

Psychiatric Disorders and Epigenetics

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SUMMARY

The term epigenetic refers to long-lasting changes in gene expression that are beyond the DNA base sequence. Understanding the dynamic role of epigenetic mechanisms in the regulation of gene expression in adulthood has led researchers to investigate epigenetic mechanisms in psychiatric disorders. The aim of this review was to describe epigenetic mechanisms and to discuss the role of epigenetic modifications in stress, depression, schizophrenia, and substance dependence. For this purpose PubMed was searched using the keywords epigenetic, stress, depression, schizophrenia, and substance dependence; studies published between 2000 and 2011 were reviewed.

Different maternal behavioral patterns and early life stress have been reported to yield heritable changes in gene expression via epigenetic mechanisms, which are reversible. Studies that investigated the role of epigenetic modifications in stress and depression focused on the proteins involved in the regulation of the hypothalamo-pituitary adrenal (HPA) axis, whereas epigenetic studies of schizophrenia primarily focused on changes in the GABAergic system. Studies on substance dependence, on the other hand, showed that substance use might change the expression of many genes by causing short- or long-lasting epigenetic modifications. These findings have led to the development of new therapeutic strategies that target epigenetic mechanisms. Among these strategies, histone deacetylase inhibitors are especially promising. More studies are needed to improve our understanding of the role of epigenetic modifications in the development of psychiatric disorders, and to aid in the development of new treatment strategies that focus on epigenetic mechanisms.

Keywords: Epigenetic, stress, depression, schizophrenia, substance dependence

INTRODUCTION

Epigenetics refers to the various processes leading to long-term changes in gene expression without alteration of the genetic code—namely, the DNA base sequence (Delcuve et al. 2009). Epi—meaning in addition to—refers to changes that occur without changing the sequence of the adenine, guanine, cytosine, and guanine bases that make up the genetic code. The term was originally used by Waddington in 1942 in his explanation of how all cells in the body express different genes even though they have the same DNA sequence (Sweatt 2009). For example, proteins expressed in the liver and the brain are quite different, even though they possess the same genetic code. In order to account for this, Waddington suggested that during development, mechanisms beyond

the DNA sequence control these differences. Recent studies showed that epigenetics plays a role in the acute regulation of genotypic expression—not only during development, but also throughout adulthood (Kouzarides 2007; Siegmund et al. 2007; Metivier et al. 2008).

Epigenetic changes are quite stable/permanent (Kouzarides 2007). Despite their stable structure, they are also reversible (Metivier et al. 2008). This dynamism makes it possible for epigenetic mechanisms to regulate gene expression according to changing circumstances. In other words, it is possible to control gene expression via alterations in environmental conditions and external interventions, such as drug therapy. This characteristic rendered epigenetic mechanisms the focus of studies on new treatment strategies. In addition, epigenetic

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Table 1. Epigenetic changes and their function.

Epigenetic Change	Effect on Gene Expression	Enzyme Involved	Enzyme Removing Bond
Histone acetylation	Increase	Histone acetyl transferase (HAT)	Histone deacetylase (HDAC I-IV)
Histone phosphorylation	Increase	Kinase	Phosphorylase
Histone-3 Methylation			
4. Residue lysine methylation (H3-K4)	Increase	Histone methyl transferase (HMT)	Histone demethylase (HDM)
9. Residue lysine methylation (H3-K9)	Decrease		
27. Residue lysine methylation (H3-K27)	Decrease		
Histone Ubiquitination	Increase	Ubiquitin ligase	Ubiquitin protease
Histone Sumoylation	Decrease	SUMO E2/E3	SUMO protease
DNA Methylation	Decrease	DNA methyl transferase (DNMT)	DNA demethylase

changes are inheritable, i.e. the effect of environmental conditions on gene expression, and the advantages or disadvantages caused by this can be transmitted to subsequent generations (Richards 2006; Kaminsky et al. 2009).

In many psychiatric disorders hereditary susceptibility and environmental factors play an etiological role. The interaction between environmental and hereditary factors in the development of disease was reported by Caspi et al. (2003). They observed that childhood abuse or stressful life events during adulthood were predictive of depression only in individuals carrying a short allele in the promoter region of the serotonin transporter gene. Epigenetic regulation enabling integration of internal and external signals in the genome may play a role in the development of psychiatric disorders, and may aid in the identification of targets for new treatment options (Jaenisch and Bird 2003).

The aim of the present review was to introduce epigenetic mechanisms and to discuss the role of epigenetic regulation in stress, depression, schizophrenia, and substance dependence. PubMed was searched using the key words epigenetic, stress, depression, schizophrenia, and substance abuse; studies and reviews published between 2000 and 2011 were evaluated.

EPIGENETIC MECHANISMS

Epigenetic mechanisms are closely associated with the structure of chromatin, which tightly packs DNA in order for it to fit into the cell nucleus. Histone proteins play a key role in the packing of DNA. There are 5 histone proteins: histone 1 (H1), histone 2A (H2A), histone 2B (H2B), histone 3 (H3), and histone 4 (H4). The structure formed by the combination of DNA and histone proteins is a nucleosome and this organization causes DNA to be 5-10-fold more tightly packed (Kornberg 1974). The condensation of the nucleosome

structure regulates the access of transcription factors to DNA in the nucleus and hence, whether or not a gene is expressed. Epigenetic mechanisms regulate the expression of genes via control of nucleosome condensation (Felsenfeld and Groudine 2003). If chromatin has a condensed structure that does not allow gene expression it is referred to as heterochromatin, and if it has an open structure allowing gene expression it is referred to as euchromatin. Epigenetic changes are primarily mediated by 2 mechanisms, and occur via covalent changes in histone structure or DNA methylation (Table 1).

Changes in Histone Structure

Changes that occur via covalent binding of groups, such as acetyl, methyl, phosphate, and ubiquitin, or SUMO groups, to amino acids (AAs) located on the tails of histone proteins (amino-terminal ends of histone proteins) are involved in the regulation of gene expression via changing the condensation of the nucleosome structure (Tsankova et al. 2007; Renthal and Nestler 2008). Among these changes, acetylation or phosphorylation activates gene expression, whereas methylation may have both suppressive and activating effects on gene expression, depending on the residue undergoing methylation (Lachner and Jenuwein 2002) (Table-1).

Among the changes in histone structure, methylation and acetylation are the most commonly investigated. For the purpose of this review only enzymes leading to these changes will be considered. The methyl group is added to the histone by histone methyl transferase (HMT) and removed by histone demethylase (HDM). The acetyl group is added to the histone by histone acetyl transferase (HAT) and removed by histone deacetylases (HDACs) (Tsankova et al. 2007) (Table 1). HDACs are divided into 4 classes: class I includes HDAC1, HDAC2, HDAC3, and HDAC8; class II includes HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10; class

III includes sirtuins; class IV includes HDAC11 (Renthal and Nestler 2009). The HDACs known to play a role in epigenetic regulation of psychiatric disorders are in class I and II.

DNA Methylation

DNA methylation occurs via the binding of the methyl group to cytosine among succeeding cytosine (C)-guanine (G) base sequences in DNA. The DNA methyl transferase (DNMT) enzyme transfers the methyl group from S-adenosylmethionine (SAM), which is a methyl donor, to DNA (Table 1). It has recently been reported that promoter regions of genes (the region that is immediately in front of a gene region and enables its expression by binding transcription factors) are actively methylated and that methyl is removed by means of demethylase enzymes (Metivier et al. 2008). DNA methylation inhibits expression of the involved gene.

EPIGENETIC REGULATION IN STRESS AND DEPRESSION

It is known that stress is an important factor in the development of depression. Stressful life events may lead to mood disorders or aggravate an existing disorder (Kendler et al. 1999; Gold and Chrousos 2002; Caspi et al. 2003). It has been established that exposure to stress during the prenatal or early postnatal period promotes development of the stress response, increases glucocorticoid release and endocrine response following stressful life events in adulthood, and impairs regulation of the hypothalamo-pituitary-adrenal (HPA) axis. In addition, it has been reported that these alterations continue throughout life, impair coping skills in adulthood and increase the prevalence of psychiatric disorders, such as depression and anxiety disorders (Glover 1997; de Kloet et al. 2005; Fumagalli et al. 2007; Gluckman et al. 2008; Lupien et al. 2009); therefore, the impact of stress on the behavioral and molecular levels is frequently experimentally studied in animals.

The importance of a healthy mother-baby relationship to the psychological development of the baby is well known. When the mother-baby relationship is not healthy the infant is stressed and its development is negatively affected (Green and Goldwyn 2002). Hence, many studies on stress have focused on this relationship. Rats exhibit individual variations in maternal behavior, as do humans. Some rats have more contact with their offspring, exhibiting high levels of pup licking, grooming, and arched-back nursing (high LG-ABN), whereas others exhibit these behaviors to a significantly lesser degree (low LG-ABN). When the pups of high LG-ABN rats were compared with the pups of low-LG-ABN rats, the former group was observed to experience less anxiety as adults and their HPA response to stress was lower (Liu et al. 1997; Caldji et al. 1998). When the pups born to low-LG-ABN mothers were reared by high-LG-ABN mothers, their

development was reported to be similar to that of the pups born to high-LG-ABN mothers. Likewise, pups born to high LG-ABN mothers that were reared by low-LG-ABN mothers exhibited development similar to that observed in the pups born to low-LG-ABN mothers (Francis et al. 1999). These findings suggest that the effects of maternal behavior on anxiety are mediated by non-hereditary factors.

Since it became clear that epigenetic processes regulate genes dynamically in adults, studies focused on the epigenetic changes in genes critical to mood disorders that are induced by stressful life events during different periods of life. The majority of such studies targeted molecules involved in the regulation of the HPA axis. Among the molecules studied are the glucocorticoid receptor (GR) gene, which regulates the HPA axis via negative feedback inhibition, and arginine vasopressin (AVP) and corticotrophin releasing factor (CRF) genes, which regulate the effect of stress on the HPA axis by increasing the release of ACTH from the pituitary gland.

Glucocorticoid Receptor (GR) Gene

It has been reported that prenatal stress and early life stress increase DNA methylation of the GR gene promoter, and decrease GR expression in the hippocampus and hypothalamus (Weaver et al. 2004, 2005; Mueller and Bale 2008) (Table 2). In rat pups born to low-LG-ABN mothers and reared by high-LG-ABN mothers, such change in GR methylation was not observed. Interestingly, it was reported that administration of an HDAC inhibitor, trichostatin A, increased GR levels in the pups of low-LG-ABN mothers (Weaver et al. 2004). The same group investigated the effects of systemic administration of L-methionine (a methyl donor) in adult rats on methylation of the GR gene and GR levels in the hippocampus, and behavior in pups born to high- or low- LG-ABN mothers. This intervention increased DNA methylation in GR promoter and decreased GR levels in the hippocampus of the pups born to high-LG-ABN mothers, and increased depression-like behavior. A significant difference was not observed between the pups of low-LG-ABN mothers that were administered L-methionine and vehicle (Weaver et al. 2005) (Table 2). These findings are extremely important because they show that epigenetic changes that occur early in life can be modified in adulthood and therefore, changes in gene expression engendered by negative factors via epigenetic mechanisms may be reversed by treatment interventions in adulthood and new treatments may be developed in this context.

Epigenetic changes observed in the GR gene in animal studies were replicated in humans in a recent postmortem brain study (McGowan et al. 2009). In this study the GR expression levels and GR promoter methylation were investigated in the hippocampus of people that committed suicide or died of natural causes. In order to differentiate the effects of stress, those that committed suicide were divided into 2 groups:

Table 2. Epigenetic changes observed in psychiatric disorders.

Relevant Gene	Intervention/Disorder	Examined Species tür/Brain Region	Effect on DNA Methylation	Effect on Gene Expression	Effect on Behavior
GR	Early life stress ^a	Rat/hippocampus	Increase	Decrease	Impairment of early stress response
	L-methionine administration in adulthood	Rat/hippocampus	Increase ^b	Decrease ^b	Increase in depression-like behavior
	Prenatal stress	Mouse/hypothalamus	Increase	Decrease	Anhedonia, impairment in adult stress response
	Sexual abuse in childhood	Human/hippocampus	Increase	Decrease	
AVP	Early life stress ^c	Mouse/hypothalamus	Decrease	Increase	Increase in depression-like behavior, impairment in adult stress response, impairment in learning
CRF	Prenatal stress	Mouse/hypothalamus	Decrease	Increase	Anhedonia, impairment in adult stress response
ER- α	Early life stress ^a	Rat/hypothalamus	Increase	Decrease	
BDNF	Prenatal stress	Mouse/hypothalamus	No change	No change	Anhedonia, impairment in adult stress response
	Early life stress ^a	Rat/PFC Rat/hippocampus	Increase ^d No change	Decrease ^d No change	Inheritance of maternal behavior
Reelin	Schizophrenia	Human/PFC and occipital cortex	Increase in DNMT1 and DNMT3a	Decrease	
	L-methionine administration in adulthood	Mouse/frontal cortex	Increase	Decrease	Decrease in social interaction, impairment in prepulse inhibition
GAD1	Schizophrenia	Human/PFC	Increase DNMT1 and DNMT3a increase	Decrease	
	L-methionine administration in adulthood	Mouse/frontal cortex	Increase	Decrease	Decrease in social interaction, impairment in prepulse inhibition
	L-methionine + VPA administration L-methionine + sulpiride/ clozapine	Mouse/frontal cortex	Decrease	Increase	Reverses the effects of L-methionine administration on behavior
COMT	Schizophrenia	Human/frontal lobe	Decrease	Increase	
BDNF	Chronic social defeat stress	Mouse/hippocampus	H3-K27 methylation increase	Decrease	Decrease in social interaction
	Chronic imipramine	Mouse/hippocampus	H3-K4 methylation increase	Increase	Increase in social interaction
GAD-1	Healthy individuals		H3-K4 methylation increase	Increase	
	Schizophrenia		H3-K4 methylation decrease ^e and HDAC1 increase	Decrease	
	Clozapine	Human/PFC	H3-K4 methylation increase	Increase	
Many genes	Acute cocaine administration	Mouse/nucleus accumbens	H3-K9 methylation increase	Decrease	
	Chronic cocaine administration	Mouse/nucleus accumbens	H3-K9 methylation decrease HMT enzyme i G9a decrease	Increase	Increased preference for the compartment in which cocaine is administered in conditional place preference test

(Table 2. Continued)

Relevant Gene	Intervention /Disease	Examines Species/Brain Region	Effect on Histone Acetylation	Effect on Gene Expression	Effect on Behavior
BDNF	Repeated electroconvulsive seizure	Rat/hippocampus	H3 acetylation increase	Increase	Antidepressant effect
	Chronic cocaine administration	Mouse/nucleus accumbens	H3-acetylation increase	Increase	Increased preference for the compartment in which cocaine is administered in conditional place preference test
Many genes	Chronic social defeat stress	Mouse/nucleus accumbens	H3-acetylation increase HDAC2 and HDAC5 decrease		Decrease in social interaction
	Chronic imipramine/HDAC inhibitors	Mouse/nucleus accumbens	H3-acetylation and HDAC5 increase		Increase in social interaction and antidepressant effect
	Major depression	Human/nucleus accumbens	H3-acetylation increase and HDAC2 decrease		
Many genes	Chronic cocaine administration	Mouse/nucleus accumbens	H3-acetylation increase H4-acetylation increase	Increase	Increased preference for the compartment in which cocaine is administered in conditional place preference test
c-Fos	Acute cocaine administration	Mouse/nucleus accumbens	H4-acetylation increase	Increase	
FosB	Acute cocaine administration	Mouse/nucleus accumbens	H4-acetylation increase	Increase	
cdk5	Chronic cocaine administration	Mouse/nucleus accumbens	H3-acetylation increase	Increase	Increased preference for the compartment in which cocaine is administered in conditional place preference test

^aReared by low-LG-ABN mothers.^bOnly in pups reared by high-LG-ABN mothers.^cSeparated from the mother for 3 h each day between postnatal days 1-10.^dThe same epigenetic change was detected in the next generation.^eOnly in women.

AVP: Arginine vasopressin; BDNF: brain-derived neurotrophic factor; cdk5: cyclin-dependent kinase-5; COMT: catechol-O-methyl transferase; CRF: corticotrophin releasing factor; DNMT: DNA methyl transferase; ER- α : estrogen receptor- α ; GAD: glutamic acid decarboxylase; GR: glucocorticoid receptor; HDAC: histone deacetylase; HMT: histone methyl transferase; PFC: prefrontal cortex; VPA: valproic acid.

those that experienced sexual and/or physical abuse or severe neglect during childhood and those that did not. Among the individuals that committed suicide, only those that were abused as children had low GR levels in the hippocampus and elevated DNA methylation in GR promoter (Table 2).

In summary, research has shown that early stressful experiences increase DNA methylation in the promoter region of the GR gene, causing epigenetic changes via suppression of gene expression. This, in turn, decreases GR gene expression, which determines the stress response in adulthood (Weaver et al. 2004, 2005; Mueller and Bale 2008; McGowan et al. 2009).

Arginine Vasopressin (AVP) and Corticotrophin-Releasing Factor (CRF) Genes

In addition to the GR gene, epigenetic changes were reported in hypothalamic AVP and CRF genes, which regulate the effects of stress on the HPA axis induced by prenatal or early life

stress (Mueller and Bale 2008; Murgatroyd et al. 2009). Early life stress was induced by a commonly used model—separating the mother and offspring repeatedly and for certain periods during the early postnatal period in rodents. A decrease in DNA methylation in the promoter region of the CRF gene and the regulator region of the AVP gene, and a subsequent increase in CRF and AVP mRNA expression were reported in the hypothalamus of the offspring exposed to the stress (Mueller and Bale 2008; Murgatroyd et al. 2009) (Table 2).

Estrogen Receptor- α (ER- α) Gene

It is known that estrogen is also important to maternal behavior (Fahrbach et al. 1985; Numan and Sheehan 1997; Champagne et al. 2001; Champagne and Meaney 2006). Champagne et al. (2006) investigated the effects of different maternal styles on epigenetic changes in estrogen receptor- α (ER- α). They observed that rat pups reared by high-LG-ABN

mothers, irrespective of their biological mother, had less ER- α gene methylation and higher ER- α levels in the medial preoptic nucleus of the hypothalamus (Table 2).

Brain-Derived Neurotrophic Factor (BDNF) Gene

Another target molecule in studies on epigenetic changes caused by stressful life events is the brain-derived neurotrophic factor (BDNF) gene (for a detailed review see Duman and Monteggia 2006). One study examined epigenetic changes in the BDNF gene in adult mice subjected to chronic social defeat stress (Tsankova et al. 2006). Mice were exposed to a larger and more aggressive mouse for 10 min, and then kept in an adjacent compartment of the same cage separated from the aggressive mouse by a plastic divider for the next 24 h for 10 d. Social interaction decreased in the defeated mice and this decrease could be reversed by chronic antidepressant treatment (imipramine) administered after the social defeat stress was completed. In addition to these behavioral findings, chronic social defeat stress was shown to increase methylation of the 27th lysine residue in H3 (H3-K27) and to decrease BDNF mRNA expression in the hippocampus (Table 2).

Changes caused in the BDNF gene by prenatal or early postnatal stress were investigated, but findings are inconsistent. One study examined methylation in the promoter region of the BDNF gene in the hypothalamus caused by prenatal stress and reported that there were no changes (Mueller and Bale 2008). Another study reported an increase in the methylation of BDNF promoter in the prefrontal cortex (PFC) following early life stress, but this finding could not be replicated in the hippocampus (Roth et al. 2009) (Table 2). In that study rat pups were reared by mothers known to have abusive behaviors towards their offspring (dropping, dragging, stepping on, and active avoidance) or by mothers with good maternal behavior. BDNF mRNA expression was lower and DNA methylation of the BDNF gene was higher in the PFC of the pups reared by abusive mothers. Interestingly, it was observed that maternal behavior was inherited by succeeding generations; i.e. pups reared by abusive mothers abused their own pups and those that received good care from their mothers cared well for their pups (Roth et al. 2009). In addition, elevated methylation in the BDNF gene was observed to be inherited by third generation rats born to abused pups. Methylation of the BDNF gene could be reduced partly by cross fostering. This finding is significant because it demonstrates the possibility of modification of inherited epigenetic changes via environmental conditions later in life.

Antidepressant Treatment Strategies Targeting Epigenetic Mechanisms

The findings outlined above resulted in epigenetic mechanisms becoming a focus in the development of novel antidepressant

treatment strategies. The number of studies that present evidence that known antidepressant drugs exert their effects via epigenetic mechanisms continues to increase. It was reported that chronic imipramine treatment increased acetylation of H3 and methylation of the 4th lysine residue of H3 (H3-K4) of the BDNF gene in the hippocampus of animals exposed to chronic social defeat stress (Tsankova et al. 2006) (Table 2). In consideration of the fact that chronic social defeat stress exerts its effect on BDNF via increasing H3-K27 methylation, this finding indicates that new treatment approaches that target epigenetic mechanisms may be effective without correcting the epigenetic changes observed in diseases. In another study by Tsankova et al. (2004) repeated electroconvulsive seizures, an effective antidepressant treatment method, was reported to increase H3 acetylation and BDNF mRNA expression in the rat hippocampus (Table 2). Additionally, the fact that valproic acid—a mood stabilizer—is an HDAC inhibitor and hence increases histone acetylation in neurons, supports the findings of the aforementioned studies (Tremolizzo et al. 2002; Yildirim et al. 2003; Dong et al. 2005). As such, the role of HDACs in mood disorders has become the subject of many studies; however, findings concerning the effects of chronic stress and antidepressant administration on HDAC expression are inconsistent.

One study reported that administration of chronic imipramine following chronic social defeat stress resulted in a decrease in expression of HDAC5 mRNA in the hippocampus (Tsankova et al. 2006), whereas others reported that chronic social defeat stress decreased the expressions of HDAC5 and HDAC2, and that chronic imipramine administration increased the expression of HDAC5 in the nucleus accumbens (Renthal et al. 2007; Covington et al. 2009) (Table 2). If one considers that BDNF expression moves in opposite directions in relevant brain regions in response to stress (stress increases BDNF expression in the nucleus accumbens, but decreases it in the hippocampus) (Nestler et al. 2002), the inconsistency of reported findings are understandable. Based on these data, research on the effects of antidepressants on HDAC inhibitors may offer some promising insights into the treatment of depression. It has been reported that the non-selective HDAC inhibitors sodium butyrate and suberoylanilide hydroxamic acid (SAHA), and the selective HDAC inhibitor MS-275 exerted antidepressant effects in many tests employed to evaluate depression-like behavior (Tsankova et al. 2006; Schroeder et al. 2007; Covington et al. 2009) (Table 2).

These findings suggest the presence of a common antidepressant mechanism, in which epigenetic changes involve an increase in H3 acetylation or H3-K4 methylation—in other words, an increase in gene expression may play a role in the mechanism of antidepressant actions; however, reports of an increase in H3 acetylation, and a decrease in HDAC2 and HDAC 5 expression in the nucleus accumbens of

socially defeated animals and in postmortem brains of clinically depressed humans do not support the above suggestion (Renthal et al. 2007; Covington et al. 2009). In addition, it was shown that non-selective monoamine oxidase inhibitors prevent H3-K4 methylation, which is an activating epigenetic change in cell cultures (Lee et al. 2006); therefore, rather than being a mechanism for antidepressant action, the increase in H3 acetylation may occur as a response to any chronic stimuli.

EPIGENETIC REGULATION IN SCHIZOPHRENIA

Studies that sought to identify a probable biological marker for the schizophrenia in the brains of schizophrenia patients have examined >100 markers, of which reelin and glutamic acid decarboxylase (GAD) have been investigated frequently (Impagnatiello et al. 1998; Guidotti et al. 2000; Costa et al. 2004; Torrey et al. 2005). Both proteins are expressed in cortical GABAergic neurons. Whereas GAD plays a role in GABA synthesis, reelin—an extracellular matrix protein—plays a role in long-term potentialization important for learning and memory by binding to dendrites. Low-level reelin and GAD1 mRNA are among the most common findings in the brains of schizophrenia patients (Akbarian et al. 1995; Fatemi et al. 2000; Guidotti et al. 2000; Benes et al. 2007; Benes et al. 2008; Hashimoto et al. 2008), which suggests impairment in the regulation of the GABAergic system in schizophrenia. It has also been reported that such impairment is associated with the working memory deficit observed in schizophrenia patients (for a detailed review see Lewis et al. 2005).

Epigenetic Changes Reported in The Structure of Histone in Genes That Play a Role in The GABAergic System

It has been shown that in healthy people the GABAergic system is regulated dynamically during development (Huang et al. 2007). During the development of the human prefrontal cortex, an increase in H3-K4 methylation in GAD and other GABAergic genes, neuropeptide Y, and somatostatin gene promoters was reported to begin during the prenatal period and continue until adolescence (Table 2). This increase was reported to be mediated by an HMT enzyme expressed in cortical intermediate neurons. As expected, this increase in methylation was reported to parallel the increase in mRNA expression of the involved genes. In female schizophrenia patients a decrease in H3-K4 methylation of the GAD1 gene, which was reversed by clozapine, was observed (Huang et al. 2007) (Table 2). Additional evidence of changes in histone structure in schizophrenia patients comes from postmortem brain studies that reported an increase in the HDAC1 enzyme level (Benes et al. 2007; Sharma et al. 2008) (Table 2).

Changes in DNA Methylation in Genes That Play a Role in the GABAergic System

Many studies reported an increase in DNA methylation in the promoter regions of reelin and GAD1 genes, and a decrease in expression of the involved genes, as well as changes in histone structure (Abdolmaleky et al. 2005; Grayson et al. 2005; Huang and Akbarian 2007; Costa et al. 2009) (Table 2). In addition, an increase in DNMT1 and DNMT3 in GABAergic neurons of cortical layers I, II, and IV was reported in schizophrenia patients (Veldic et al. 2004, 2005; Ruzicka et al. 2007; Costa et al. 2009; Zhubi et al. 2009) (Table 2). It was observed that administration of DNMT inhibitors to cell cultures or knockout of the DNMT1 enzyme resulted in an increase in the expression of reelin mRNA (Noh et al. 2005; Kundakovic et al. 2007). Findings indirectly suggest that this increase in DNMT enzyme accounts for elevated methylation of the reelin and GAD1 genes. On the other hand, some studies did not report any changes in reelin and GAD1 methylation (Tamura et al. 2007; Mill et al. 2008; Tochigi et al. 2008), which may be due to differences in gene regions screened or in methods used to detect methylation.

In a postmortem brain study of schizophrenia patients, screening of the entire genome showed changes in methylation levels of many genes involved in neurodevelopmental, glutamatergic, and GABAergic systems (Mill et al. 2008). The fact that administration of L-methionine (a methyl donor) to schizophrenia patients aggravates their symptoms suggests that methylation might be important in the neurobiology of the disorder (Antun et al. 1971; Cohen et al. 1974). Moreover, repeated injection of L-methionine was reported to impair prepulse inhibition in mice, enhance DNA methylation in the promoter regions of the reelin and GAD genes, and decrease mRNA expression of these genes (Tremolizzo et al. 2002; Dong et al. 2005) (Table 2).

Epigenetic Changes Reported in Genes That Play a Role in The Dopaminergic System

Epigenetic research has also focused on the dopaminergic system, but to a limited extent. Catechol-O-methyl transferase (COMT) is an enzyme involved in the metabolism of catecholamines and an increase in its expression may cause a decrease in dopamine in the frontal cortex by increasing dopamine breakdown (Abdolmaleky et al. 2006) (Table 2); however, this finding could not be replicated in other studies (Murphy et al. 2005; Dempster et al. 2006; Iwamoto and Kato 2009).

Antipsychotic Treatment Strategies Targeting Epigenetic Mechanisms

Compensation for the epigenetic changes in schizophrenia has become the aim of many drug studies. Drugs that modify

the chromatin structure hold promise for the treatment of the negative symptoms that do not respond to known antipsychotic drugs (Kirkpatrick et al. 2001). As such, HDAC inhibition, HMT or HDM inhibition, DNMT inhibition, and DNA demethylase activation were tested (Gavin and Sharma 2010). The findings of many studies suggest that HDAC inhibitors may be beneficial in the treatment of schizophrenia. Dong and et al. (2008) compared the effects of the antipsychotic drugs sulpiride and clozapine, both of which have HDAC inhibition properties, and those of antipsychotics without HDAC inhibition properties—namely haloperidol and olanzapine—in mice treated with methionine. They reported that only sulpiride and clozapine reversed the increase in methylation in the reelin and GAD promoter regions caused by methionine administration (Table 2). It was also reported that valproic acid (VPA)—a HDAC inhibitor—reverses schizophrenia-like behavioral and epigenetic changes in mice induced by methionine (Tremolizzo et al. 2002; Dong et al. 2005; Tremolizzo et al. 2005) (Table 2). VPA was observed to increase reelin and GAD mRNA levels via inhibition of the DNMT enzyme (Kundakovic et al. 2009). In addition to these effects, it was also reported that HDAC inhibitors exert their effects via inducing DNA methylase enzyme activity (Detich et al. 2003; Weaver et al. 2004; Dong et al. 2008).

EPIGENETIC REGULATION IN SUBSTANCE DEPENDENCE

It is thought that changes in gene expression in the brain's reward regions are important in the development and maintenance of substance dependence. Recent studies indicate that such gene expression is regulated—in part—by epigenetic mechanisms (Kumar et al. 2005; Levine et al. 2005; Renthal et al. 2007).

Histone Acetylation in Substance Abuse

One of the most common epigenetic changes observed in cases of substance abuse is histone acetylation. Considering that histone acetylation is an epigenetic change that activates gene expression, this may be expected to cause an increase in the expression of many genes. It was previously shown that the predominant effect of cocaine is activation of gene expression (McClung and Nestler 2003); epigenetic findings are in agreement. A recent genome-wide screening study reported an increase in H3 acetylation in 1004 genes and an increase in H4 acetylation in 692 genes following cocaine intake (Table 2). On the other hand, a decrease in H3 and H4 acetylation was reported in fewer genes (83 and 123, respectively) (Renthal et al. 2009). Another study reported that repeated cocaine administration dynamically regulated the quantity of heterochromatin in the nucleus accumbens and reduced the quantity of heterochromatin 24 h later (Maze et al. 2011).

Thus, cocaine increases the expression of many genes by decreasing condensation of the DNA-histone package.

Acute cocaine administration in animals increased H4 acetylation in the promoter regions of *c-Fos* and *FosB* (immediate early genes), and expression of these genes in the nucleus accumbens (Kumar et al. 2005) (Table 2). In addition, an increase in H3 phosphoacetylation in the nucleus accumbens and dorsal striatum was reported (Brami-Cherrier et al. 2005; Kumar et al. 2005). It is known that repeated administration of cocaine increases expression of the *BDNF* and *cyclin-dependent kinase-5* (*cdk5*) genes (Bibb et al. 2001; Grimm et al. 2003). In accord with this, chronic cocaine administration was reported to increase H3 acetylation in the promoters of both genes (Kumar et al. 2005; Renthal et al. 2009) (Table 2).

Changes in Histone Acetylation Caused by Substance Withdrawal

In patients with substance dependence craving occurs frequently and is a cause of recurrence following withdrawal of the substance, especially when exposed to environmental cues related to the substance (Drummond 2000); hence, even if abuse of the substance ceases, its impact on the brain continues. In order to determine if molecular effects last as long as behavioral effects, expression and histone acetylation of various genes were measured 1, 10, and 100 d after withdrawal of chronic cocaine administration (Freeman et al. 2008). It was reported that expression of many immediate early genes decreased both in the medial PFC and nucleus accumbens, and that among these immediate early genes, there was a decrease in H3 acetylation in early growth response gene-1 (*egr-1*) promoter. Interestingly, it was shown that the decrease in H3 acetylation in the nucleus accumbens was maintained on the 10th d of withdrawal (Freeman et al. 2008). In addition, whereas expression of some genes increases during substance use, they revert to normal during withdrawal. For example, there was an increase in H3 and H4 acetylation in the cocaine and amphetamine regulated transcript (*CART*) gene in response to repeated cocaine administration, but *CART* expression returned to control levels following discontinuation of cocaine (Freeman et al. 2008; Renthal et al. 2009).

Histone Deacetylase Inhibitors in Substance Dependence

Another target of epigenetic research on substance dependence is enzymes that change histone structure. Among HDAC inhibitors, different HDAC classes were investigated and it was reported that HDAC inhibitors enhanced the behavioral effects of cocaine and H3 phosphoacetylation (Kumar et al. 2005; Renthal et al. 2007). It was also reported that HDAC inhibition potentiated the behavioral effects of D1 receptor antagonists and amphetamine (Kalda et al. 2007;

Schroeder et al. 2008). Apart from the class I and class II HDAC inhibitors previously mentioned, it was reported that sirtuins—class III HDAC enzymes—may also play a role in substance dependence. Increased acetylation and expression of sirtuin 1 and sirtuin 2 genes in the nucleus accumbens was observed following repeated cocaine administration (Renthal et al. 2009). Interestingly, it was also reported that when sirtuin antagonists were administered the behavioral response to cocaine was amplified, indicating that the sirtuin antagonists exerted the opposite effect.

It was reported that chronic cocaine use had no effect on HDAC5 expression in the nucleus accumbens, but changed its phosphorylation (Renthal et al. 2007). Specifically chronic cocaine use was shown to increase HDAC5 phosphorylation, which in turn caused the export of HDAC5 from the nucleus to cytoplasm. This change was not observed after acute cocaine administration, which suggests that this epigenetic mechanism may contribute to the behavioral effects of chronic cocaine use. Accordingly, it was reported that increased expression of HDAC5 in the nucleus accumbens decreases the behavioral effects of cocaine, whereas knockout of the HDAC5 gene increases susceptibility to the rewarding effects of cocaine (Renthal et al. 2007).

Histone Methylation in Substance Dependence

In addition to acetylation, cocaine also affects histone methylation. It was reported that acute or chronic cocaine dynamically regulated H3-K9 methylation in opposite directions in the nucleus accumbens (Maze et al. 2010; Maze et al. 2011) (Table 2). Specifically acute cocaine administration rapidly increased H3-K9 methylation, which returned to control levels within 24 h; however, chronic cocaine administration initially caused a temporary increase in H3-K9 methylation, followed by a decrease that lasted for >1 week following withdrawal of the substance. As it is expected that a decrease in H3-K9 methylation will result in a decrease in gene expression, these findings are compatible with those reported in histone acetylation studies and it suggests that interventions that increase gene expression will increase susceptibility to substances of abuse (Renthal and Nestler 2008). It was reported that G9a—an HMT enzyme that plays a role in histone methylation—regulates the behavioral response to cocaine (Maze et al. 2010). It was reported that expression of G9a and H3-K9 methylation decreased in the nucleus accumbens after repeated cocaine administration (Table 2). Additionally, it was observed that an increase in G9a expression in the nucleus accumbens increased H3-K9 methylation, decreased expression of many genes induced by repeated cocaine administration, and reversed the behavioral and morphological changes caused by cocaine (Maze et al. 2010).

These findings suggest that at least some of the effects of long-term substance use are mediated by epigenetic mechanisms,

during both use and withdrawal of the substance; therefore, pharmacological or genetic interventions targeting these mechanisms are potential treatments for substance dependence.

CONCLUSION

Numerous studies have reported that epigenetic mechanisms mediate the effects of environmental factors and changes in gene expression, and that these changes can be inherited. It is clear that this is a very important mechanism necessary to survival and adjustment to the environment. Epigenetic research has provided important data regarding human behavior and psychiatric diseases, and complement the data provided by various psychiatry and psychology schools on behavior and psychopathology. As is the brain, the genome is dynamic and interacts with the environment. Beginning with the prenatal period, each event we experience influences our behavior, personality, and which psychological disorders we develop, and it is recognized that changes in gene expression play an important role in the effects of these experiences. Another important and exciting epigenetic finding is that alterations in gene expression are reversible. A better understanding of the epigenetic mechanisms involved in the development of diseases may guide the development of new treatment strategies for psychiatric disorders, and may even be useful for their prevention. As such, research conducted with the collaboration of psychiatrists, neuroscientists, and geneticists is required.

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