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Epigenetic signaling in psychiatric disorders: stress and depression

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Introduction

Psychiatric disorders are complex multifactorial disorders involving chronic alterations in neural circuit structure and function. While genetic factors play a role in the etiology of disorders such as depression, addiction, and schizophrenia, relatively high rates of discordance among identical twins clearly point to the importance of additional factors. Environmental factors, such as stress, play a major role in the psychiatric disorders by inducing stable changes in gene expression, neural circuit function, and ultimately behavior. Insults at the developmental stage and in adulthood appear to induce distinct maladaptations. Increasing evidence indicates that these sustained abnormalities are maintained by epigenetic modifications in specific brain regions. Indeed, transcriptional dysregulation and associated aberrant epigenetic regulation is a unifying theme in psychiatric disorders. Aspects of depression can be modeled in animals by inducing disease-like states through environmental manipulations, and these studies can provide a more general understanding of epigenetic mechanisms in psychiatric disorders. Understanding how environmental factors recruit the epigenetic machinery in animal models is providing new insights into disease mechanisms in humans.

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exposing animals to drugs of abuse. To date, most studies have focused on experimenter-administered drug exposure and it should be noted that, although many effects are recapitulated in self-administration models, clearly some mechanisms are distinct. DNA methylation, histone modifications, and noncoding RNAs have all been implicated in regulating addiction processes, and this literature has been extensively reviewed in several recent publications. 1–4 In contrast, the complex symptomatology of schizophrenia has proven more difficult to model in rodents, hindering efforts to advance the understanding of epigenetic mechanisms. However, limited data from human postmortem brains, complemented by findings from available animal models, suggest a potential role for DNA methylation of genomic targets implicated in this disorder, including glutamic acid decarboxylase 67 (GAD67) and Reelin (RELN), as well as alterations in histone acetylation. For a detailed discussion, we refer the reader to several recent reviews. 5–7 The current review focuses on the growing literature detailing modification of epigenetic regulation in the context of depression. The majority of these findings come from stress-related animal models of depression, although interesting insights in humans are starting to accumulate.

Figure 1. Epigenetic dysregulation in the HPA axis and reward circuitry is implicated in psychiatric disorders. A majority of research on altered epigenetic regulation in depression and other stress-related disorders has focused on changes within the HPA axis (A) and the brain’s reward circuitry (B), depicted here in the rodent brain. Studies examining the effects of early-life manipulations on epigenetic regulation of behavior have focused on changes within the HPA axis, in contrast to adult studies, which have concentrated on epigenetic alterations in the reward circuitry. A) Main components of the HPA axis: CRF and AVP from the paraventricular nucleus of the PVN stimulates ACTH release from the anterior pituitary, which induces glucocorticoid (cortisol [human] or corticosterone [rodent]) release from the adrenal cortex. GRs in the HPC and other brain regions mediate negative feedback to reduce the stress response. B) Depicted are the major components of the limbic-reward circuitry: dopaminergic neurons (green) project from the VTA to the NAc, PFC, AMY, and HPC, among other regions. The NAc receives excitatory glutamatergic innervation (red) from the HPC, PFC, and AMY. ACTH, adrenocorticotropic hormone; AMY, amygdala; AVP, vasopressin; CRF, corticotropin releasing factor; GRs, glucocorticoid receptors; HPA, hypothalamic-pituitary-adrenal axis; HPC, hippocampus; PFC, prefrontal cortex; PVN, hypothalamus; VTA, ventral tegmental area.
The complexity and heterogeneity of depression, as well as the ubiquity of many of the symptoms of depression, render clear identification of its etiology very difficult. Stressful life events represent a major risk factor in determining an individual’s vulnerability to depression. Animal models offer a useful approach to study these questions. The development of chronic stress paradigms, combined with the ability to objectively measure anhedonia and certain stress susceptibility symptoms in rodents, have helped clarify the neural circuitry and neuroadaptations underlying depression. Chronic stress exposure induces functional and transcriptional alterations in several limbic regions implicated in regulating stress and reward responses (Figure 1).1-12 Research, to date, has focused on relatively distinct neural circuits in exploring consequences of developmental vs adult stress. The present review brings together findings relating to epigenetic mechanisms in depression from both adult and developmental studies—in animal models and in humans—and elaborates the potential offered by epigenetic analyses to understand this complex disorder better.

**Overview of epigenetic regulatory mechanisms**

Epigenetic modes of gene regulation can be grouped into three general domains: (i) histone post-translational modifications (PTMs) and histone variant exchange; (ii) chromatin remodeling; and (iii) DNA methylation. While individually important, these mechanisms work together to orchestrate precise phenotypic outputs in mammalian cells. Also important for epigenetic control is the regulation of noncoding RNAs, which is not discussed here due to space limitations.

**Histone modifications**

The best-characterized mode of epigenetic regulation in brain is the post-translational, covalent modifications of histones.13 Histones are proteins that stably interact with DNA to form nucleosomes, which package DNA into chromatin (Figure 2). The nucleosome consists of DNA wrapped around an octamer of core histone proteins, two copies each of H3, H4, H2A, and H2B. For each of the core histones in mammals, with the exception of H4, variants exist that can exhibit significantly distinct structures, temporal regulation, and cell-type specificity from their canonical counterparts. Histone variants may also provide an alternative mechanism of encoding and transmitting epigenetic information.

Interactions between DNA and core histone proteins can be altered by covalent modifications to histone N-terminal and C-terminal tails.13 A large variety of histone PTMs have been identified, including phosphorylation, acetylation, methylation, adenosine diphosphate (ADP) ribosylation, ubiquitination, crotonylation, and small ubiquitin-like modifier (SUMO)ylation. Histone acetylation and phosphorylation decrease the affinity of histone octamers for DNA to loosen chromatin structure. This relaxed chromatin state, referred to as euchromatin, allows the transcriptional machinery, DNA binding proteins, and chromatin remodeling complexes access to genes and is often associated with active gene transcription. Methylation of lysine or arginine residues in histone tails is generally thought to be more stable than other histone PTMs, and plays roles in both transcriptional activation and repression depending on the residue being methylated. Histone methylation can also exist in multiple valence states (e.g., mono-, di-, or trimethylation), with each state associated with distinct molecular consequences. The roles of histone ADP ribosylation, ubiquitylation, crotonylation, and SUMOylation are less well understood.

The enzymes that mediate histone modifications and their reversal can be understood as “writers” and “erasers,” respectively. For example, histone acetyltransferases (HATs) catalyze acetylation and histone deacetylases (HDACs) catalyze removal (deacetylation) of this mark. Similarly, histone methyltransferases (HMTs) catalyze methylation and histone demethylases (HDMs) catalyze removal of methylation marks. Proteins that bind to specific modified residues, termed “readers,” mediate the functional consequences of histone PTMs through effecting transcriptional change. Distinct roles for histone PTMs, along with their writers, readers, and erasers, led scientists to develop what is commonly referred to as the “histone code hypothesis,” which proposes that specific histone modifications work sequentially or in combination to form a code that can be read by other proteins to effect downstream changes in gene expression.14 While it is true that certain histone PTMs are read in this way, it is becoming increasingly clear that a histone code per se does not work in isolation to direct the complex mechanisms of epigenetic regulation. Rather, this code cooperates with many oth-
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er mechanisms, such as DNA methylation and chromatin remodeling, to produce a given phenotype.

Chromatin remodeling

With or without histone PTMs, nucleosomes themselves function as physical barriers to transcription. The transcription start sites (TSS) of actively transcribed genes are commonly depleted of nucleosomes; conversely, occlusion of TSSs by nucleosomal occupancy is often associated with gene repression. The precise positions of nucleosomes along DNA are controlled by chromatin remodeling complexes, which act to insert, slide, and eject histone octamers from the chromatin template. These multi-subunit complexes regulate the expression of many transcription factors. Chromatin remodelers also regulate alternative splicing, events that occur cotranscriptionally. It is likely that interactions between remodelers and associated transcription factors, other DNA binding proteins, histone PTMs, and DNA methylation, work together to direct remodeling activity in a manner that alters nucleosome positioning to affect gene transcription. Several major families of chromatin remodeling proteins have been described in cultured cell systems and are just now being studied in nervous tissue.

DNA methylation

Historically, the most studied epigenetic modification is the direct methylation of DNA, involving the addition of a methyl group to cytosine. DNA methylation

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Figure 2. Chromatin structure and histone modifications at N-terminal histone tails. (A) The eukaryotic genome is organized by wrapping DNA around histone octamers to form the basic units of chromatin and nucleosomes, which are then further organized and compacted into higher ordered structures. (B) The histone octamer consists of two copies each of H2A, H2B, H3, and H4. In addition to globular domains, they each have N-terminal tails that protrude from the nucleosome, while H2A also has a C-terminal tail that displays similar regulatory features. These tails can be post-translationally modified, and all known mammalian acetylation and methylation modifications on lysine residues on each tail are highlighted. The molecules are drawn roughly to proportion to the size of the protein, although the number of residues shown is not meant to reflect the exact size of the N-terminal tails.

Adapted from ref 105: Sun H, Kennedy PJ, Nestler EJ. Epigenetics of the depressed brain: role of histone acetylation and methylation. Neuropsychopharmacology. 2013;38:124-137. © 2013, American College of Neuropsychopharmacology
is classically regarded as a highly stable epigenetic mark and can be maintained throughout the lifetime of an organism. DNA methyltransferase (DNMTs) catalyzes DNA methylation and occurs most commonly at CpG dinucleotides. DNA methylation generally exerts a repressive effect on gene transcription, as exemplified by the X chromosome inactivation in females and genomic imprinting, where hypermethylation of one parental allele for a given gene results in monoallelic expression. There are instances, however, in which DNA methylation may promote gene expression. One mechanism through which DNA methylation inhibits gene expression is through the masking of DNA sequences to prevent their recognition by activating transcription factors. Additionally, methylated DNA is recognized by methyl-CpG-binding domain (MBD) proteins, such as MECP2 (protein-coding) and MBD1, whose binding can further recruit histone modifying enzymes and chromatin-remodeling complexes to compact nucleosomes and inhibit gene expression. DNA methylation has also been associated with alternative splicing although the mechanisms are still unclear.

Recently, additional DNA modifications have been discovered, including 5-hydroxymethylcytosine (5-hmC), 5-formylcytosine, and 5-carboxylcytosine. These chemical modifications are thought to be derived from 5-methylcytosine through oxidation steps catalyzed by members of the ten-eleven translocation (TET) enzyme family, potentially representing a process of active DNA demethylation. DNA methylation in the brain may be more dynamic than in other tissues. Support for this idea comes from the discovery that: (i) the de novo DNA methyltransferase, DNMT3a, is the main DNMT expressed in neurons; (ii) the highest levels of oxidized forms of methylcytosine are found in the brain; and (iii) active DNA repair results in demethylated DNA in nondividing neurons. There is also evidence that the primary effect of 5-hmC is to promote gene expression through mechanisms that remain poorly understood.

Epigenetics and depression: studies in adulthood

Our understanding of the role of epigenetics in adult depression comes primarily from animal models. While acute stress paradigms are designed to evaluate an animal’s initial coping response, chronic stress paradigms involve prolonged exposure to either physical or psychological stressors, such as social subordination. Such chronic stress paradigms recapitulate certain behavioral features of human depression. Chronic stress produces anhedonia-like symptoms, characterized by a decrease in reward-related behaviors such as reduced preference for sucrose and social interaction that are rarely seen following acute stress. Additionally, certain behavioral alterations induced by chronic stress are long-lasting and can be effectively reversed by chronic, but not acute, treatment with existing antidepressant medications, a treatment course comparable with that required in humans. Together, these findings suggest that chronic stress paradigms are more effective at modeling at least certain features or subtypes of the human depression syndrome, while acute studies may provide insight into neuronal adaptations that regulate short-lived responses to stressful events.

Histone modifications

As mentioned above, modifications of histone tails widely affect gene expression and stress is believed to interfere profoundly with this process. While these effects are not perfectly understood, ongoing research is providing important insights into the role that these marks may have in the pathophysiology of depression (Table I).

Histone acetylation

The potential importance of histone acetylation in depression was initially suggested by observations that HDAC inhibition alone, or in combination with, antidepressant treatment ameliorated depression-like behaviors in rodents. In mice, chronic social defeat stress (CSDS) induces genome-wide reprogramming of transcriptional profiles. These changes associate with a transient decrease in H3K14 acetylation in the nucleus accumbens (NAc) and with a persistent reduction in HDAC2; both findings are also seen in the NAc of depressed humans. Interestingly, fluoxetine treatment, intra-NAc infusion of a class I HDAC inhibitor, or overexpression of an Hdac2 dominant-negative mutant yields antidepressant-like effects, suggesting that the persistent increase in histone acetylation in the NAc may facilitate adaptation to chronic stress. However, expression of the class II HDAC, Hdac5, is decreased...
in the NAc of mice susceptible to CSDS and increased by chronic imipramine treatment, and Hdac5 knockout mice are more susceptible to CSDS. In view of these opposing effects, it is likely that HDAC2 and HDAC5 regulate distinct populations of genes and, based on HDAC5’s shuttling between the cytoplasm and nucleus, HDAC5 could also regulate nonhistone targets.

Chronic stress paradigms also robustly regulate histone acetylation in the hippocampus (HPC), a brain region implicated in the regulation of stress responses. In contrast to effects in the NAc, CSDS transiently increases, then persistently decreases, global H3K14 acetylation; effects that are reversed by chronic imipramine. As well, imipramine induction of brain-derived neurotrophic factor (BDNF) in the HPC is associated with increased H3 acetylation at Bdnf promoters. However, the fact that intra-HPC HDAC inhibition does not restore social interaction in defeated mice suggests that

| Epigenetic mark                  | Age of stress | Brain region/direction | Specific genes regulated | References |
|----------------------------------|---------------|------------------------|--------------------------|------------|
| H2BAc (general)                  | Adult         | HPC                    |                          | 34         |
| H3Ac (general)                   | Postnatal     | HPC, PFC               | ↑                        | 69         |
|                                  | Adult         | PFC                    | ↑                        | 24, 39     |
|                                  | Adult         | HPC, AMY               | ↓                        | 34, 38     |
| H3K9Ac                           | Postnatal     | HPC                    | ↓                        | 32, 37     |
| H3K14Ac (general)                | Adult         | AMY                    | ↑                        | 36         |
|                                  | Adult         | HPC (transiently)      | ↑                        | 33         |
|                                  | Adult         | HPC (chronic)          | ↓                        | 25         |
| H3K18Ac (general)                | Adult         | PFC                    | ↑                        | 40         |
| H4Ac (general)                   | Postnatal     | HPC                    | ↑                        | 69         |
| H4K12Ac (general)                | Postnatal     | forebrain              | ↑                        | 67         |
| Hdac 1, 3, 7, 8, 10 (general)    | Postnatal     | forebrain, HPC         | ↓                        | 67, 68     |
| Hdac2 (general)                  | Adult         | NAc                    | ↓                        | 25         |
| Hdac3 (general)                  | Adult         | HPC                    | ↑                        | 34         |
| Hdac5 (general)                  | Adult         | NAc, AMY               | ↓                        | 32, 37     |
|                                  | Adult         | NAc, with imipramine   | ↑                        | 24         |
| CEBP Binding protein (general)   | Adult         | HPC                    | ↓                        | 34         |
| H3K4me3                          | Adult         | PFC                    | ↑                        | 47, 48     |
| H3K9me1 (general)                | Adult         | HPC                    | ↓                        | 44         |
| H3K9me2                          | Adult         | NAc                    | ↓                        | 33         |
|                                  | Adult         | NAc, with fluoxetine   | ↑                        | 41         |
| H3K9me3 (general)                | Adult         | HPC                    | ↑                        | 44, 45     |
| G9a (general)                    | Adult         | NAc                    | ↓                        | 33         |
| H3K27me3                         | Adult         | NAc, HPC               | ↑                        | 43, 44     |
|                                  | Adult         | PFC                    | ↑                        | 49, 50     |
|                                  | Adult         | PFC (with treatment)   | ↓                        | 52         |

Table 1. Effect of stress on histone post-translational modifications and gene expression. Stress at different ages alters histone modifications within different brain regions, as well as proteins and enzymes responsible for these marks. General: global changes in total cellular levels of these marks. Green indicates increases associated with stress and blue indicates decreases with stress.
other mechanisms may be involved, most likely histone methylation. In addition, whereas Hdac5 expression in the NAc is antidepressant, in the HPC, Hdac5 is downregulated by imipramine in defeated mice and HPC overexpression of Hdac5 blocks the antidepressant actions of imipramine. These findings underscore the region-specific influence of epigenetic proteins on complex behavior. In a genetic rat model of stress susceptibility, high responders (HR), which exhibit basal reductions in anxiety and increased sucrose preference relative to low responders (LR), have increased cAMP response element-binding protein (a type of HAT), lower HDAC3, and higher global H3 and H2B acetylation levels in the HPC.34 However, HR rats are behaviorally more susceptible to CSDS than LR rats and, after CSDS, HR rats have decreased the global H3 and H2B acetylation in the HPC. In contrast, LR rats have increased H3 acetylation, suggesting that dynamic regulation of H3 acetylation in the HPC regulates depression-like behavior. Repeated electroconvulsive seizures (ECS) are robustly antidepressant, and regulate H3 and H4 acetylation at the Bdnf, c-Fos, and Creb promoters in a time-dependent manner that correlates with gene expression changes. Downregulation of c-Fos was linked to reduced H4 acetylation, whereas sustained induction of Bdnf was linked to increased H3 acetylation.35 Potentially, H3 and H4 acetylation differentially modulates depression-like states in the HPC, further highlighting the complexity of histone mechanisms in depression. H3K14 acetylation is transiently increased in the amygdala after CSDS.36 Intra-amygdala HDAC inhibition reverses social avoidance, but not sucrose-preference deficits, suggesting that histone acetylation in the amygdala and the HPC may regulate different aspects of depression-like behavior. Chronic unpredictable stress in rats reduced Hdac5 expression in the amygdala37 and acute, but not chronic, defeat transiently decreased amygdala H3 acetylation.38 Data on the role of histone acetylation in depression in the prefrontal cortex (PFC) is limited. Although some studies report no global change in acetylation levels,36,38 conflicting reports suggest that CSDS increases global H3 acetylation in the PFC.39 A recent study found that rats less resilient to CSDS had increased levels of H3K18 acetylation in the PFC.40 At this point, the lack of data documenting effects of manipulating histone acetylation in the amygdala and PFC prohibits a clearer understanding of the importance of potential stress-induced acetylation changes in these brain regions.

Histone methylation

CSDS robustly decreases global levels of the repressive H3K9me2 in the NAc, with the coincident down-regulation of the histone methyltransferases G9a and G9a-like protein.33 Overexpression of G9a in the NAc is antidepressant33 and increased H3K9me2 at specific gene promoters is implicated in the antidepressant effect of fluoxetine.41 Indeed, chronic exposure to fluoxetine reduces Camkii expression by reducing H3 acetylation and increasing H3K9me2 levels at the Camkii promoter in the NAc. Interestingly, similar effects are found in the NAc of depressed humans exposed to antidepressants, suggesting that the stress-induced loss of repressive methylation is maladaptive and that therapeutic effects of antidepressant drugs may act via the reinstatement of these marks at specific gene loci. The decreases in H3K9me2 in the NAc would be expected to mediate a more permissive transcriptional state similar to the effect of the global increases in H3 acetylation. However, manipulations that decrease repressive methylation induce susceptibility, whereas manipulations that increase acetylation induce resilience. Genome-wide promoter microarrays revealed dynamic changes in H3K9me2 and H3K27me2 levels in the NAc after CSDS or protracted social isolation, with more genes evidencing increased H3 methylation. Interestingly, approximately 20% of genes were similarly regulated in both stress models.42 This opposes the finding of reduced global levels of H3K9me2 in the NAc of susceptible mice.33 Another repressive histone mark, H3K27me3, is increased upstream of the Rac1 gene promoter in the NAc of susceptible mice and this is associated with a sustained reduction in transcript expression that influences characteristic dendritic spine changes in defeated mice.43 These findings are corroborated in humans as H3K27me3 levels are inversely correlated with Rac1 expression, which is also decreased in the NAc of depression patients.44 Stress regulates histone methylation in the HPC in a complex, time-dependent manner, potentially reflecting different processes of initial stress adaptation subsiding into eventual maladaptations with sustained stress.44 For instance, acute stress increases global H3K27me3 and H3K9me3 levels, but decreases H3K9me1, effects
that return to basal levels with chronic stress. In addition, subchronic and chronic stress has opposing effects on global H3K4me3 levels, which can be reversed by antidepressant treatment. Acute stress also increases H3K9me3 levels at transposable elements, which may be important in limiting potential genomic instability. Whole forebrain overexpression of Setdb1, a histone methyltransferase that catalyzes H3K9me3, reduced depression-like behavior, suggesting that the increase in H3K9me3 seen after acute stress may represent an adaptive response. However, experimental manipulations of such modifications are needed to interpret the functional consequences of these adaptations.

Aside from the few examples cited above, human postmortem studies examining histone modifications in depression are sparse. Elevated H3K4me3 levels were reported in the synapsin gene family, which was associated with higher expression of SYNAPSIN 2 in the PFC from depression, but not bipolar disorder cases, suggesting that these changes may be specific to major depression. Similarly, higher levels of H3K4me3 in the polyamine gene OAZ were associated with higher expression in the PFC of suicide completers. Decreased expression of the tyrosine receptor kinase B (TRKB), the receptor for BDNF in the PFC of depressed cases is also associated with an enrichment of H3K27me3 levels in the promoter of both TRKB and its astrocytic variant, TRKB.T1. The elevated H3K27me3 levels are associated with changes in DNA methylation in the gene promoter, suggesting the presence of dual epigenetic control over TRKB.T1 expression. In addition, mice overexpressing TRKB.T1 are more susceptible to CSDS, which raises the possibility that epigenetic changes at the TRKB.T1 promoter could define vulnerability to chronic stress and the development of depression. Human postmortem studies also suggest that antidepressants promote open chromatin by decreasing H3K27me3 levels at BDNF promoters in the PFC of a depression sample, an effect supported by follow-up studies in peripheral blood revealing an inverse correlation between H3K27me3 levels and both BDNF IV expression levels and symptom severity.

DNA methylation

A growing body of evidence supports a role for DNA methylation in mediating the impact of stress. Several of these alterations have been described in different animal models and more recently in human brains (Table II).

CSDS increases transcript levels of Dnmt3a in the NAc. Overexpressing Dnmt3a in NAc increases depression-like behavior after submaximal social defeat and intra-NAc infusion of a DNMT inhibitor, RG108, reverses defeat-induced social avoidance. DNMT3a activity is generally associated with transcriptional repression, suggesting that susceptibility may be associated with downregulation of transcriptional expression in the NAc. Genome-wide analysis of DNA methylation will be important in establishing the precise mechanisms of this epigenetic modification in defeat-induced susceptibility. DNA methylation in NAc may play a role in regulating Gdnf (glial cell-derived neurotrophic factor). Chronic mild stress induces depression-like behavior and increases Gdnf expression in the NAc of a stress-sensitive mouse line (BALB/C), but increases Gdnf expression in a more resilient line (C57BL/6). Although DNA methylation was increased at the Gdnf promoter in the NAc of both mouse lines, MECP2 was reported to complex with different proteins in the two lines and to thereby repress vs facilitate transcription. The authors suggest that these differences are mediated by differing patterns of methylation at the Gdnf promoter, although more work is required to confirm this speculation and elucidate the underlying mechanisms involved.

DNA methylation is implicated in the regulation of corticotropin-releasing factor (CRF) in the paraventricular nucleus of the hypothalamus (PVN) (see Figure 1A). CRF is a critical regulator of the HPA-axis activation and other stress actions in the brain. CRF is increased in the PVN of mice that are susceptible to social defeat and this is accompanied by decreased DNA methylation at the Crf promoter. Both effects are reversed by chronic imipramine treatment. DNA methylation is also increased at the Crf promoter in the PVN of female rats subjected to chronic mild stress, suggesting that DNA methylation may play a role in determining sex-specific regulation of the HPA-axis function. Knockout of MeCP2 in PVN results in an exaggerated physiological stress response, however, the precise mechanism of MeCP2 action remains to be fully elucidated.

The studies elaborated above highlight epigenetic modifications targeted toward specific genes frequently associated with behavioral alterations. However, it...
is clear that stress effects are not restricted to a subset of candidate genes. Genome-wide studies mapping DNA methylation alterations induced by stress are lacking in animals. A series of recent genome-wide studies address this issue in humans in the context of early-life adversity, as discussed below. Furthermore, analysis of the PFC of psychotic and bipolar cases reported numerous sites of differential methylation that were enriched in various functions such as glutamatergic and GABAergic neurotransmission, brain development, and response to stress.\textsuperscript{57} Importantly, these studies compared different tissues (blood vs brain) and brain regions (HPC vs PFC) and globally suggest that stress-induced epigenetic adaptations are region specific and cell-type specific, which is consistent with the emerging principle of epigenetic heterogeneity across tissues\textsuperscript{58} and cell types\textsuperscript{59,60}.

### Epigenetics and depression: development vulnerability

It is well established that adults who experienced childhood stress or maltreatment are at a significantly greater lifetime risk for a range of mood or other disorders.\textsuperscript{61-64} Early-life adversity is modeled in animals using maternal separation (MS) or maternal deprivation, and this leads to changes in DNA methylation in the hypothalamus and other brain regions.\textsuperscript{65-68}

| Gene          | Gene region | Age of stress | Brain region or tissue/direction | References |
|---------------|-------------|---------------|----------------------------------|------------|
| Sert (Slc6a4) | promoter    | prenatal      | hypothalamus                     | ↓          | 84         |
| Crf           | promoter    | prenatal      | PVN (males)                      | ↓          | 55         |
| Crf           | promoter    | adult         | PVN (females)                    | ↑          | 37         |
| Hsd11b2       | promoter/exon| prenatal      | hypothalamus                     | ↓          | 75         |
| Gr (Nr3c1)    | exon 1      | prenatal      | hypothalamus                     | ↑          | 80         |
| Gr (Nr3c1)    | exon 1      | prenatal      | infant cord blood                | ↑          | 81-83      |
| Grm1          | promoter    | postnatal     | HPC                              | ↑          | 70         |
| Gad1          | promoter    | postnatal     | HPC                              | ↑          | 72         |
| Esr1          | promoter/exon| postnatal     | hypothalamus                     | ↑          | 87         |
| Avp           | enhancer    | postnatal     | PVN                              | ↓          | 99         |
| Bdnf          | exon IX promoter | postnatal | PFC                              | ↓          | 103, 104  |
| Th            | promoter    | adolescent    | VTA                              | ↑          | 100        |
| Gdnf          | promoter    | adult         | NAc                              | ↑          | 31         |

Table II. Effect of stress on DNA methylation and gene expression. Stress at different ages alters DNA methylation at specific genes within different brain regions, as well as proteins and enzymes related to DNA methylation. Green indicates increases associated with stress and blue indicates decreases with stress.
tion. Natural variations in maternal care—maternal licking and grooming (LG)—likewise associate with differential stress responses among adult offspring. Research in the last decade suggests that epigenetic mechanisms partly mediate these effects by altering the expression of key genes in response to subsequent environmental perturbations, thereby enhancing vulnerability to psychiatric disorders. This section describes epigenetic alterations resulting from developmental (in utero, early postnatal, and periadolescent) exposures to stress, with distinct consequences for depression and related disorders.

**Histone modifications**

Very little is known about the prenatal effects of stress on histone modifications. Treatment with the nonspecific HDAC inhibitor valproic acid, which has many additional pharmacological actions, after prenatal stress was shown to ameliorate several behavioral measures, although more work is needed to elucidate the mechanisms responsible for these effects. More is known concerning the consequences of postnatal adversity in the form of maternal separation. In stress-susceptible BALB/C mice, MS reduces levels of Hdac1, -3, -7, -8, and -10 in the forebrain in adulthood, and increases acetylation of histone H4. Adult male rats that underwent maternal separation had reduced levels of Hdac1 mRNA, consistent with the elevated H3 and H4 acetylation levels reported in the HPC of juvenile mice after maternal separation. Adolescent fluoxetine treatment potentiated effects of maternal separation, but coadministration of fluoxetine with an HDAC inhibitor ameliorated the effects of maternal separation. These findings suggest that adolescence may be a relevant period for pharmacological intervention and that it may be possible to erase at least some of the damaging epigenetic signature of early-life stress. Similarly, low maternal LG is associated with decreased HPC H3K9 acetylation at the glucocorticoid receptor (Gr) exon 1, promoter. These modifications are associated with the expression of depressive-like symptoms, reduced gene expression, and changes in DNA methylation spanning large regions of the genome. Treatment with the nonselective HDAC inhibitor trichostatin A, infused either intracerebroventricularly (ICV) or intrahippocampus, reversed both the molecular and behavioral effects of low maternal care.

**DNA methylation**

*Prenatal stress*

Under normal conditions, the developing fetus is largely protected from maternal glucocorticoids by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which converts active glucocorticoids to their inactive form. However, 10% to 20% of maternal cortisol is estimated to pass through the placenta to the fetus. Evidence suggests that maternal stress during pregnancy induces a hypermethylation of Hsd11b2 in the placenta and hypomethylation in the fetal hypothalamus that may consequently interfere with 11β-HSD2 enzymatic activity and induce heightened stress responses among offspring.

Exposure to early prenatal stress is also associated with persistent changes in DNA methylation in the brains of adult mice. Within the hypothalamus, early prenatal stress increases DNA methylation in Gr noncoding exon 1, and decreases DNA methylation in the Crf promoter. In humans, hypermethylation in the GR promoter 1r was likewise found in infant cord blood from mothers who experienced depression during the third trimester of pregnancy and from mothers reporting intimate partner violence during their pregnancy. These effects were not reversed by antidepressant treatment. Altered DNA methylation at the serotonin transporter (SERT, SLC6A4) in offspring cord blood is likewise associated with prenatal maternal depression. However, a recent study found no association between maternal depression and altered DNA methylation with modest methylation differences in two genes (TNFRSF21 and CHRNA2) associated with maternal antidepressant use. Further, methylated CpGs were found in the promoter regions of Dnmt3a and Dnmt1 in the PFC and HPC at birth, changes that persisted at postnatal day 7, 14, and 60. Furthermore, prenatal stress increased binding of DNMT1 and MECP2, along with increased 5-methylcytosine and 5-hydroxymethylcytosine, within the Reelin and Gad67 promoters.

Thus, existing evidence points to a role of prenatal stress in altering adult vulnerability to depression, in part...
via changes in DNA methylation. These alterations occur in specific genes and in specific brain regions, highlighting the difficulty in using peripheral tissues to predict functionally relevant changes within the brain. Genome-wide analyses should facilitate comparisons of potential epigenetic biomarkers in peripheral tissues with epigenetic and gene expression changes in specific brain regions. Even if changes that occur in the periphery are different from those in brain, it is conceivable that specific peripheral changes might predict central regulation; this is ultimately an empirical question. In addition, the inconsistencies reported among studies reflect the need for more precise tools to manipulate epigenetic gene regulation in functional preclinical studies.

**Postnatal stress**

Postnatal experience, particularly variations in the level and quality of maternal care, alters DNA methylation levels in genes thought to be critically involved in behavioral stress responses. For instance, the offspring of low-LG mothers, compared with those reared by high-LG mothers, exhibit robust DNA methylation changes that colocalized with chromatin modifications.\(^86,87\) This coincides with lower HPC expression of several variants of Gr, including the HPC specific variant 17.\(^28,71\) These alterations preferentially affect promoters, as evidenced in the cluster of protocadherin genes, and follow a nonrandom, discontinuous pattern across large genomic regions.\(^86\) However, it is still unclear how both DNA methylation and chromatin conformation are coregulated in the context of stress. Similar alterations have been reported in the HPC of suicide completers with a history of child abuse. Individuals with a history of abuse who committed suicide exhibit lower expression levels of the 1\(_p\), 1\(_m\), and 1\(_p\) variants of Gr compared with nonabused suicides and controls.\(^80,85\) These changes coincide with altered DNA methylation within respective promoters that may interfere with transcription factor binding. Furthermore, similar alterations within Gr positively correlate with different features of child abuse in individuals with major depressive disorders.\(^90,91\) Importantly, these alterations appear to be specific to early-life adversity, as negative findings have been reported in the brains of depressed patients with no history of child abuse.\(^92\)

Low maternal care in rats also reduces Gad1 and Grml1 expression in the HPC.\(^70,72\) These expression changes are accompanied by promoter hypermethylation and lower levels of H3K9Ac compared with pups raised by high-LG dams. As these findings have been associated with elevated levels of Dnmt1, it is believed that this hypermethylated state originates from the overactivity of different DNMTs. Indeed, human studies in schizophrenia and bipolar disorder reported correlations between promoter hypermethylation and lower expression of Reelin and GAD1 genes\(^93-97\) that are associated with altered levels of all three DNMTs (DNMT1, 3A, and 3B).\(^98\)

Exposure to early life stress likewise alters epigenetic gene regulation within the HPA axis and reward circuitry (Figure 1). Early maternal separation is associated with Avp overexpression and hypomethylation of an Avp enhancer region (rather than promoter) in the PVN of mice 6 weeks, 3 months, and 1 year after stress.\(^99\) Interestingly, gene expression, but not enhancer methylation changes were found within 10 days of stress, suggesting a dual regulatory mode depending on the timing of stress and highlighting the importance of investigating mechanisms beyond the traditional promoter-centric focus.

Stress also alters epigenetic marks beyond the early neonatal period. Three weeks of adolescent isolation induced depressive-like behaviors accompanied by a sustained (12 weeks) hypermethylation of the tyrosine hydroxylase (Th) gene promoter in the VTA of a Disc1 mutant mouse.\(^100\) Promoter hypermethylation was associated with both Disc1 mutations and adolescent isolation, and these effects were additive, although only in specific cell populations.\(^100\) Importantly, these changes were rescued by treatment with a GR antagonist, suggesting that GR-mediation of the stress response in this chronic adolescent stress paradigm underlies stress-induced alterations in the mesocortical reward pathway.\(^101\) DNA methylation is also altered by extreme childhood adversity in the form of abuse. Recently, hundreds of differentially methylated sites were identified in the HPC of suicide completers with a history of abuse (childhood sexual or physical) compared with healthy controls.\(^101\) Interestingly, DNA methylation levels in gene promoters were inversely correlated with gene expression at a genome-wide level, supporting the globally repressive role of DNA methylation at promoters, as reported by other groups.\(^57,102\) The impact of abuse becomes obvious when assessing the gene functions enriched with differential methylation: differential
methylation in the abused suicide group is enriched in genes related to cellular plasticity, while learning and memory genes were particularly affected in suicide. This suggests that among depressed suicide completers, intense early-life adversity might induce distinct long-lasting epigenetic alterations. Importantly, the changes in DNA methylation levels reported in these studies occurred in specific cell types as most of the methylation changes were found exclusively in neuronal DNA. Rodent studies have likewise found DNA methylation alterations subsequent to maternal abuse (tramping, dragging, rough treatment). Rat maternal maltreatment decreases expression of Bdnf transcripts III and IV in the HPC and PFC and is associated with chronic hypomethylation at the Bdnf exon IX gene promoter in the PFC.103,104 These effects were at least partially rescued by ICV treatment for 7 days with zebularine, a DNA methylation inhibitor.

These studies suggest that the experience of stress, whether during early-life or adulthood, has profound, genome-wide epigenetic consequences in the brain and peripheral tissues. Modifications of DNA methylation signatures in different regions of the brain are a plausible mechanism to explain how stress can induce enduring behavioral alterations. Peripheral tissues may provide biomarkers of stress exposure and vulnerability, although this remains to be determined. Future studies should investigate correlated regulation of genome-wide DNA methylation between blood and brain and across numerous brain regions in animal models to facilitate interpretation of peripheral-based assays in humans.

Limitations, future directions, and concluding remarks

A wealth of data from animal models and evolving evidence from postmortem human samples has established the important role of diverse epigenetic regulatory mechanisms in mediating the transcriptional abnormalities that contribute importantly to depression. However, as our understanding of epigenetic mechanisms improves, several new questions emerge. Understanding how diverse epigenetic mechanisms, including histone modifications, DNA methylation, and noncoding RNAs, interact to ultimately orchestrate the characteristic abnormalities in gene expression is critical. There is an urgent demand for increased specificity in studies attempting to understand the interplay of developmental stress, epigenetics, and adult neuropsychiatric disorders. It is also imperative that the field move beyond the study of individual candidate genes and make far greater use of genome-wide determinations of stress- and depression-associated epigenetic abnormalities. Indeed, recent efforts have begun to generate significant data sets profiling genome-wide alterations in DNA methylation and other epigenetic patterns after stress. The current challenge is to refine these analyses to understand how epigenetic regulation of multiple genes and gene networks in specific brain regions relate to depression-related outcomes, first in animal models and ultimately in the human brain.

Although existing studies document how early developmental stress leads to life-long changes in gene expression and behavior, to understand these altered trajectories fully, it will be important to profile the epigenetic landscape across development. For instance, certain epigenetic modifications could conceivably be altered proximal to the time of stress, whereas other epigenetic modifications may incubate over time, but may be more stably maintained. A more precise understanding of such temporal dynamics obtained from genome-wide studies will facilitate attempts to identify critical windows for therapeutic intervention.

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Señales epigenéticas en los trastornos psiquiátricos: estrés y depresión

Los trastornos psiquiátricos son complejas enfermedades multifactoriales que incluyen alteraciones crónicas en la estructura y función de los circuitos neurales. Aunque los factores genéticos juegan un papel en la etiología de trastornos como la depresión, las adicciones y la esquizofrenia, las frecuencias relativamente altas de discordancia entre gemelos idénticos apuntan claramente a la importancia de otros factores. Los factores ambientales, como el estrés, juegan un importante papel en los trastornos psiquiátricos al inducir cambios estables en la expresión génica, en la función de los circuitos neurales y finalmente en la conducta. Lesiones en la etapa del desarrollo y en la adultez parece que inducen distintas malas adaptaciones. Hay creciente evidencia que indica que estas Persistentes anormalidades se mantienen por modificaciones epigenéticas en regiones cerebrales específicas. Ciertamente, la falta de regulación en la transcripción y la regulación epigenética aberrante asociada son temas comunes en los trastornos psiquiátricos. Algunos aspectos de la depresión se pueden modelar en animales al inducir estados que simulan la enfermedad mediante manipulaciones ambientales; y estos estudios pueden aportar una comprensión más general de los mecanismos epigenéticos en los trastornos psiquiátricos. La comprensión de cómo los factores ambientales reclutan la maquinaria epigenética en los modelos animales está aportando nuevas perspectivas en los mecanismos del enfermar en humanos.

Signalisation épigénétique dans les troubles psychiatriques : stress et dépression

Les troubles psychiatriques sont complexes et multifactoriels et ils sont associés à des modifications chroniques dans la structure et la fonction des circuits neuronaux. Les facteurs génétiques jouent un rôle dans l’étiologie des troubles comme la dépression, l’addiction et la schizophrénie, mais des taux relativement élevés de discordance parmi les vrais jumeaux indiquent clairement l’importance de facteurs supplémentaires. Des facteurs environnementaux, comme le stress, jouent un rôle majeur dans les troubles psychiatriques en provoquant des modifications stables de l’expression des gènes, de la fonction des circuits neuronaux et enfin du comportement. Des lésions au cours du développement ou à l’âge adulte peuvent entrainer des inadaptations particulières. Selon des données de plus en plus nombreuses, ces anomalies prolongées sont maintenues par des modifications épigénétiques dans des régions cérébrales spécifiques. En effet, la dysrégulation transcriptionnelle et la régulation épigénétique aberrante associée sont un thème commun des troubles psychiatriques. Certains aspects de la depression peuvent être modelés chez les animaux en induisant des états mimant la maladie grâce à des manipulations environnementales. Ces études permettent une compréhension plus générale des mécanismes épigénétiques dans les troubles psychiatriques. Connaître la façon dont les facteurs environnementaux recrutent la machinerie épigénétique dans les modèles animaux apporte une nouvelle perspective des mécanismes pathologiques chez l’homme.

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