 and K14 and repressing histone methylation at H3K9 (Fischle *et al*, 2005). In addition to recruiting HATs, H3S10 phosphorylation enhances transcription factor binding by modifying the interaction between DNA and the histone tail (Cheung *et al*, 2000).

Several studies have revealed a role for histone phosphorylation at H3S10 in regulating memory formation. Mutations in the gene encoding RSK2, which has been shown to phosphorylate H3, produces Coffin–Lowry syndrome, an X-linked disorder that is associated with psychomotor retardation and physical abnormalities (Delaunoy *et al*, 2001; Merienne *et al*, 2001). In animal models, H3S10 phosphorylation and H3S10/K14 phosphoacetylation increases rapidly in the hippocampus following contextual fear conditioning, and these increases are blocked by ERK inhibition (Chwang *et al*, 2006). Likewise, mice lacking MSK1 exhibit impaired fear conditioning and spatial memory (Chwang *et al*, 2007). Interestingly, this deficit is not reversed by treatment with an HDAC inhibitor, revealing that the histone phosphorylation pathway occurs in parallel to (rather than downstream of) histone acetylation. Accordingly, inhibition of nuclear PP1, the major histone phosphatase, improves long-term object recognition memory and spatial memory without affecting short-term memory (Koshibu *et al*, 2009). Together, these findings suggest that enhancing histone phosphorylation via inhibition of PP1 may be a distinct and even complementary treatment for learning and memory disorders. However, this remains to be examined experimentally.

In addition to learning and memory, changes in H3S10 phosphorylation have also been implicated in behavioral responses to drugs of abuse. Thus, cocaine induces increases in H3S10 phosphorylation in the striatum and MSK1 knockout mice display impaired behavioral responses to cocaine administration (Brami-Cherrier *et al*, 2005). Importantly, this change occurs downstream of phosphorylation and nuclear accumulation of DARPP-32, which influences behavioral responses to both cocaine and natural rewards like sucrose (Stipanovich *et al*, 2008). Histone phosphorylation has also been identified as a major downstream target of anti-psychotic and anti-Parkinsonian drugs, revealing major therapeutic potential in the development of compounds that specifically target this epigenetic modification (Bertran-Gonzalez *et al*, 2008, 2009; Santini *et al*, 2009). Interestingly, the protein kinase MSK1 is found mainly in neurons and is enriched in several brain regions, including the striatum, amygdala, and hippocampus (Heffron and Mandell, 2005). This cellular and regional selectivity indicates that MSK1 may be a good candidate for therapeutic intervention in drug addiction.

Other Histone Modifications: Ubiquitination and Poly-ADP Ribosylation

Although the three modifications reviewed above (acetylation, methylation, and phosphorylation) represent the bulk of ongoing research in the area of epigenetic control in cognitive processes, a number of additional histone modifications can occur *in vivo* and regulate many aspects of cellular signaling and function. Among these are histone ubiquitination, poly-ADP ribosylation, sumoylation, and O-GLCNAcylation. Below we will consider two specific modifications (ubiquitination and poly-ADP ribosylation), which through recent discoveries have been linked to cognition.

Histone ubiquitination occurs at all four histone proteins, but is most well characterized at the carboxy terminus of H2A and H2B. It is regulated by a three-step enzymatic process in which the enzyme E1 first activates ubiquitin, and the ubiquitin-carrier enzyme E2 directs ubiquitin to the substrate. Finally, ubiquitin is linked to a lysine residue by the E3 ubiquitin ligase family of enzymes (Wang *et al*, 2004; Higashi *et al*, 2010). Likewise, a wide family of deubiquitinases (DUBs) remove ubiquitin from lysine residues (Atanassov *et al*, 2010; Higashi *et al*, 2010). Although histone ubiquitination is known to have a wide range of cellular functions, most notably controlling transcriptional initiation and elongation (Zhu *et al*, 2007). In fact, it is known that ubiquitination/deubiquitination enzymes interact with other epigenetic machinery, and thus correlate (or are even prerequisites for) other histone marks, specifically histone methylation (Jason *et al*, 2002; Lee *et al*, 2007; Sadri-Vakili *et al*, 2007; Zhu *et al*, 2007).

However, perhaps the clearest link between histone ubiquitination and neurodegenerative impairments comes from Huntington's disease, which is characterized by a mutation in the gene-encoding huntingtin protein and aberrant transcriptional regulation. Interestingly, huntingtin interacts with the ubiquitin ligase hPRC1L, suggesting a role for histone ubiquitination in Huntington's disease (Kim *et al*, 2008). Moreover, ubiquitinated H2A is increased in a mouse model of Huntington's disease, whereas ubiquitinated H2B is decreased, resulting in modified histone methylation patterns and transcriptional dysregulation (Kim *et al*, 2008). Accordingly, targeting ubiquitin ligases may be a potential therapeutic avenue for patients with Huntington's disease.

Poly-ADP ribosylation of histones occurs at all histone proteins as well (Quenet *et al*, 2009; Messner *et al*, 2010), and is catalyzed by Poly (ADP-ribose) polymerases such as PARP1 and PARP2, with NAD^+ acting as a substrate. Likewise, poly-ADP ribosylation is reversed by poly (ADP-ribose)glycohydrolase (Quenet *et al*, 2009). Interestingly, although poly-ADP ribosylation and PARP1 activity are most well known for their role in DNA repair following damage, PARP1 activation has been shown to increase in cortical neurons following depolarization (Homburg *et al*, 2000). Likewise, PARP1 is required for long-term synaptic facilitation and long-term memory in aplysia, suggesting a functional role in the nervous system (Cohen-Armon *et al*, 2004; Hernandez *et al*, 2009). Likewise, in mouse models, poly-ADP ribosylation is increased at the histone linker protein H1 following novel object exposure, and PARP1 is required for hippocampal LTP and novel object recognition memory (Fontan-Lozano *et al*, 2010). These findings indicate that, in addition to the mechanisms reviewed above, histone poly-ADP ribosylation may be an interesting target for novel therapeutics for learning and memory disorders.

DIRECT COVALENT MODIFICATION OF DNA

Methylation and Demethylation

Methylation of cytosine nucleotides on DNA itself is the so-called 'fifth-base' of DNA and the 'prima donna' of the epigenetic landscape (Santos *et al*, 2005). This modification is catalyzed by DNA methyltransferases (DNMTs), which are divided into two groups (see Figure 2). DNMT1 is a maintenance methyltransferase, meaning that it recognizes hemi-methylated DNA and initiates methylation of the complementary strand. In contrast, DNMT3a and 3b are *de novo* methyltransferases, which can methylate both unmethylated and hemimethylated DNA (Klose and Bird, 2006). The methyl donor for this reaction is S-adenosyl methionine. Methylated cytosine residues serve as a binding site for a variety of methyl-binding domain (MBD) proteins (Ho *et al*, 2008), with MeCP2 being the prototypical MBD (Nan *et al*, 1997). When bound, MeCP2 can direct both

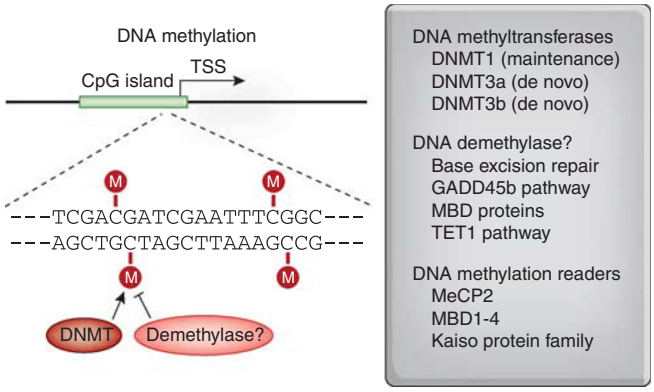

Figure 2. DNA methylation and demethylation. A majority of mammalian gene promoters contain dense clusters of cytosine-guanine dinucleotides called CpG islands, at which methylation can occur to dramatically influence gene transcription. In this example, the CpG island (green bar) overlaps the transcription start site. At CpG dinucleotides, methylation is catalyzed by DNA methyltransferases (DNMTs). *De novo* DNMTs direct the methylation of unmethylated CpGs, whereas maintenance DNMTs recognize hemi-methylated DNA and methylate the complementary strand. The existence of a direct demethylase is controversial, but a number of different mechanisms have been proposed to regulate removal of the methyl moiety, including excision and replacement of the entire base pair. DNA methylation marks are read by a family of proteins with methyl binding domains (MBD proteins), which includes MeCP2. Each of these targets may represent candidates for therapeutic treatments of disorders characterized by aberrant DNA methylation. See text for additional details.

transcriptional repression and transcriptional activation in different contexts (Chahrour *et al*, 2008).

The general chemical reaction of DNA methylation suggests that it should be static and long lasting. Direct removal of the methyl moiety from cytosine is extremely difficult given the strength of the carbon-carbon bond. In cases where a methyl group is passively removed from one strand, maintenance DNMT activity will recognize hemi-methylated DNA, leading again to double-stranded methylation (Ma *et al*, 2009a). Therefore, this modification is seemingly ideal for the long-term perpetuation of cellular phenotype, gene imprinting, and silencing of repetitive DNA elements (Dulac, 2010). However, despite their clear roles in embryonic development and cellular proliferation and differentiation (Wu and Zhang, 2010), DNMTs and MBD proteins are also found in relatively high levels in postmitotic, non-proliferating neurons (Goto *et al*, 1994; Dulac, 2010). This fact alone suggests that DNA methylation may have an active function beyond the static role in cellular phenotype that had long been assumed.

DNA Methylation in Learning and Memory

Interestingly, the general form of the chemical reaction, which maintains DNA methylation is precisely what memory biochemists hypothesized would be necessary for the perpetuation of long-term memory traces (Razin and Friedman, 1981; Crick, 1984; Lisman, 1985). Thus, the

ability of maintenance DNMTs to recognize hemi-methylated DNA and re-methylate the complementary strand ensures that this modification could remain stable over time despite ongoing molecular turnover within a cell, even in the absence of the initiating agent (Day and Sweatt, 2010). Consistent with this idea, a number of reports over the past several years have indicated that DNA methylation does indeed have a key role in memory formation and other types of long-term behavioral change. Initial studies revealed that contextual fear conditioning increases DNMT3a expression and induces changes in DNA methylation at the promoters of several key plasticity genes in the hippocampus (Miller and Sweatt, 2007; Lubin *et al*, 2008). These changes correspond with gene expression profiles, as increases in DNA methylation at the promoter for the memory suppressor gene *PP1* was associated with decreased gene expression, whereas decreased DNA methylation at promoters for memory-enhancing genes such as *reelin* and *BDNF* were associated with increases in the expression of these genes. Moreover, blocking DNMT activity in the hippocampus with distinct DNMT inhibitors zebularine, 5-aza-deoxycytidine, or RG-108 immediately after learning impaired the consolidation of conditioned freezing (Miller and Sweatt, 2007; Lubin *et al*, 2008).

It is important to note that the use of DNMT inhibitors comes with several caveats. First, both zebularine and 5-aza-deoxycytidine are nucleoside analogs that operate by first incorporating into DNA, a process that is thought to require cell division (Szyf, 2009). Thus, the mechanism of these drugs in non-dividing neurons is unclear. However, RG-108, which blocks the active site on DNMTs, has a well-understood mechanism and is therefore the preferred compound. A second caveat is that there is no evidence that the activity of these drugs is limited to neurons, and in fact this is likely not the case. Nevertheless, additional studies using genetic tools have revealed that neuron and forebrain-specific deletion of both DNMT isoforms impairs contextual fear conditioning, spatial memory, and hippocampal LTP (Feng *et al*, 2010). Together, these results reveal that changes in DNA methylation in adult neurons are critical transcriptional components of the memory consolidation process. However, these studies also reveal that very few of these learning-induced changes in DNA methylation in the hippocampus are enduring, suggesting that these changes alone do not form the basis of a molecular memory switch.

In contrast, DNA methylation changes within the cortex and in response to other types of behavioral experience have been found to be long lasting. For example, contextual fear conditioning induces sustained increases in promoter methylation and a corresponding downregulation of the *calcineurin* gene within the anterior cingulate cortex. Additionally, inhibition of DNA methylation via three distinct compounds (RG-108, zebularine, and 5-aza-deoxycytidine) prevents the remote maintenance of a previously formed memory, suggesting that long-term DNA methylation changes are necessary for the persistence of behavioral memory (Miller *et al*, 2010). Likewise, differences in maternal care in infants produces enduring changes in DNA methylation at several gene targets and in several brain regions (including the hippocampus) that are maintained well into adulthood (Weaver *et al*, 2004, 2005; Roth *et al*, 2009). Thus, changes in DNA methylation are characterized by regional differences as well as temporally distinct responses to different environmental events.

One interesting finding from these studies is that in addition to increases in DNA methylation at one set of genes, learning experiences just as often result in decreases in methylation at another set of genes. Furthermore, very rapid increases in methylation often return back to baseline levels. In combination, these results appear to conflict with previous assertions that DNA methylation is always a stable and self-perpetuating epigenetic modification. However, several recent reports indicate that DNA methylation is much more cyclical than previously assumed (Kangaspeska *et al*, 2008; Metivier *et al*, 2008), leading to the hypothesis that a separate mechanism was governing rapid demethylation of DNA (Ma *et al*, 2009a; Wu and Zhang, 2010). A number of distinct mechanisms have now been proposed for this demethylation activity, most notably control of DNA demethylation by the growth arrest and DNA damage inducible protein 45 (GADD45) protein family (Ma *et al*, 2009a, b; Wu and Zhang, 2010). Importantly, these possible mechanisms indicate that DNA methylation is a two-way street, and reveal a number of novel candidates for potential therapeutic regulation of DNA methylation (see Figure 2).

DNA Methylation in Rett Syndrome

Aberrant DNA methylation and changes in DNA methylation machinery or binding proteins have been implicated in a number of cognitive disorders. The prototypical example of this is Rett syndrome, which is an X-linked disorder associated with progressive mental retardation in females (Amir *et al*, 1999; Wan *et al*, 1999). The vast majority of Rett syndrome cases are caused by either sporadic or germline mutations in the *MeCP2* gene, and the specific nature of these mutations correlates highly with phenotypic outcomes (Amir *et al*, 1999; Amir and Zoghbi, 2000). Given that MeCP2 binds selectively to methylated DNA, this indicates that aberrant readout of DNA methylation is a critical component of the cognitive impairments observed in this syndrome.

Various aspects of Rett syndrome impairments have now been recapitulated in animal models. For example, a range of studies using mice with selective mutations in the *MeCP2* gene have revealed that loss of MeCP2 function produces deficits in spatial memory, contextual and cued fear conditioning memory, and deficits on social interaction tests (Shahbazian *et al*, 2002; Moretti *et al*, 2005, 2006; Pelka *et al*, 2006; Stearns *et al*, 2007). Likewise, MeCP2 mutant mice exhibit deficits in hippocampal LTP and LTD (Asaka *et al*, 2006; Moretti *et al*, 2006), revealing a physiological correlate for impaired learning and memory

in Rett syndrome. Importantly, deficits observed in MeCP2 mutant mice may not completely represent developmental problems alone, but also disruption of neuronal function in the mature nervous system. Thus, selective deletion of MeCP2 in the adult basolateral amygdala induces impaired anxiety and learning and memory deficits (Adachi *et al*, 2009).

The most straightforward treatment for MeCP2 mutations in Rett syndrome would presumably be to overexpress or enhance the function of MeCP2. Along these lines, overexpression of MeCP2 results in enhanced fear conditioning and hippocampal LTP (Collins *et al*, 2004), revealing some therapeutic potential. However, given that MeCP2 function is in part linked to interaction with transcriptionally repressive HDACs (Nan *et al*, 1998; Chahrour *et al*, 2008), another possibility is to target HDAC function. Thus, deficits in learning and memory and hippocampal LTP induced by DNMT inhibitors can be rescued by pre-treatment with HDAC inhibitors (Miller *et al*, 2008). However, treatment with HDAC inhibitors in other brain regions like the basolateral amygdala can mimic the behavioral deficits associated with MeCP2 deletion in this area (Adachi *et al*, 2009), indicating that caution must be used when generalizing results from hippocampus-dependent memory tasks to memory functions supported by other brain structures.

DNA Methylation in Schizophrenia

A second psychiatric condition in which altered DNA methylation has long been implicated is schizophrenia (Pollin *et al*, 1961; Bredy *et al*, 2010). The first evidence for a role of DNA methylation in schizophrenia came from the observation that treatment with an S-adenosyl-methionine precursor L-methionine, actually intensifies a number of schizophrenic symptoms (Pollin *et al*, 1961). Given that S-adenosyl-methionine is the methyl donor for the DNA methylation reaction, this result suggests that hypermethylation of DNA may contribute to schizophrenia. Consistent with this hypothesis, patients with schizophrenia exhibit hypermethylation at the synaptic plasticity gene *reelin* in the cortex, which is associated with decreased reelin expression (Grayson *et al*, 2005). Additionally, post-mortem samples from schizophrenic patients have revealed an overexpression of DNMT1 and DNMT3a in GABAergic neurons (Zhubi *et al*, 2009), which is consistent with the observation that DNMT1 regulates *reelin* methylation *in vivo* (Noh *et al*, 2005).

A number of drug treatments appear to be capable of reversing DNA hypermethylation (Szyf, 2009). Interestingly, the anti-psychotic drugs clozapine and sulpiride, which are both used for schizophrenia treatment in clinical settings, have been found to demethylate the *reelin* gene *in vivo* (Dong *et al*, 2008). Likewise, a number of HDAC inhibitors are capable of inducing demethylation in the brain, and co-application of the HDAC inhibitor valproate along with clozapine and sulpiride dramatically enhances the ability of these drugs to reverse *reelin* methylation (Dong *et al*, 2008, 2010; Szyf, 2009). Thus, treatment with HDAC inhibitors may provide a new avenue of treatment for schizophrenia, whether alone or in combination with existing pharmacotherapies. Finally, another obvious option for decreasing aberrant DNA methylation in schizophrenia is the DNMT inhibitors, such as zebularine, 5-aza-deoxycytidine, and RG108. However, the success of HDAC inhibitors and DNMT inhibitors in alleviation of schizophrenic symptoms remains to be investigated in human populations.

ADDITIONAL TARGETS

Epigenetic mechanisms are traditionally defined as mitotically and/or meiotically heritable changes in gene expression that do not involve changes in DNA sequence (Russo *et al*, 1996). This definition has undergone revision in recent years, in large part to include marks that occur at chromosomes in non-dividing cells such as neurons. Thus, a more inclusive definition considers epigenetic mechanisms to be as follows: 'the structural adaptation of chromosomal regions so as to register, signal, or perpetuate altered activity states' (Bird, 2007). Although this definition includes the mechanisms discussed above, it excludes a number of additional molecular mechanisms that, while not considered 'epigenetic' in the strict sense, are capable of exerting powerful control over gene expression or protein function, and therefore are of potential interest when considering therapies for cognitive disorders. Additionally, these mechanisms have considerable interplay with traditionally defined epigenetic mechanisms (Rouhi *et al*, 2008), such as DNA methylation and it is therefore important to address these mechanisms in the context of epigenetics.

MicroRNA

The first of these mechanisms derive from the activity of small RNA molecules, which include microRNAs, small interfering RNA, and small nuclear RNA. Small RNAs have multiple functions within a cell, including activation, repression, or interference with gene expression (He and Hannon, 2004), and have been implicated in a number of cognitive disorders. For example, microRNA binds to 3′ untranslated regions of messenger RNA and thereby either cleaves and degrades the messenger RNA or controls its expression through translational mechanisms (Bartel, 2004; Vasudevan *et al*, 2007). MicroRNA thereby control expression of the majority of genes within the genome, and represent a critical component of normal physiology and function in the developing and adult nervous system (Bartel, 2004; Miranda *et al*, 2006).

An example of the importance of microRNA regulation of gene expression comes from Fragile X syndrome, a commonly inherited disorder characterized by mental retardation and autism-like behavioral abnormalities. Fragile X is caused by a mutation in the *FMR1* gene, which causes gene hypermethylation and resulting absence of its

product, Fragile X mental retardation protein (FMRP) (Penagarikano *et al*, 2007). Interestingly, FMR1 is a RNA-binding protein that interacts with several microRNAs to regulate gene expression that is critical for neural development (Jin *et al*, 2004). In fact, FMR1's association with a specific microRNA, miR125b, has been shown to underlie NMDA receptor expression in mouse models, providing a specific mechanism for behavioral impairments in Fragile X syndrome (Edbauer *et al*, 2010).

Further implicating a role for microRNAs in psychiatric diseases, recent evidence has revealed that Alzheimer's Disease is associated with a altered expression of several microRNAs, some of which interact with the amyloid precursor protein's cleavage machinery, which has long been associated with this disease (Provost, 2010). Similarly, in an animal model of drug addiction, prolonged experience with cocaine self-administration dramatically increased expression of miR-212 in the striatum (Hollander *et al*, 2010). However, in this case, this overexpression was associated with a dampening of the motivational properties of the drug by modulating CREB pathways linked to the stimulatory effects of cocaine. These data, together with the substrate specificity of microRNAs, suggest that microRNA targets may be excellent therapeutic candidates for cognitive disorders.

Prion-Like Proteins

A second set of mechanisms, prion-like proteins, involves proteins capable of two conformational states. Interestingly, prion proteins are able to not only undergo a conformational change, but are also then capable of converting normal isoforms into the conformationally altered version. Prion proteins have recently been shown to have functional roles in memory maintenance, and therefore represent a potential therapeutic candidate for treatment of memory disorders. For example, cytoplasmic polyadenylation element binding protein (CPEB), which exhibits prion characteristics, is essential for synaptic facilitation in aplysia as well as normal memory function in both mice and drosophila (Si *et al*, 2003a, b, 2010; Berger-Sweeney *et al*, 2006; Keleman *et al*, 2007; Miniaci *et al*, 2008), indicating that prion function may be a necessary and common component of synaptic plasticity. Likewise, another prion protein, PrPC, is critical for inhibitory avoidance memory in rats (Coitinho *et al*, 2006), and mice that overexpress PrPC fail to show age-related declines in social recognition memory (Rial *et al*, 2009). Together, these results reveal that prion proteins may have a normal functional role in the establishment of long-term memory.

FUTURE RESEARCH DIRECTIONS AND CONCLUSIONS

Taken together, the wide variety of findings reviewed above suggest that a range of cognitive disorders are characterized by aberrant epigenetic changes and that epigenetic drug targets may be useful for treatments for these disorders (see Table 1). However, interpreting these results comes with a number of caveats. For example, for a number of disorders discussed above, it remains unclear if epigenetic changes represent the root cause of the behavioral symptoms or instead simply reflective of other neuronal changes. As epigenetic mechanisms like histone acetylation and DNA methylation represent downstream integration templates for a number of signal transduction and second messenger cascades, it is possible that epigenetic alterations are only one of many functional outcomes resulting from altered intracellular signaling. An example of this is the specific impairment in learning-induced H4K12 acetylation in aged animals (Peleg *et al*, 2010). Conceptually, this deleterious lack of epigenetic function could result from dysregulation in many components of neuronal physiology, including neurotransmitter release, receptor function, and upstream molecular signaling. Therefore, continued investigation of whether epigenetic changes are the cause or outcome of specific cognitive disorders will enhance our ability to treat or in some cases prevent those disorders. However, even when altered epigenetic function is known to be the cause of a disorder, such as Rett syndrome, it is still unclear in many cases how this change plays out across thousands of gene targets and across functionally diverse brain structures. Thus, in addition to examining the epigenetic endpoints of a disorder, it remains a clear necessity to continue to evaluate how these endpoints affect gene expression and function of entire neural circuits.

The use of drugs that alter epigenetic mechanisms also comes with a number of challenges. A major difficulty is that available epigenetic compounds such as HDAC inhibitors and DNMT inhibitors are not selective for specific brain regions, neuronal subtypes, or specific genes. This lack of selectivity becomes a key issue for treatment of disorders that are characterized by changes in epigenetic state at a small group of gene sites or impaired generation of a specific histone modification (eg, H3S10). For example, as mentioned above, schizophrenia is associated with hypermethylation of the *reelin* gene (Grayson *et al*, 2005). However, applying DNMT inhibitors systemically or even in a region-specific manner would presumably result not only in decreased *reelin* methylation, but also in decreased methylation of multitudes of other genes. Likewise, treatment with HDAC inhibitors, which are also capable of reversing *reelin* hypermethylation, would result in increased histone acetylation of other unrelated genes. A related challenge is that as histone modifications and DNA methylation work in concert to regulate transcription, altering one mechanism will consequently affect other mechanisms in a complex manner. In terms of epigenetic treatments, each of the challenges will likely produce a number of side effects that may be deleterious and prohibit widespread applications. Thus, future research will be required to develop more specific regulators of epigenetic machinery.

One promising avenue for the development of more specific epigenetic treatments is the HDACs. As these

TABLE 1 Selected List of Psychiatric Disorders and Syndromes with Epigenetic Origins or Treatments

Disorder/disease	Epigenetic dysregulation	Potential treatments
Rett syndrome	Mutation in *MeCP2* gene	HDAC inhibitors HDAC inhibitors
Age-associated cognitive decline	Impaired H4K12 acetylation in response to learning event	
Schizophrenia	Hypermethylation of *reelin* gene, decreased H3K4me3, and increased H3K27me3 at GAD 67 promoter	DNMT inhibitors, HDAC inhibitors
Rubenstein–Taybi syndrome	Mutation of *CBP* gene	HDAC inhibitors
Drug addiction	Multiple changes in DNA methylation and histone modifications at striatal plasticity genes, increased MeCP2	HDAC inhibitors specifically during extinction training
Coffin–Lowry syndrome	Mutation in *RSK2* gene	PP1 inhibitor
Alzheimer's disease	Aberrant histone acetylation and phosphorylation, DNA hypomethylation at several genes	HDAC inhibitors, S-adenosylmethionine, methyl-donor rich diets
Depression	Increased H3K27me2 at specific promoters of *BDNF* gene, downregulation of HDAC5 in hippocampus, DNA methylation differences in catecholamine-signaling genes	HDAC inhibitors, specific HMTs or HDM inhibitors
Angelman syndrome	Abnormal DNA methylation-related imprinting of maternal alleles	–
Prader–Willi syndrome	Abnormal DNA methylation-related imprinting of paternal alleles	–
Fragile-X syndrome	Hypermethylation of DNA at *FMR* genes	–

enzymes exist in many different isoforms (see Figure 1a) that differ in their expression across brain structures as well as their molecular functions, it may be possible to enhance spatial and genetic specificity by targeting only one HDAC isoform. For example, given that HDAC2 and HDAC3 have been found to negatively regulate learning and memory, it may be useful to create a compound, which targets these isoforms for learning and memory disorders (Guan *et al*, 2009; McQuown *et al*, 2011). Likewise, given the diverse range of specific HDM and methyltransferase enzymes, it may be worthwhile to investigate the manipulation of these enzymes in disorders characterized by aberrant histone methylation. However, in cases where this type of targeting may not be a possibility, such as the DNMT inhibitors, another strategy would be to focus on the specific factors and proteins that target histone and DNA-modifying enzymes to specific gene targets. This approach would ensure that resulting epigenetic changes are restricted to a smaller group of genes than global interference with epigenetic machinery.

Although the majority of epigenetic changes discussed in this review center upon individual modifications and their contribution to disease in a single lifetime, a final consideration for future research is the transgenerational inheritance of epigenetic alterations (Richards, 2006). Indeed, it has recently been appreciated that complex environmentally induced epigenetic changes may influence epigenetic state in offspring (Roth *et al*, 2009), providing a mechanism for non-genetic behavioral traits to be inherited. In addition, it is now clear that a large number of genes are imprinted in the brain (Gregg *et al*, 2010a, b), resulting in favored expression of either the maternal or paternal allele.

Likewise, it has long been understood that epigenetic mechanisms (in particular DNA methylation) regulate this imprinting process (Li *et al*, 1993). In our view, transcriptional inheritance of epigenetic states has the potential to revolutionize our understanding of disease vulnerability, specifically for behavioral disorders such as drug addiction, depression, and anxiety. However, future research will be required to tease apart the complex effects of environmental experience, parental history, and genetic makeup on epigenetic patterns. Nevertheless, along with the development of more specific epigenetic drugs, understanding how epigenetic patterns develop and how they affect diverse brain systems will greatly enhance our ability to treat and possibly even prevent cognitive disorders.

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DISCLOSURE

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