



The Molecular Basis of Depression: Implications of Sex-Related Differences in Epigenetic Regulation

Ayako Kawatake-Kuno¹, Toshiya Murai^{1,2} and Shusaku Uchida^{1*}

¹SK Project, Medical Innovation Center, Kyoto University Graduate School of Medicine, Kyoto, Japan, ²Department of Psychiatry, Kyoto University Graduate School of Medicine, Kyoto, Japan

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*Correspondence:

Shusaku Uchida
Uchida.shusaku.3n@kyoto-u.ac.jp

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Major depressive disorder (MDD) is a leading cause of disability worldwide. Although the etiology and pathophysiology of MDD remain poorly understood, aberrant neuroplasticity mediated by the epigenetic dysregulation of gene expression within the brain, which may occur due to genetic and environmental factors, may increase the risk of this disorder. Evidence has also been reported for sex-related differences in the pathophysiology of MDD, with female patients showing a greater severity of symptoms, higher degree of functional impairment, and more atypical depressive symptoms. Males and females also differ in their responsiveness to antidepressants. These clinical findings suggest that sex-dependent molecular and neural mechanisms may underlie the development of depression and the actions of antidepressant medications. This review discusses recent advances regarding the role of epigenetics in stress and depression. The first section presents a brief introduction of the basic mechanisms of epigenetic regulation, including histone modifications, DNA methylation, and non-coding RNAs. The second section reviews their contributions to neural plasticity, the risk of depression, and resilience against depression, with a particular focus on epigenetic modulators that have causal relationships with stress and depression in both clinical and animal studies. The third section highlights studies exploring sex-dependent epigenetic alterations associated with susceptibility to stress and depression. Finally, we discuss future directions to understand the etiology and pathophysiology of MDD, which would contribute to optimized and personalized therapy.

Keywords: epigenetics, stress, depression, resilience, sex differences, neural plasticity

INTRODUCTION

Depression is a heterogeneous and multifactorial disorder with a very high prevalence worldwide and is the single most important risk factor for suicide (Turecki, 2014). A meta-analysis of a large body of genetic epidemiological studies indicated that the heritability of major depressive disorder (MDD) is between 31% and 42%, which is relatively low compared to that of schizophrenia and bipolar disorder (approximately 80% and 85%,

respectively). This suggests that factors other than genetic factors also contribute to the risk of depression. Indeed, human genome-wide association studies (GWAS) have largely failed to produce reproducible gene loci that contribute significantly to MDD. Although a recent GWAS identified more than 100 independent loci that are significantly associated with depression, many of which are related to synaptic structure and function (Howard et al., 2019; Ormel et al., 2019), such studies only indicate associations between genetic loci and traits and do not provide insight into causal links to underlying biological mechanisms. Moreover, the effect sizes of individual genetic variants are very small (Ormel et al., 2019). While genetic factors are important, environmental factors, such as stress, are also known to contribute to the etiology of this complex psychiatric disorder (Russo et al., 2012; Southwick and Charney, 2012). As stressful life events are known to be associated with a high risk of MDD (Hammen, 2005), the current working hypothesis is that highly complex genetic differences and environmental factors work together to determine resilience and susceptibility to MDD (Russo et al., 2012; Sun et al., 2013; Nestler, 2014; Uchida et al., 2018; **Figure 1**).

There is accumulating evidence for macroscopic and microscopic brain alteration in patients with MDD. Large numbers of postmortem and neuroimaging studies have reported reductions in gray matter volume and glial density in the prefrontal cortex (PFC) and the hippocampus of MDD patients, which are related to the cognitive and emotional aspects of depression, including feelings of worthlessness and guilt (Drevets, 2001; Harrison, 2002). In addition, functional neuroimaging studies using functional magnetic resonance imaging (fMRI) or positron-emission tomography (PET) demonstrate chronic increases in the activity within the amygdala and subgenual cingulate cortex (Cg25, a subregion of the PFC) in depressed individuals (Mayberg et al., 1999; Drevets, 2001; Furmark et al., 2002; Siegle et al., 2006). An electron microscopy study demonstrated reduced numbers of dendritic spines within the dorsolateral PFC of patients with MDD (Kang et al., 2012). Preclinical studies also suggested that environmental factors, such as stress, have adverse effects on the structural and functional plasticity of the nervous system (Flavell and Greenberg, 2008; Greer and Greenberg, 2008; Maze et al., 2013). For example, chronic stress was shown to induce shrinkage of dendrites of hippocampal CA3 and dentate gyrus neurons as well as loss of spines in CA1 neurons (McEwen, 1999). Other studies indicated reductions in dendritic spine density in the hippocampus and prefrontal cortex in animal models of depression (Abe-Higuchi et al., 2016; Higuchi et al., 2016; Nie et al., 2018; Moda-Sava et al., 2019). These preclinical studies together with human studies suggest that dysregulation of neuronal plasticity caused by chronic stressful life events may contribute to the pathophysiology of MDD.

Exposure to stressful environments has been shown to play a significant role in sustained alterations in gene expression (Tsankova et al., 2007; Nestler, 2014; Uchida et al., 2018). The term epigenetics refers to changes in gene expression without underlying DNA sequence alterations. These changes

are heritable but environmentally modifiable (Jaenisch and Bird, 2003). Epigenetic regulation of gene expression plays fundamental roles in cellular function, neuroplasticity, and behavior (Borrelli et al., 2008), and has been suggested to be associated with not only physiological processes but also pathological conditions (**Figure 1**). In fact, both clinical and preclinical studies have shown that epigenetics plays an important role in the etiology and pathophysiology of depression.

Females are two to three times more likely to develop depression (Kessler et al., 2005; Whiteford et al., 2013; Malhi and Mann, 2018) and exhibit greater symptom severity, greater functional impairment, and more atypical depressive symptoms than males (Kessler et al., 1993; Kornstein et al., 2000b). Furthermore, there are differences in response to antidepressant treatment between males and females with MDD (Kornstein et al., 2000a; Khan et al., 2005). Therefore, it is necessary to understand the mechanisms underlying these sex-related differences to gain insight into the etiology and pathophysiology of depression.

Here, we review the current consensus regarding the roles of epigenetic regulation in neuronal plasticity, behavioral responses to stress, and depression, as well as their implications for the sex-related differences in the etiology and pathophysiology of depression. We focus mainly on epigenetic modulators that have been suggested to play roles in the response to stress and depression in both clinical and preclinical studies.

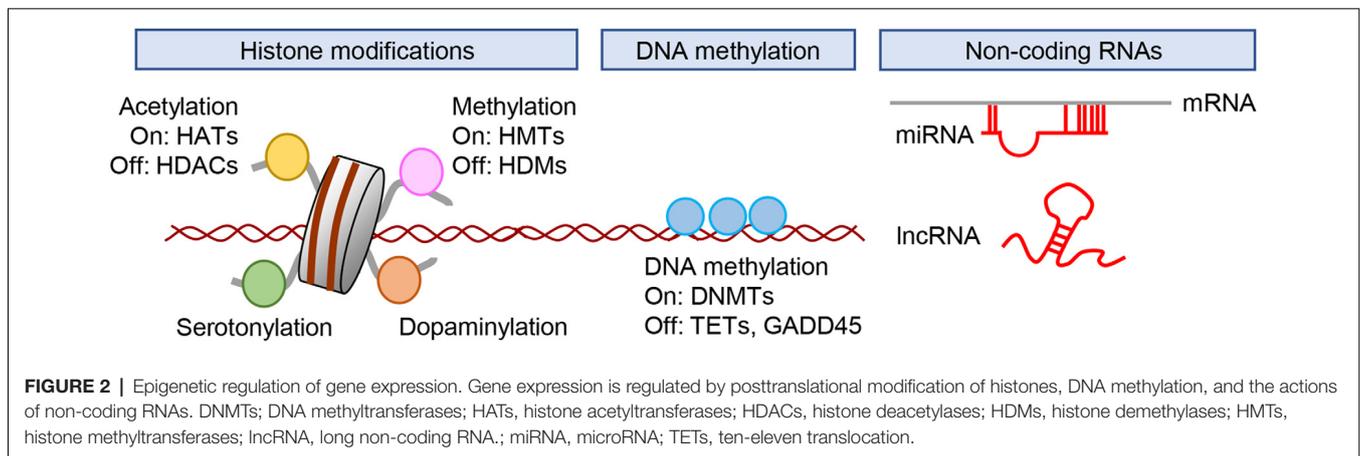
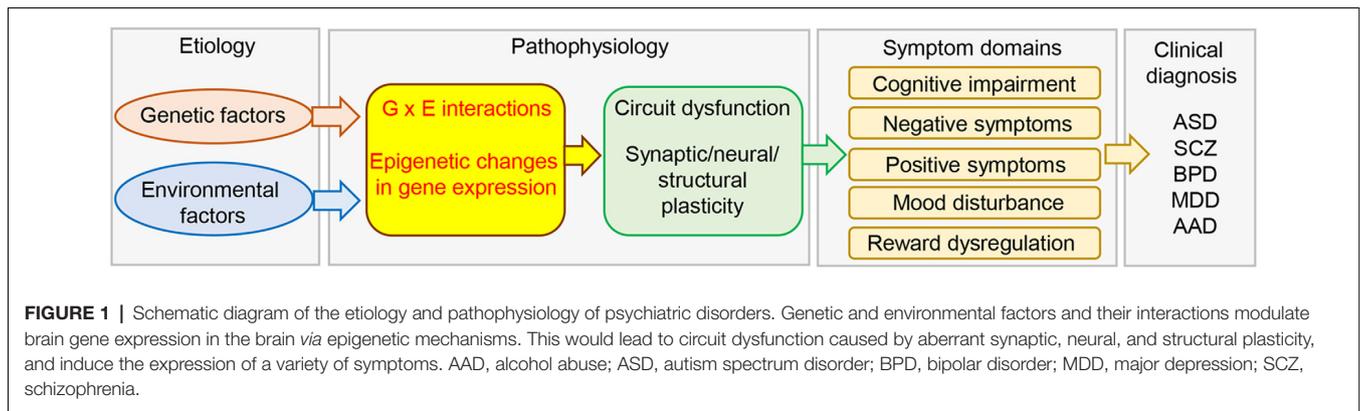
EPIGENETIC MODIFICATIONS

The definition of epigenetics has changed over time, and the term is now used to refer to the potentially heritable but environmentally modifiable regulation of genetic function and expression. These alternations are mediated mainly through histone acetylation and methylation, DNA methylation, and mechanisms that are not encoded in the DNA (Kouzarides, 2007; Suzuki and Bird, 2008; Sun et al., 2013; Uchida et al., 2018). Here, we present a brief summary of major epigenetic modifications, including histone acetylation, histone methylation, DNA methylation, and non-coding RNAs (**Figure 2**).

Histone Modifications

Histone acetylation is associated with the regulation of gene expression. Acetylation at lysine residues negates the positive charges of lysine residues in histone tails and increases the spacing between nucleosomes. This results in increased gene expression due to the decondensation of chromatin and enhanced accessibility of transcription factors to promoters (Kouzarides, 2007). The enzymes that add acetyl groups to histone tails are called histone acetyltransferases (HATs), whereas those that remove acetyl moieties from lysine residues are called histone deacetylases (HDACs; **Figure 2**).

Histone methylation at lysine residues has been reported in depression. A lysine residue can be mono-, di-, or trimethylated. Lysine methylation is catalyzed by a group of lysine methyltransferases (KMT) and is reversed by histone lysine



demethylases (**Figure 2**). Site- and state-specific methylation have different functional effects possibly mediated by the recruitment of different complexes of proteins with reader domains that specifically recognize these various modifications (Sun et al., 2013). Among the five residues in the N-terminal tails of histones H3 and H4 (H3K4, H3K9, H3K27, H3K36, and H4K20), H3K9, H3K27, and H4K20 methylation are related to transcriptional silencing and heterochromatin formation/maintenance, whereas H3K4 and H3K36 methylation activate transcription (Sun et al., 2013).

In addition to histone acetylation and methylation, there are many other types of histone modifications, including phosphorylation, adenosine diphosphate (ADP) ribosylation, ubiquitination, and SUMOylation. Given that the roles of these histone modifications in stress and depression are less well understood, this review mainly focuses on histone acetylation and methylation.

DNA Methylation

DNA methylation involves the covalent addition of a methyl group to the C5 position of cytosine (5mC) predominantly at cytosine-guanine dinucleotides (CpG sites; Suzuki and Bird, 2008). CpG islands are genomic regions with high CpG density where methylation occurs frequently, and are located in nearly 60% of promoters of protein-coding genes in the

human genome (Dworkin et al., 2009). DNA methylation within gene promoters generally prevents the association of DNA binding factors with their target sequences or binding to methyl-CpG binding proteins to recruit transcriptional corepressors and exerts a repressive effect on gene transcription (Lister et al., 2013). Methylation of DNA within the promoter regions of gene plays an important role in cell differentiation, imprinting, and X chromosome inactivation (Barakat and Gribnau, 2012; Nishiyama et al., 2013; Inoue et al., 2017). Methyl-CpG-binding protein 2 (MeCP2) is a member of the methyl-CpG binding proteins, and is capable of binding specifically to methylated DNA, thereby recruiting HDACs to induce chromatin condensation and/or block transcription factor binding, both of which reduce gene expression. In addition to its role in the repression of transcription, DNA methylation is also involved in transcription activation by the recruitment of MeCP2 and transcription coactivators, such as CBP (Chahrour et al., 2008; Uchida et al., 2011). DNA methylation is catalyzed by DNA methyltransferases (DNMTs; **Figure 2**), while several candidate demethylases have been suggested to affect DNA demethylation. These include members of the ten-eleven translocation (TET) proteins, which oxidize 5mC to 5-hydroxymethylcytosine (5hmC) and subsequently to 5-formylcytosine and 5-carboxylcytosine. In contrast to the generally repressive effect of 5mC on gene

expression, 5mC is correlated more with transactivation (Nestler et al., 2016).

Non-coding RNAs

Non-coding RNAs (ncRNAs) are thought to play key roles in regulating gene expression, RNA splicing, and RNA editing to determine how the genotype gives rise to the phenotype (Sumazin et al., 2011). ncRNAs are abundantly expressed in the brain in a region- and cell-type specific manner (Lau et al., 2008; Webb et al., 2015). MicroRNAs (miRNAs) are small (generally <200 bp) non-coding RNAs that play important roles in the post-transcriptional regulation of mRNA (Figure 2). They regulate the translation of mRNAs by binding to the 3' untranslated region (UTR) or 5' UTR of mRNAs in a sequence-specific manner (Kosik, 2006). Roles of miRNAs have been suggested in various aspects of neuronal function, including neurogenesis, synaptic plasticity, and behavior. Long non-coding RNAs (lncRNAs) are a class of RNA molecules >200 bp in length with low protein-coding potential (Qureshi and Mehler, 2012) that have been identified as important regulators of chromatin modification, miRNA sequestration, mRNA transcription, and splicing as well as acting as protein scaffolds (Wang and Chang, 2011). Although many types of ncRNA have been identified (Cech and Steitz, 2014), this review will briefly cover miRNAs and lncRNAs and their roles in neural plasticity and behaviors, as accumulating evidence suggests that these ncRNAs may be involved in the pathophysiology of stress-related psychiatric disorders.

EPIGENETICS IN NEUROPLASTICITY AND DEPRESSION

Changes in gene expression are required for long-term neuronal plasticity in the brain (McCullung and Nestler, 2008; Cholewa-Waclaw et al., 2016). Gene expression is controlled by a series of DNA binding proteins known as transcription factors, one of the best characterized of which is the cAMP response element-binding protein (CREB) that binds to the cAMP response element (CRE) in many gene promoters, including growth factors, enzymes, structural proteins, and other transcription factors (Lonze and Ginty, 2002). Alterations in CREB activity and expression levels are associated with the pathophysiology of depression and the efficacy of treatments (Conti et al., 2002; Manners et al., 2019). CREB activity is downregulated in the hippocampus by stress, leading to a reduction of brain-derived neurotrophic factor (*Bdnf*) mRNA (Nestler et al., 2002). Chronic antidepressant administration increases the expression of *Creb* mRNA, and activation of CREB in the hippocampus can produce antidepressant behaviors (Nibuya et al., 1996; Chen et al., 2001; Blendy, 2006). These findings indicate that alterations in CREB expression are common effects of the stress response or antidepressant treatments that may lead to the regulation of the expression of plasticity-related genes, such as *Bdnf* and its receptor, *Trkb*, which has recently been reported as a common target for the antidepressant actions of imipramine, fluoxetine, and ketamine (Casarotto et al., 2021).

It should be noted that antidepressants and psychotherapy combined can be more effective for the treatment with depression than either treatment alone in humans (Pampallona et al., 2004). This was confirmed in the animal model of anxiety and fear disorders such as posttraumatic stress disorder (PTSD). Chronic antidepressant (fluoxetine) treatment increases neuroplasticity and leads to long-term loss of fearful memories through a combination of fluoxetine treatment and extinction training, whereas fluoxetine or extinction training alone did not produce long-term fear removal (Karpova et al., 2011). Its underlying mechanism is that chronic treatment with fluoxetine reactivates juvenile-like plasticity by increasing the *Bdnf* transcript in the amygdala (Karpova et al., 2011). Similar effects of antidepressant treatment on long-term synaptic plasticity were reported previously in the adult rat visual cortex (Maya Vetencourt et al., 2008). In addition, hippocampal neurogenesis is a unique form of neural circuit plasticity that is regulated by environmental factors, including chronic stress (Van Praag et al., 2000; Sahay and Hen, 2007; Wan et al., 2015), and the reactivation of developmental plasticity also occurred in this brain structure during adulthood. The chronic antidepressant treatment induces dematuration of neurons in the dentate gyrus of the hippocampus (Kobayashi et al., 2010). Thus, the evidence suggests that plasticity-inducing treatments such as antidepressant treatment reorganize brain networks rendered more plastic by the drug treatment (Castrén and Hen, 2013). This “network hypothesis” has recently emerged as one of the mechanisms for depression and antidepressant action. This hypothesis proposes that deficits in activity-dependent neuroplasticity and neural communication might be associated with depression, and antidepressant treatment may improve the affected neural networks (Castrén, 2005; Leistedt and Linkowski, 2013). Here, we focus on how epigenetics influences the expression of genes associated with neuroplasticity and the implications in stress and depression.

Histone Modifications

Many studies have demonstrated that HDACs affect depression and/or the actions of antidepressants. HDAC2 was reported to be involved in neural and synaptic plasticity. Guan et al. (2009) reported that HDAC2 activation reduced the number of synapses and decreased synaptic plasticity. They also demonstrated that HDAC2 is bound to the promoters of several genes involved in synaptic plasticity, including *Bdnf*. Moreover, loss-of-function mutation of HDAC2 restores synaptic plasticity deficits and increases synapse number (Gräff et al., 2012). Thus, HDAC2 is known to play a critical role in the epigenetic control of neuronal and synaptic plasticity.

Several lines of evidence suggest a key role of HDAC2 in the response to stress and depression. A genotype × environment (GxE) animal model of depression showed increased *Hdac2* expression in the nucleus accumbens, whereas a GxE animal model of resilience showed no alterations of *Hdac2* expression (Uchida et al., 2011). Mice overexpressing HDAC2 in the nucleus accumbens exhibit more depression-like behavior (Uchida et al., 2011), and HDAC inhibitor was shown to ameliorate the depression-like behavior associated with exposure to chronic

stress (Covington et al., 2009; Uchida et al., 2011). Glial cell-derived neurotrophic factor (*Gdnf*) is one of the candidate target genes for HDAC2 associated with stress and depression. Chronic stress decreases the expression of *Gdnf* via epigenetic regulation of HDAC2, and HDAC2 knockdown or HDAC inhibitor treatment prevents the stress-induced reduction of *Gdnf* expression. These findings suggest that chronic stress activates HDAC2 function and that this can suppress *Gdnf* transcription, thereby inducing depression-like behaviors. It should be noted that patients with MDD show increased *Hdac2* expression and reduced *Gdnf* expression in the peripheral blood cells and whole blood (Takebayashi et al., 2006; Otsuki et al., 2008; Hobara et al., 2010), supporting a contribution of the HDAC2–GDNF pathway to the depression.

HDAC4 and HDAC5 are other important molecules involved in epigenetics. HDAC4 binds to chromatin, MEF2A, and CREB, resulting in histone deacetylation and suppression of gene expression in neurons (Chen and Cepko, 2009; Uchida and Shumyatsky, 2018). Loss-of-function mutation of HDAC4 affects the transcription of genes essential for synaptic function, including *Camk2a* and *Homer1* (Sando et al., 2012). HDAC4 knockout mice show deficits in synaptic plasticity and memory performance (Kim et al., 2012). As MDD may be considered primarily as an illness of emotional/mood dysregulation, it also involves substantial cognitive dysfunction (Talarowska et al., 2016; MacQueen and Mamedovich, 2017). Chronic stress increases HDAC4 expression in the hippocampus and treatment with HDAC4/5 inhibitor was shown to rescue aberrant structural plasticity and have antidepressant-like effects in mice (Higuchi et al., 2016). In addition, mice lacking HDAC5 exhibited increased depressive-like behaviors after chronic social defeat stress compared with control animals (Renthal et al., 2007). Other studies showed that HDAC5-mediated regulation of gene expression in the hippocampus is essential for the behavioral effects of chronic treatment with antidepressant drugs, such as imipramine, fluoxetine, and ketamine (Tsankova et al., 2006; Choi et al., 2015; Higuchi et al., 2016). Human studies also suggested that HDAC4 and HDAC5 are potential biomarkers for mood disorders. The levels of *HDAC5* and *HDAC4* expression in peripheral blood cells are upregulated in MDD and bipolar disorder, respectively (Iga et al., 2007; Hobara et al., 2010). Taken together, these observations support the associations of HDAC4/5 with structural and synaptic plasticity and abnormal behaviors in many neurological and psychiatric diseases.

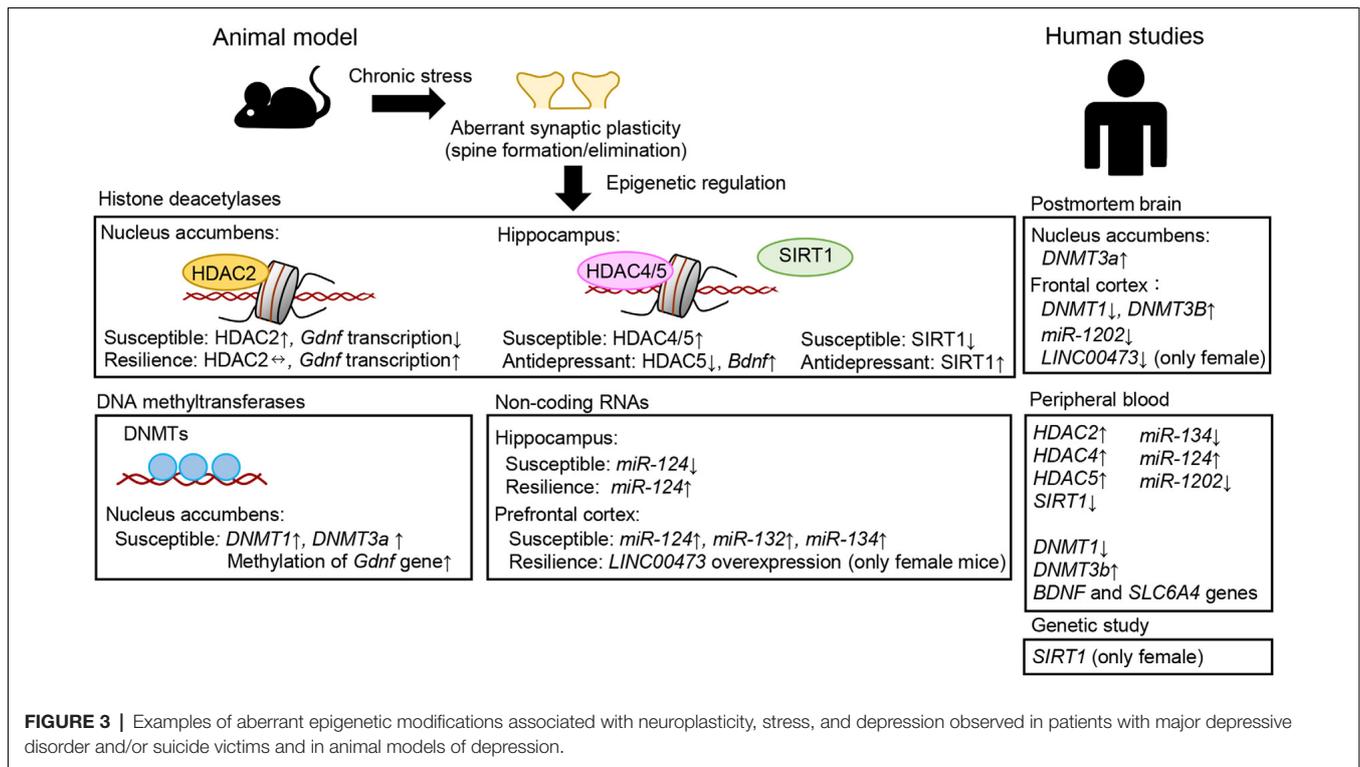
Histone methylation has been suggested to have adaptive effects in models of stress (Covington et al., 2011; Uchida et al., 2011). Chronic stress was shown to decrease global levels of H3K9 dimethylation (H3K9me₂), with coincident downregulation of the histone methyltransferase, G9a (Covington et al., 2011). Activation of G9a is involved in increased H3K9me₂ in the *Camk2a* gene, which plays an important role in synaptic plasticity, and induced antidepressant effects (Covington et al., 2011). H3K4 trimethylation (H3K4me₃) levels are also decreased by chronic stress (Uchida et al., 2011). As the pathway related to H3K4 methylation has been suggested to

be involved in major psychiatric disorders (Akbarian and Huang, 2009; Shen et al., 2014; Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015), stress-mediated alteration of H3K4me₃ may underlie common mechanisms of stress-related psychiatric symptoms.

Postmortem analysis of the brains of depressed suicide victims demonstrated enrichment of H3K9me₃ in the connexin 30 and 43 genes in the prefrontal cortex, the expression of which was previously reported to be downregulated in the prefrontal cortex of depressed suicide victims (Nagy et al., 2017). Cruceanu et al. (2013) reported significantly increased levels of H3K4me₃ in the *Synapsin* gene, which is related to plasticity, in patients with MDD and bipolar disorder, and this effect was correlated with significant increases in gene expression, suggesting that synapsin dysregulation in mood disorders is at least partially mediated by epigenetic mechanisms.

Recently, Farrelly et al. (2019) reported that H3 is modified by the neurotransmitter, serotonin. This is the first report of a histone modified by monoamination and provides novel insight into the role of neurotransmitter signaling in a myriad of emotions and behaviors. They also showed that H3 glutamine 5 (H3Q5) serves as the primary site of serotonylation and that H3Q5 serotonylation co-occurs with H3K4me₃, which is correlated with active transcription. In addition to histone serotonylation, Lepack et al. (2020) recently reported that dopamine associates with chromatin to initiate a previously unknown form of epigenetic regulation called dopaminylation. The dopaminylation of histone is associated with aberrant expression of reward-related behavior and synaptic plasticity-related neuronal genes. These observations suggest that serotonylation and dopaminylation of histone may have an impact on the etiology of neurotransmitter-related diseases (Anastas and Shi, 2019). Further studies are required to determine whether chronic stress exposure and antidepressant drugs, including the selective serotonin reuptake inhibitors (SSRIs) or other small molecules acting on monoamines, exert their effects through direct chromatin modifications, such as histone serotonylation/dopaminylation, and whether these chromatin changes determine therapeutic efficacy.

Overall, existing data indicate that histone modifications are robustly modulated by adverse environmental factors across brain regions, including the hippocampus, prefrontal cortex, and nucleus accumbens, which are brain areas known to be associated with MDD (Russo and Nestler, 2013). Accordingly, aberrant structural plasticity, such as decreased dendritic spine density in neurons, is seen in these brain areas of animal models of depression. Although the evidence presented here provides critical data showing that focal knockdown and/or overexpression of HDACs leads to alterations in gene expression, spine density, and the behavioral response to chronic stress (Figure 3), it remains unclear how histone acetylation and methylation regulate the expression of specific target genes involved in spine development, spinogenesis, or spine elimination. In addition, much effort is needed to clarify how these mechanisms are associated with depression-like behaviors and the molecular



and cellular pathways that can be targeted for the treatment of depression. It should be noted that epigenetic studies will inform the development of strategies for new compounds by moving beyond monoamine transporters and receptors as targets for the treatment of depression. Indeed, as mentioned earlier, HDAC inhibitors exert potential antidepressant-like actions in several chronic stress models. Moreover, several lines of evidence have shown altered expression of HDACs in the peripheral blood cells of patients with MDD, thus highlighting the potential of HDACs to be used as biomarkers of MDD. Although genetic and environmental factors are critical to the development of depression risk and resilience, it is still unclear whether and how these factors influence individual differences in histone modifications and depression susceptibility and resilience. Thus, deciphering how genes and the environment interact at the molecular level to characterize disease risk and resilience will allow for a better understanding of the disease mechanisms and their treatment.

DNA Methylation

The DNA methyltransferases (DNMT1, DNMT2, DNMT3A, and DNMT3B) catalyze DNA methylation. DNMT3A is responsible for the de novo establishment of DNA methylation patterns, and DNMT1 maintains the methylation pattern in a replication-coupled manner. These molecules have been shown to play important roles in neuroplasticity, depression, and antidepressant actions. A human postmortem brain study revealed decreased and increased expression levels of DNMT1 and DNMT3B, respectively, in the frontopolar cortex of

depressed individuals (Poulter et al., 2008). Increased DNMT3A expression was observed in the nucleus accumbens of individuals with MDD (Hodes et al., 2015). Moreover, in peripheral blood cells, the levels of DNMT1 mRNA were significantly decreased in a depressive but not in a remissive state of MDD (Higuchi et al., 2011). Conversely, the levels of DNMT3B mRNA in MDD were significantly increased in a depressive but not in a remissive state. DNMTs are involved in the effects of stress and depression in animals. Chronic stress has been shown to increase DNMT1 and DNMT3a levels in the nucleus accumbens and treatment with DNMT inhibitors reversed depression-like behaviors (Uchida et al., 2011). Another study also indicated that DNMT regulates dendritic spine density and chronic stress-induced depression-like behaviors (LaPlant et al., 2010). Sales et al. (2011) showed that treatment with DNMT inhibitors exhibited antidepressant-like effects mediated via the inhibition of DNA methylation in the hippocampus and rescued stress-induced reduction of *Bdnf* expression (Tian et al., 2009). Taken together, these observations suggest that there may be an association between DNMT activity and depression.

A number of clinical studies have demonstrated associations between DNA methylation and depression. Several studies showed that DNA methylation in the promoter of the *BDNF* gene is associated with MDD. Fuchikami et al. (2011) reported that patients with MDD showed an absence of DNA methylation at certain CpG sites in exon 1 of the *BDNF* gene, and Tadić et al. (2014) reported that absence of DNA methylation in the *BDNF* gene promoter was associated with reduced response to antidepressant drugs. These observations suggest

that the *BDNF* gene is related to MDD and responsiveness to antidepressants.

The neurotransmitter serotonin (5-HT) is known to play important roles in synaptic plasticity and mood/emotion, and the level of DNA methylation in the promoter of the *SLC6A4* gene, which encodes serotonin transporter (SERT), has been shown to be associated with its mRNA expression as well as depression and antidepressant responsiveness (Philibert et al., 2007; Sugawara et al., 2011; Okada et al., 2014).

As mentioned here, a growing body of evidence supports a role for DNA methylation and DNMTs in modulating the effects of chronic stress and depression. Although these studies highlight epigenetic modifications targeting specific genes associated with behavioral abnormalities, the effect of chronic stress is not restricted to a subset of candidate genes. In addition, MDD is not monogenic, but rather associated with many genes. Thus, genome-wide profiling of DNA methylation in behaviorally and/or physiologically classified animals subjected to chronic stress (Cerniauskas et al., 2019), together with the categorized MDD subgroups, will allow us to better understand the pathophysiology of this disorder. Furthermore, it is still unclear how DNA methylation-mediated regulation of changes in gene transcription influences neural plasticity and circuit homeostasis. Recently developed genome engineering tools, such as epigenome editing platforms (Yim et al., 2020) that can modulate locus-specific epigenetic modifications and subsequent gene transcription, may resolve this issue and provide novel insights into the role of locus-specific and cell-type specific epigenetic modifications in neuroplasticity and behaviors.

MicroRNAs

Many studies have demonstrated altered expression of miRNAs in patients with psychiatric disorders, including MDD, as summarized in detail elsewhere (Allen and Dwivedi, 2020; Yoshino and Dwivedi, 2020). This review preferentially focuses on miRNAs that are known to be involved in both synaptic plasticity and depression-like behaviors in animal models, as well as those suggested to be associated with clinical depression.

Several miRNAs are involved in modulating synaptic and neuronal functions and behavior. Brain-specific miR-134 negatively regulates the size of hippocampal dendritic spines, which is mediated by inhibition of translation of the mRNA encoding a protein kinase, Limk1, which controls spine development (Schratt et al., 2006). Exposure of neurons to BDNF ameliorates this inhibition of Limk1 translation by miR-134, and may thus contribute to synaptic maturation and plasticity. In addition, miRNA-134 was reported to affect synaptic plasticity and behavior through the modulation of HDAC expression (Gao et al., 2010). Upregulation (downregulation) of SIRT1, a type III HDAC, enhances (impairs) synaptic plasticity and memory performance, and these effects are mediated *via* post-transcriptional regulation of CREB expression by miR-134. In addition, chronic stress was shown to increase miR-134 expression in the medial prefrontal cortex of rats and decrease the expression of

Limk1 (Fan et al., 2018). Intracerebral infusion of miR-134-sponge into this brain region of stressed rats, which blocks miR-134 function, significantly ameliorated aberrant neuronal structures, biochemical changes, and depression-like behaviors. Another study showed that miR-124 overexpression enhanced dendritic spine density in the hippocampus under conditions of stress, whereas miR-124 inhibitor reduced dendritic spine density (Higuchi et al., 2016). Behaviorally, miR-124 overexpression drives stress resilience in mice. These changes in spine density and depression-like behaviors are mediated in part by translational inhibition of HDAC4/5 (Higuchi et al., 2016). These observations suggest that miRNAs (e.g., miR-124, miR-134) act as functional links to chromatin modification by modulating translational control of HDACs, thereby modulating neural plasticity and higher brain function. It should be noted that both miR-124 and miR-134 are associated with MDD (He et al., 2016; Roy et al., 2017; Fang et al., 2018; Zhang et al., 2020). Therefore, miR-124- and miR-134-mediated translational control may be involved in the pathophysiology of depression and the actions of antidepressants.

SERT is the pharmacological target of antidepressant drugs and is a target of miR-16 (Baudry et al., 2010). miR-16 is enriched in noradrenergic cells compared to serotonergic cells. Chronic treatment with the antidepressant drug fluoxetine increases the miR-16 expression in the serotonergic raphe nuclei, thus reducing SERT expression. In contrast, fluoxetine treatment decreases the miR-16 level and upregulates SERT expression in the noradrenergic locus coeruleus. Thus, the miR-16-SERT pathway is associated with behavioral responses to antidepressant drugs. A postmortem study showed decreased miR-16 expression in the dorsal raphe of suicide victims (Issler et al., 2014). These observations suggest that miR-16 may contribute to the therapeutic action of fluoxetine in depression and anxiety disorders.

Issler et al. (2014) reported that miR-135 is essential for stress resilience and efficacy of antidepressants. The expression of miR-135 in the dorsal raphe was shown to be upregulated by chronic treatment with the antidepressants, imipramine and fluoxetine. Overexpression of miR-135 in serotonergic neurons resulted in behavioral resilience to chronic stress, possibly due to inhibition of *SERT* and *Htr1a* mRNA translation, while miR-135 knockdown increased anxiety behavior and attenuated antidepressant responsiveness in mice. In addition, the expression of miR-135 was shown to be downregulated in patients with depression. Taken together, these results suggest that miR-135 is an essential regulatory element responsible for the responses to both stress and antidepressants.

With regard to synaptic plasticity, miRNAs may directly regulate synaptic function, as some miRNAs and their processing enzymes (e.g., Dicer, Drosha) were shown to be highly enriched at synaptic sites (Lugli et al., 2005, 2008; Yoshino et al., 2021). Importantly, neural activity facilitated local protein translation by releasing miRNAs from certain mRNAs (Bicker et al., 2013; Hu et al., 2014). Yoshino et al. (2021) reported that a large number of miRNAs are enriched in synapses and that patients with MDD showed altered expression of

synaptic miRNAs, thus providing new insights into the roles of synaptic miRNAs and suggesting their involvement in the pathogenesis of MDD. However, there have been few studies regarding the roles of synaptic miRNAs and their involvement in neuropsychiatric disorders.

There have also been reports regarding the relations of miRNAs with antidepressant treatment response. The miRNAs miR-46a/b-5, miR-425-3p, and miR-24-3p show alterations in their expression levels in response to chronic antidepressants, which are known to regulate MAPK/Wnt-system genes (Lopez et al., 2017). miR-598-5p has been shown to be a common target of three treatments for depression, i.e., antidepressant (fluoxetine), ketamine, and electroconvulsive therapy (O'Connor et al., 2013). Moreover, Lopez et al. (2014) reported that miR-1202 dysregulation detected in the postmortem brain and peripheral blood was associated with the pathophysiology of MDD. They postulated that miR-1202 may be a useful biomarker of MDD and a predictor of antidepressant treatment response. Thus, these studies highlight the roles of miRNAs in MDD and may facilitate the development of novel methods for effective pharmacological treatment of mood disorders.

Early life stress is a potent neurodevelopmental disruptor and increases the risk for MDD (Heim and Nemeroff, 2001; Park et al., 2019). Early life stress leads to hypothalamic-pituitary-adrenal (HPA) axis impairment and immune reactions, which increase vulnerability to MDD and suicidal behavior (Fagundes et al., 2013; Allen and Dwivedi, 2020; Juruena et al., 2020). There is accumulating evidence that the underlying mechanisms involve epigenetic modifications by miRNAs. For example, although maternal separation enhances the risk of a depression-like phenotype in adulthood, this early life stress was shown to increase miR-504 expression in the nucleus accumbens and miR-132, miR-124, miR-9, and miR-29a expression in the medial prefrontal cortex of rodents (Uchida et al., 2010; Zhang et al., 2013). Interestingly, in a study investigating the relations between miR-9 levels in blood samples, fMRI data, and experience of childhood maltreatment in human MDD patients, He et al. (2021) reported that machine learning has the potential to allow differentiation of MDD patients from healthy controls by integrating miR-9 levels, the severity of childhood maltreatment, and strength of amygdala functional connectivity in the prefrontal-limbic regions.

To date, there is accumulating evidence for the involvement of brain miRNAs in the epigenetic effects of chronic stress and the development of stress-related psychopathologies. However, there is a need for a multiscale analysis to decipher how miRNA-mediated epigenetic regulation influences spine development, neuroplasticity, and behaviors. As mentioned earlier, miRNAs are localized at synaptic sites, but their functions are still unknown. In addition, many miRNAs are expressed in a cell-type-specific manner, and nearly all studies to date have assessed miRNA function in heterogeneous populations of cells. The recent advancements in technology, including cell type- and circuit-specific viral-mediated gene transfer, epigenome editing, and single-cell

analysis, allow us to analyze specific cell populations *in vivo*; nevertheless, the elucidation of the epigenetic mechanisms of miRNAs in distinct cell types, including neurons, astrocytes, microglia, and oligodendrocytes, and in distinct neural circuits are required. Indeed, recent evidence has implicated epigenome/transcription changes in astrocytes and oligodendrocytes in patients with MDD (Nagy et al., 2015, 2020; Lutz et al., 2017).

Long Non-coding RNAs

lncRNAs have emerged as key components of gene regulatory networks in concert with other key molecules, such as epigenetic modifiers and transcription factors, which are associated with brain function. Indeed, accumulating evidence suggests the important roles of lncRNAs in neuronal development and plasticity. The lncRNA BDNF-AS, which prevents *Bdnf* transcription by recruiting a key component of epigenetic silencing complex, was reported to be associated with many psychiatric disorders, including depression (Ng et al., 2013). In addition, inhibition of BDNF-AS was shown to induce the upregulation of *Bdnf* expression, leading to increased *Gdnf* expression as well as enhanced neuronal maturation (Modarresi et al., 2012), which were suggested to be associated with antidepressant action and stress resilience. Thus, BDNF-AS lncRNA may contribute to the pathophysiology of depression and/or antidepressant action by regulating transcription of *Bdnf*.

Experimental studies demonstrated altered lncRNA expression in animal models of depression. In a microarray study, Roy et al. (2018) demonstrated transcriptome-wide changes in lncRNAs in the hippocampus of male rats that showed susceptibility (learned helplessness model) or resilience (non-learned helplessness) to the development of depression. Treatment with fluoxetine was also shown to be associated with changes in lncRNA expression in animals susceptible to the development of depression (Wang et al., 2019). This study suggested that specific classes of lncRNAs with distinctive roles in modulating target gene expression may be involved in susceptibility or resilience to the development of depression. They further examined how lncRNAs are coexpressed with gene transcripts and whether specific lncRNA/mRNA modules are associated with susceptibility or resilience to stress and depression by weighted gene coexpression network analysis (WGCNA) to correlate the expression status of protein-coding transcripts with lncRNAs. Their results identified five hub mRNAs (*Tas2r116*, *Expi*, *Rnf29*, *Oprs1*, and *LOC690326*) and 20 lncRNAs that are associated with susceptibility and resilience to the development of depression. These studies suggested that lncRNA-associated networks may play crucial roles in the development of depression.

Some authors have suggested that lncRNAs may be useful as diagnostic biomarkers or therapeutic targets for depression. Indeed, recent studies have detected regulatory lncRNAs that may be involved in psychiatric disorders. For example, a global non-coding RNA expression analysis of depressed suicide victims detected 23 differentially

expressed lncRNAs as well as their differentially expressed overlapping and antisense protein-coding genes in the rostral anterior cingulate cortex (Zhou et al., 2018). Notably, in this analysis, one of the top differentially expressed lncRNAs was identified as RP1-269M15.3, the expression of which in the nucleus accumbens was reported previously to be upregulated by 30 MDD-related SNPs (Zeng et al., 2017; Zhou et al., 2018). In the prefrontal cortex, RNA-Seq analysis demonstrated that expression of the lncRNA, LINC01268, was upregulated in victims of violent suicide compared to both non-suicides and victims of non-violent suicide (Punzi et al., 2019).

To examine the roles of lncRNAs in depression, Seki et al. (2019) measured the expression of 83 lncRNAs in the peripheral blood leukocytes of MDD patients. Their results showed that the expression level of one lncRNA (RMRP) was lower, while those of four lncRNAs (Y5, MER11C, PCAT1, and PCAT29) were higher in MDD patients than in healthy controls. The RMRP expression level was correlated with the severity of depression as measured by the Hamilton Depression Rating Scale. Moreover, they found reduced expression of RMRP in the blood of a widely used corticosterone-induced mouse model of depression, corroborating the observations in MDD patients. This suggests that a lower RMRP level may serve as a potential biomarker for MDD. Another study using peripheral blood cells also found negative associations of six lncRNAs with suicide risk in MDD patients (Cui et al., 2017), and these lncRNAs could be potential markers for preventing suicide in MDD patients.

Here, we have described the current knowledge regarding the roles of lncRNAs in neural plasticity and summarized the contributions of some lncRNAs to stress and depression. Transcriptome analyses have highlighted alterations in the transcriptional regulatory machinery in patients with MDD, consistent with recent findings indicating that genetic mutations and/or polymorphisms linked to psychiatric disorders fall into non-coding regions of the genome. Although these studies have provided some insight into the diverse roles of lncRNAs in depression, many unanswered questions remain. For example, mammalian cells encode about 170,000 lncRNAs (Zhao et al., 2016), but little is known about how chronic stress and/or therapeutic drugs influence their expression, localization, and function in the brain. In addition, the association of lncRNAs with (epi)genetics and specific phenotypical characteristics remains largely unknown. Further studies of the roles of lncRNAs in psychiatric disorders are required to discover new targets for the development of effective drugs to treat depression.

In this part of this review, we mainly summarized the role of epigenetic molecules in chronic stress-induced maladaptive changes in structural plasticity and behaviors. In many cases, alterations in spine density and the expression of epigenetic molecules following chronic stress lead to maladaptive and susceptible phenotypes, whereas stress-resilient animals do not show any changes. What happens in the resilient brain? Studies have demonstrated that such resilience is mediated not only by the lack of key molecular changes that occur in stress-susceptible

animals to block their ability to cope with chronic stress but also by the presence of distinct molecular adaptations that occur in resilient animals to help and maintain normal behavioral function (Uchida et al., 2011; Russo et al., 2012; Sakai et al., 2021). An important finding from animal studies demonstrated that gene expression changes and chromatin modifications in the reward pathway (ventral tegmental area-nucleus accumbens) contribute to dopamine transmission and adaptive behaviors. Examples of genes and epigenetic modifications involved in resilience include HDAC2, histone acetylation, and miRNAs (Krishnan et al., 2007; Uchida et al., 2011; Dias et al., 2014), as described here. However, the factors involved in stress resilience are just beginning to be identified. It should be noted that there is a great need for human brain imaging studies to identify the brain structures and circuits that mediate stress resilience. This information could be used for reverse translational research in animals and for the development of treatment strategies (e.g., the potential for deep brain stimulation) for clinical depression.

SEX-RELATED DIFFERENCES IN SYNAPTIC PLASTICITY

There have been many studies of the effects of sex steroid hormones on sexual differentiation of the brain. Estrogens are sex steroid hormones synthesized and secreted by both sexes, although the levels are considerably higher in young reproductively mature females than in males. It has been suggested that estrogen underlies the mechanism of sex-specific brain development by regulation of neuronal transmission and neuroplasticity as well as neuroprotective effects and immune functions (Zhang et al., 2001; Raison and Miller, 2013; Marrocco and McEwen, 2016). For example, the hippocampus, which plays critical roles in both mood regulation and higher cognitive functions, shows high levels of estrogen receptor expression, and this hormone has been shown to have a profound effect on hippocampal structure and function (Li et al., 2004). Estradiol shows synapse induction within the hippocampus in females but not in males, whereas aberrant hippocampal synaptic remodeling of CA3 dendrites after chronic stress exposure was seen in males but not in females, suggesting that gonadal hormones are related to susceptibility or resilience to stress (Galea et al., 1997; Leranthe et al., 2003). However, whether there is a mechanism underlying the sex-specific development of MDD remains to be clarified.

The plasticity of neuron structure, including spine density, is sex-dependent, and sex steroids have significant effects on this disparity. For example, hippocampal spine density was shown to change in response to fluctuations in ovarian steroid levels across the estrous cycle in female rats (Gould et al., 1990). Furthermore, it has been suggested that hormone-dependent modifications of the NMDA receptor can lead to sex-related differences in synaptic plasticity following exposure to stress (Hyer et al., 2018). The molecular mechanisms underlying sex-dependent differences in synaptic plasticity are also related to the effects of estrogen. Estradiol is known to drive potentiation of glutamatergic synapses in both males and females. However, the mechanisms underlying

the initiation of potentiation are sex-dependent. Estrogens bind with estrogen receptors ER α , ER β , and G protein-coupled estrogen receptor 1 (GPER1). Estradiol drives potentiation through GPER1 in females, but through ER β in males. On the other hand, presynaptic potentiation is driven by ER α in males but by ER β in females (Oberlander and Woolley, 2016). ER α and ER β have been shown to activate different metabotropic glutamate receptors. ER α activation triggers mGluR1 signaling and subsequently drives CREB phosphorylation. Signaling through ER β activates mGluR2/3 and results in downregulation of calcium-mediated CREB phosphorylation (Boulware et al., 2013). These results showed that sex-specific interactions with ER α and ER β activate different downstream regulatory pathways, which in turn affect synaptic plasticity.

SEX-RELATED DIFFERENCES IN DEPRESSION

Etiologically, depression is two times more prevalent in females than in males. Female depressed patients show greater severity, earlier age of onset, and increased duration of depressive episodes than male patients (Marcus et al., 2005). A meta-analysis of neuroimaging studies demonstrated sex-related differences in the effects of stress on brain structure and function. The Enhancing NeuroImaging Genetics through MetaAnalysis Consortium performed brain morphometric analyses and showed that greater severity of maltreatment is related to overall lower gray matter thickness and smaller caudate volume in female depressive patients, but a decreased thickness of the rostral anterior cingulate cortex in males (Thompson et al., 2020). Also, there is accumulating evidence for sex-specific effects of stress on synaptic and neural plasticity (Shors et al., 2004; Carvalho-Netto et al., 2011; McEwen et al., 2016). Female rodents have been shown to mount a greater neuroendocrine response to stress in comparison to males (Heck and Handa, 2019; Zuloaga et al., 2020). This response may be hormone-dependent, as higher estrogen levels are associated with greater stress responses (Viau and Meaney, 1991; Lund et al., 2006; Liu et al., 2011). Furthermore, stress events can often have the opposite effects on behavior in males and females (Bowman et al., 2001; Luine, 2002; Conrad et al., 2003; Ortiz et al., 2015; Peay et al., 2020).

The efficacy of commonly used antidepressants also differs between males and females, although there is no clear consensus; men show a better therapeutic response to tricyclic antidepressants (TCAs) than women (Kornstein et al., 2000a), whereas women respond better to SSRI treatment than men (Kornstein et al., 2000a; Khan et al., 2005). Preclinical studies have shown that female mice are more responsive to ketamine, a fast-acting antidepressant, than males (Carrier and Kabbaj, 2013; Franceschelli et al., 2015). Taken together, these observations suggest that sex-dependent molecular mechanisms underlie the differences in responsiveness to antidepressants between males and females.

There is accumulating evidence that this disparity in susceptibility to depression between males and females is related to sex-specific differences in neuronal circuitry, hormone

levels, and metabolism (Li et al., 2004; Fernández-Guasti et al., 2012). Notably, downregulation of the expression of a hub gene has been shown to underlie sex-related differences in depression susceptibility. *DUSP6*, which encodes dual-specificity phosphatase-6, has been shown to mediate several brain-related functions through the inactivation of the ERK pathway (Muda et al., 1996). *DUSP6* expression was shown to be downregulated in female but not male patients with depression, and in an animal study knockdown of *DUSP6* was shown to increase stress susceptibility by enhancing the excitability of a population of glutamatergic pyramidal neurons in the ventromedial prefrontal cortex *via* the activation of ERK signaling (Labonté et al., 2017). However, these factors cannot fully explain the sex-related differences in susceptibility to depression, and it is possible that X-chromosome inactivation (XCI) and epigenetic factors also play major roles in the molecular and cellular mechanisms underlying these differences.

EPIGENETIC MECHANISMS OF SEX-RELATED DIFFERENCES IN DEPRESSION

Epigenetic mechanisms have pivotal roles in sex-related differences in gene expression and sexual differentiation of the brain (Tsai et al., 2009; Shen et al., 2015). Estrogen acts through epigenetic mechanisms in addition to rapid-acting non-genomic functions *via* second messengers relevant to sex-related differences in brain function and behavior (Kelly and Levin, 2001; Li et al., 2004). Importantly, methylation of the estrogen receptor and histone acetylation are involved in the process of masculinizing the brain (Kurian et al., 2010; Matsuda et al., 2011). When testosterone reaches the brain and is converted in part to estradiol, the nuclear receptors ER α (encoded by *ESR1*) and ER β (encoded by *ERS2*) are activated to initiate male brain organization. CpG sites in *ESR1* and *ESR2* show sex-dependent DNA methylation levels that interact with hormones at critical periods of development, affecting downstream trajectories of brain development that differ between males and females. These epigenetic sex-related differences result in disparities between males and females in vulnerability to mental disorders in humans or to repeated social defeat stress in adulthood (Golden et al., 2013; Kim et al., 2015).

Furthermore, interactions between the hypothalamic-pituitary-gonadal (HPG) and HPA axes could lead to sex differences in the regulation of stress responsivity (Oyola and Handa, 2017). Estrogens drive HPA axis activation in females, resulting in the elevation of glucocorticoids during proestrus and estrus in rodents (Figueiredo et al., 2002). Of note, estradiol inhibits restraint-induced ACTH release but strongly enhances the sensitivity of the adrenal to ACTH, which results in a net increase in stress-induced glucocorticoid release (Ulrich-Lai et al., 2006). The paraventricular nucleus of the hypothalamus (PVN) plays an important role in the activation of the HPA axis, integrating neuronal and humoral inputs to secrete corticotropin-releasing hormone (CRH; Ferguson

et al., 2008; Oyola and Handa, 2017). CRH neurons in the rat PVN express ER β , but not ER α . *In vitro* studies have demonstrated that ER β , but not α , strongly stimulates the *Crh* promoter, suggesting that estradiol-dependent effects in the regulation of the HPA axis may be driven by their direct action through ER β in the CRH neurons of the PVN (Miller et al., 2004). In addition, peripheral administration of the ER β agonist, R-DPN, blocked the increase in HPA axis reactivity and induced anxiety-like behaviors in female rats in response to the implantation of a wax pellet containing a GR agonist adjacent to the central nucleus of the amygdala (Weiser et al., 2010). Together, these results suggest a possible mechanism for the action of estradiol by inhibiting HPA axis reactivity and modulating *Crh* gene expression through ER β . However, further studies are needed to elucidate how interactions between the HPA and HPG axes cause sex-dependent differences in stress responsiveness.

The X-chromosome also plays crucial role in the development of depression and other psychiatric disorders. In female cells, most genes on one X chromosome are silenced by a mechanism known as XCI that involves packaging of the inactive X-chromosome into a transcriptionally inactive structure called heterochromatin. However, this silencing process is imperfect, requiring the silencing machinery to function throughout life, with about 15% of genes on the X chromosome “escaping” XCI and an additional 10% of genes showing variable patterns of inactivation resulting in double or various doses of the gene product in females (Carrel and Willard, 2005; Johnston et al., 2008). Overdosage of X-linked genes that have escaped XCI due to the presence of an extra X-chromosome was suggested to contribute to the development of psychiatric symptoms in both Klinefelter syndrome (XXY) and Triple X syndrome (XXX), and XCI has been shown to be an important mechanism underlying the sex-related differences in depression. Nearly all of the genes that show sex-related bias in multiple tissues are located on the X- and Y-chromosomes (Reinius et al., 2010). One of the best-studied of these genes, *Xist*, is highly sexually dimorphic, with female-specific expression, and plays a pivotal role in XCI (Sahakyan et al., 2018). In addition, several other genes, including *KDM5C*, *EIF2S3X*, *KDM6A*, and *DDX3X*, have been reported to escape XCI (Reinius et al., 2010). Overexpression of X-linked genes may be a common mechanism underlying the development of psychiatric disorders in patients with these rare genetic diseases and in the general population of female psychiatric patients with *XIST* overexpression. Among the four X-linked escapee genes stated above, *KDM5C* is especially known to be related to psychiatric disorders including X-linked syndrome, autism, and depression (Ji et al., 2015; Vallianatos and Iwase, 2015; Talebizadeh et al., 2019). Indeed, female patients with MDD show increased expression of the *XIST* gene and *KDM5C* in lymphoblastoid cells (Ji et al., 2015). In addition, a recent clinical study has reported that, in blood samples, the expression levels of *KDM5C*-3'UTR-lncRNA isoform were different in autistic females with XCI skewness compared with controls (Talebizadeh et al., 2019). Intriguingly, a study of human postmortem brains supported overexpression

of the *XIST* gene in female psychiatric patients (Ji et al., 2015).

Sex-Related Differences in Histone Modifications and DNA Methylation in Depression and Stress

One of the first SNPs identified as related to depression by GWAS was located in the *SIRT1* gene (Ledford, 2015), which encodes a type III HDAC. The authors reported a significant association of this gene with MDD only in females. In addition, this gene was reported to be associated with MDD and female suicide victims in a Japanese population (Kishi et al., 2010; Hirata et al., 2019). Moreover, the level of *SIRT1* mRNA in peripheral blood was shown to be reduced in MDD patients compared to healthy subjects (Abe et al., 2011; Luo and Zhang, 2016). An animal study suggested that *SIRT1* contributes to the development of depression (Abe-Higuchi et al., 2016). Chronic stress was shown to reduce *SIRT1* expression in the hippocampus, and this effect was rescued by chronic treatment with antidepressants. Hippocampal *SIRT1* activation reversed stress-induced aberrant dendritic spine density and increased depression-like behaviors, whereas hippocampal *SIRT1* inhibition induced reduction of spine number and increased depression-like behaviors. These observations indicated that the function of *SIRT1* in the hippocampus drives stress resilience. Although the sex-dependent role of *SIRT1* in depression is still unclear, taken together with the results of clinical studies, these observations suggest that *SIRT1* may be associated with the etiopathogenesis of sex-related differences in depression.

Stress events trigger the development of PTSD, and women are more than twice as likely to develop PTSD than men, similar to the case with depression (Breslau et al., 1998). The molecular mechanisms underlying the increased risk of PTSD in females are unclear, but Maddox et al. (2018) suggested that DNA methylation and HDAC4 regulation by estrogen may be associated with an increased risk of PTSD in some women. Importantly, they found that genetic and epigenetic variation can alter *HDAC4* expression, leading to PTSD in a sex-dependent manner. Their results indicated that higher methylation status at specific CpG sites and the genotype of the *HDAC4* gene could be associated with lower levels of *HDAC4* expression, which are associated with increased resting-state functional connectivity between areas of the brain implicated in fear expression as well as heightened fear load, particular in patients with PTSD.

Early life stress affects the HPA axis and may induce susceptibility to stress, but those effects differ between males and females through epigenetic mechanisms. For example, maternal separation was shown to result in higher exon methylation and lower expression of *Bdnf*, a gene associated with stress signaling pathways, in adulthood (Dandi et al., 2018). These effects on gene expression are significantly greater in females than in males (Coley et al., 2019). More recent studies showed that chronic stress also produces sex-specific epigenetic modifications. Chronic variable mild stress was demonstrated

to significantly increase methylation of the CRH gene, which is related to the HPA axis, in females but not in males (Sterrenburg et al., 2011). In addition, these effects were specific to females at two particular CpG sites within the promoter region (Sterrenburg et al., 2011).

Some studies have demonstrated the sex differences in DNA methylation signatures in humans. Adult male suicide victims with a history of childhood abuse were shown to have NR3C1 hypermethylation compared to suicide victims without a history of abuse or non-suicidal postmortem controls (McGowan et al., 2009). Importantly, NR3C1 methylation shows a sex-dependent association between maternal depression and symptoms of anxiety and depression in children. Anxiety, depression, and behavioral symptoms in children can be predicted by prenatal stressors, maternal depression, and anxiety, and low birth weight (Hill et al., 2019). Increased NR3C1 methylation levels were only seen in girls when their mothers had reported lower maternal depression scores during pregnancy, while no evidence of such a relation was observed in boys (Hill et al., 2019). These observations suggest that prenatal stressors, including maternal depression, produce different epigenetic and early behavioral outcomes in males and females. Another study demonstrated a sex-specific cross-tissue methylation signature in the promoter region of the *SLC6A4* gene encoding serotonin transporter, which is known to be a target of antidepressants (Palma-Gudiel et al., 2019). This study showed that the levels of methylation at five contiguous CpG sites were markedly increased in peripheral blood cells and postmortem brain tissue of women compared to men.

The function of DNMT may be associated with depression, and there is evidence that this gene may also be associated with sex-related differences in stress susceptibility. Female mice are more vulnerable to stress than male mice, and females have higher levels of *Dnmt3a* expression than males (Hodes et al., 2015). Loss-of-function mutation of *Dnmt3a* resulted in greater resistance to stress in female mice, whereas its overexpression was associated with higher susceptibility to stress in male mice, suggesting a role of this gene in stress resistance. Thus, DNA methylation by DNMTs may be associated with sex-related differences in the development of stress-induced depression.

Recent studies suggested the potential contribution of 5hmC, the oxidized form of 5mC, to stress and psychiatric disorders. The brain shows a 10-fold enrichment of 5hmC compared to peripheral tissues, and it is associated with neuronal plasticity (Kriaucionis and Heintz, 2009; Szulwach et al., 2011). It is interesting to note that stressed animals show a sex-specific genome-wide disruption of 5hmC. Papale et al. (2016) examined the genome-wide profile of hippocampal 5hmC in female mice exposed to acute stress, and reported that 363 differentially hydroxymethylated regions are linked to known (e.g., *Nr3c1* and *Ntrk2*) and potentially novel genes associated with stress response and psychiatric disorders, and that stress-related hydroxymethylation is correlated with altered transcript levels. Characterization of stress-induced sex-specific 5hmC profiles identified 778 sex-specific acute stress-induced differentially hydroxymethylated regions, some of which were correlated with altered levels of transcripts that produce sex-specific isoforms

in response to stress (Papale et al., 2016). Therefore, the molecular mechanisms underlying the sex-related differences in stress response may involve 5hmC modifications. Although some studies reported altered levels of 5hmC in patients with MDD and bipolar disorder (Soeiro-De-Souza et al., 2013; Tseng et al., 2014; Gross et al., 2017), further studies are needed to investigate the sex-specific role of 5hmC in psychiatric disorders.

Roles of Non-coding RNAs in Sex-Related Differences in Depression

The domains on the X-chromosome that escape XCI include non-coding RNAs in addition to protein-coding genes (Reinius et al., 2010). Elevated expression of X chromosome miRNAs due to XCI escape has been suggested to explain sex bias of disease risk (Pinheiro et al., 2011; Gurwitz, 2019). Indeed, elevated levels of miR-221, which is located on the human X chromosome, were observed in the cerebrospinal fluid and plasma of MDD patients (Wan et al., 2015; Enatescu et al., 2016). In addition, a recent study reported elevated miR-221 expression in the cerebrospinal fluid and serum of MDD patients as well as the hippocampus of mice exposed to chronic unpredictable mild stress. Moreover, miR-221 silencing by antisense oligonucleotides was shown to improve the behavioral symptoms in a chronic stress mouse model (Lian et al., 2018). As in the immune response, the overexpression of miRNAs, such as miR-221, may explain the observed sex-related differences in MDD (Pinheiro et al., 2011). Furthermore, it has been reported that social defeat stress resulted in miR-181a-5p overexpression in the anterior bed nucleus of the stria terminalis in female but not male mice (Luo et al., 2021).

Long non-coding RNAs may also play pivotal roles in sex-specific transcriptional regulation in human depression. A recent study showed that neuronal-enriched lncRNA LINC00473 is downregulated in the PFC of depressed females but not males (Issler et al., 2020). The authors also reported that viral-mediated overexpression of LINC00473 in mouse mPFC neurons increased behavioral resilience to chronic stress, but only in females. Interestingly, LINC00473 modulates synaptic plasticity in mPFC pyramidal neurons of female mice, but not in males, and the knockdown of this lncRNA showed a stronger effect on gene expression in human female-derived neuronal cells than in those derived from males (Issler et al., 2020). LINC00473 is known to regulate CREB signaling (Chen et al., 2016; Liang et al., 2016) and CREB function is strongly associated with depression and stress resilience. Therefore, LINC00473-mediated gene expression plays a key role in molecular adaptations in the brain that contribute to depression in a sex-specific manner.

CONCLUSIONS

Here, we briefly summarized the roles of epigenetic molecules associated with neural plasticity and behavioral regulation in animal models of depression and those that have been suggested

to be involved in human MDD patients and suicide victims (Figure 3). Translational implications for bridging research in human depression and animal models will provide a better understanding of how epigenetic mechanisms contribute to the etiology and pathophysiology of depression.

Depression is a heterogeneous condition that varies widely in severity of symptoms, symptom patterns, age of onset, course trajectory, and responses to treatment, as well as showing sex-related differences. Epigenetic mechanisms, including histone modifications, DNA methylation, and non-coding RNAs, may play important roles in the pathogenesis of MDD, and these signatures may be useful as biological markers of certain subtypes of MDD. Indeed, genome-wide DNA methylation profiling analysis indicated that adult-onset and late-onset depression have distinct epigenetic signatures (Yamagata et al., 2021). In addition, there are sex-related differences in epigenetic signatures in patients with MDD as described in this article, although these findings have yet to be confirmed. Classification and identification of more homogeneous patient groups or subtypes using epigenetic marks may improve our understanding of the etiology and pathophysiology of depression with regard to patient-specific mechanisms, which may aid in the development of more biologically informed, patient-specific diagnoses and treatments (Simon and Perlis, 2010; Beijers et al., 2019).

The sex-related differences in epigenetic markers in the brain tissue are relatively subtle (Nugent et al., 2015; Shen et al., 2015). This may be because the tissues of the brain contain a multitude of cell types, and therefore sex-related differences in cell-type-specific epigenetic signatures are masked in studies relying on homogenates. There have been a few investigations of epigenetic markers in neuronal and non-neuronal nuclei obtained from brain tissues. As predicted, neuronal and non-neuronal cells show different patterns of age-related or disease-specific epigenetic changes (Cheung et al., 2010; Iwamoto et al., 2011; Shulha et al., 2013). Despite the development of conventional techniques for investigating epigenetic markers in specific cell types, further studies are necessary to characterize sex-related differences in brain epigenetics associated with stress, psychiatric symptoms, and depression.

Another limitation at present is the lack of evidence demonstrating similarities in sex-dependent mechanisms between humans and rodent models. Labonte et al. reported that human MDD and mouse chronic variable stress cohorts have an overlap in transcriptional profiles in the vmPFC and NAc. Depressed male mice and stressed mice shared 62 upregulated differentially expressed genes (DEGs) and 90 downregulated DEGs in the vmPFC and 109 upregulated DEGs and 44 downregulated DEGs in the NAc. Likewise, depressed female humans and stressed female mice shared 128 upregulated DEGs and 123 downregulated DEGs in the vmPFC and 89 upregulated DEGs and 81 downregulated DEGs in the NAc. In a gene ontology overlap analysis, several pathways in the vmPFC and NAc have been identified as interspecies conserved in males or females (Labonté et al., 2017). Despite these numerous overlaps, there are only a limited number

of genes whose functions have been clarified. In addition, non-coding RNAs, including lncRNAs, could also be a key to opening the way for constructing valid animal models of human diseases and elucidating the mechanisms underlying sex-specific responses to stress in humans. Since lncRNAs are a recently discovered class of regulatory RNAs, analyzing the mechanism of action of lncRNAs remains challenging. Nevertheless, the research conducted by Issler et al. on the sex-specific role of LINC00473 in depression suggests a roadmap for future studies to explore inter-species mechanisms relating to how lncRNAs contribute to the sex differences in depression (Issler et al., 2020). A better understanding of the roles of epigenetic modifications in psychiatric disorders will be important to provide insights that will facilitate personalized therapy options as the epigenome could be modulated by genetic, age, sex, and environmental factors. Future studies must include both male and female subjects, and sex should be included as a variable to develop effective treatments for the whole population.

Depression is thought to be a heterogeneous disorder caused by deficits in multiple behavioral domains and regulated by many brain structures and systems (Russo et al., 2012). A large body of evidence has demonstrated that long-term neuroplasticity, such as structural plasticity (e.g., spine density), is associated with neuroepigenetic regulation of gene expression within the hippocampus, prefrontal cortex, and nucleus accumbens, and is essential for chronic stress susceptibility and resilience. However, very little is known about how epigenetic mechanisms in other brain regions could account for synaptic plasticity and subsequent depression risk and resilience. Recently, one study reported that the visual circuit may serve as a mechanism underlying the behavioral response to chronic stress and antidepressant actions. A recent report has shown that the activation of the retina-vLGN pathway inhibits neuronal activity in the lateral habenula (LHb), which is required for chronic stress resiliency in mice, and that light therapy ameliorated depression-like phenotypes *via* the retina-vLGN-LHb pathway (Huang et al., 2019). It was found that in rats, chronic treatment with fluoxetine reactivates visual cortex plasticity in adulthood, and this effect was accompanied, at least in part, by reduced intracortical inhibition and increased expression of BDNF in the visual cortex (Maya Vetencourt et al., 2008). In addition, the plasticity of neuronal circuitries in the visual cortex was lower in depressed patients than in control subjects and higher after chronic intake of an antidepressant (Normann et al., 2007). Interestingly, chronic treatment with fluoxetine promotes BDNF expression by promoting H3K9 acetylation in the visual cortex of rats (Maya Vetencourt et al., 2011). Although the epigenetic markers in the visual cortex of patients with MDD are unclear, these results shed new light on our current understanding of the mechanisms of brain plasticity underlying stress, depression, and antidepressant actions.

Of note, brain structure and systems may be modified in response to environmental factors in a sex-dependent way, through neurogenesis. It has been shown that female rats have greater levels of cell proliferation compared to males and

non-proestrous females and this may depend on the phase of the estrous cycle (Tanapat et al., 1999). Indeed, estrogens modulate neurogenesis in females but to a lesser extent in males (Barker and Galea, 2008). BDNF signaling is one of the prime candidates for mediating neurogenesis and neural plasticity of neuronal connection (Thoenen, 1995; Castrén, 2005). As mentioned earlier, *Bdnf* expression is regulated by a variety of epigenetic modifications, including DNA methylation and histone modifications, thus suggesting that hippocampal plasticity might be influenced by neurogenesis through the epigenetic regulation of *Bdnf* expression. However, it remains unclear how plasticity and neurogenesis impact depression-related behaviors and antidepressant actions. In addition, the mystery of whether neurogenesis occurs in adult human remains to be solved (Dennis et al., 2016; Boldrini et al., 2018; Cipriani et al., 2018; Sorrells et al., 2018; Moreno-Jiménez et al., 2019). Future studies will be necessary to clarify the role of epigenetic regulation in the development

and maintenance of brain networks and behaviors and their sex-related mechanisms.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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