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REVIEW

EPIGENETIC MECHANISMS IN MOOD DISORDERS: TARGETING NEUROPLASTICITY

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Abstract—Developing novel therapeutics and diagnostic tools based upon an understanding of neuroplasticity is critical in order to improve the treatment and ultimately the prevention of a broad range of nervous system disorders. In the case of mood disorders, such as major depressive disorder (MDD) and bipolar disorder (BPD), where diagnoses are based solely on nosology rather than pathophysiology, there exists a clear unmet medical need to advance our understanding of the underlying molecular mechanisms and to develop fundamentally new mechanism experimental medicines with improved efficacy. In this context, recent preclinical molecular, cellular, and behavioral findings have begun to reveal the importance of epigenetic mechanisms that alter chromatin structure and dynamically regulate patterns of gene expression that may play a critical role in the pathophysiology of mood disorders. Here, we will review recent advances involving the use of animal models in combination with genetic and pharmacological probes to dissect the underlying molecular mechanisms and neurobiological consequence of targeting this chromatin-mediated neuroplasticity. We discuss evidence for the direct and indirect effects of mood stabilizers, antidepressants, and antipsychotics, among their many other effects, on chromatin-modifying enzymes and on the epigenetic state of defined genomic loci, in defined cell types and in specific regions of the brain. These data, as well as findings from patient-derived tissue, have also begun to reveal alterations of epigenetic mechanisms in the pathophysiology and treatment of mood disorders. We summarize growing evidence supporting the notion that selectively targeting chromatin-modifying complexes, including those containing histone deacetylases (HDACs), provides a means to reversibly alter the acetylation state of neuronal chromatin and beneficially impact neuronal activity-regulated gene transcription and mood-related behaviors. Looking beyond current knowledge, we discuss how high-resolution, whole-genome methodologies, such as RNA-sequencing (RNA-Seq) for transcriptome analysis and chromatin immunoprecipitation-sequencing (ChIP-Seq) for analyzing genome-wide occupancy of chromatin-associated factors, are beginning to provide an unprecedented view of both specific genomic loci as well as global properties of chromatin in the nervous system. These methodologies when applied to the characterization of model systems, including those of patient-derived induced pluripotent cell (iPSC) and induced neurons (iNs), will greatly shape our understanding of epigenetic mechanisms and the impact of genetic variation on the regulatory regions of the human genome that can affect neuroplasticity. Finally, we point out critical unanswered questions and areas where additional data are needed in order to better understand the potential to target mechanisms of chromatin-mediated neuroplasticity for novel treatments of mood and other psychiatric disorders.

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Key words: epigenetics, chromatin, neuroplasticity, experimental medicine, mood disorders.

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Abbreviations: Bdnf, brain-derived neurotrophic factor; BPD, bipolar disorder; CBP, CREB-binding protein; CHD5, chromodomain helicase DNA-binding protein 5; ChIP-Seq, chromatin immunoprecipitation-sequencing; CREB, cAMP response element-binding protein; CUMS, chronic ultra-mild stress; DNMT, DNA methyltransferase; ECS, electroconvulsive seizures; EHMT2, euchromatic histone-lysine N-methyltransferase 2; *Gdnf*, glial cell-derived neurotrophic factor; GR, glucocorticoid receptor; H3K9me3, hippocampal histone H3 lysine (K) 9; HATs, histone acetyltransferases; HDACs, histone deacetylases; *Htr2a*, serotonin 2A receptor; iNs, induced neurons; iPSC, induced pluripotent cell; KDM, histone lysine demethylase; LTP, long-term potentiation; LSD1, lysine-specific demethylase 1; MDD, major depressive disorder; *MECP2*, methyl-CpG-binding protein 2; Msk1/2, mitogen and stress-activated kinases 1 and 2; NuRD, nucleosome remodeling and deacetylation; ncRNA, non-coding RNAs; serotonin, 5-hydroxytryptamine; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; TST, tail suspension test; PRC2, polycomb repressive complex 2.

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CRITICAL NEED FOR MOOD DISORDER RESEARCH AND NEW MECHANISM THERAPEUTICS

Remarkable advances have been made in understanding the complexity of the nervous system and its capacity to exhibit plasticity in response to a variety of stimuli both on short and long-term time scales. Continued advancement of our knowledge of the molecular mechanisms of these adaptive processes of neuroplasticity and the development of novel therapeutics based upon these findings is critical in order to improve the treatment and prevention of nervous system disorders. The mood disorders, major depressive disorder (MDD) and bipolar disorder (BPD), are both prevalent and costly. Both disorders are characterized by episodes of depressed mood and diminished interest and hedonic capacity, referred to as major depressive episodes. In addition to mood symptoms, individuals commonly experience changes in neurovegetative functions including sleep and appetite. Depressive episodes are typically recurrent, and may be chronic as well (Perlis et al., 2006). In bipolar disorder, individuals also experience periods of unusually elevated or irritable mood, referred to as manic episodes; when such episodes do not significantly impact functioning, they are considered to be hypomanic episodes. This mood elevation is generally associated with decreased need for sleep, increased physical activity, impulsive as well as goal-directed activity, and pressured speech. Notably, despite its name, bipolar disorder is not truly 'bipolar' in nature: manic and depressive symptoms can commonly co-occur or fluctuate rapidly, a phenomenon known as a mixed state. In both disorders the affective state (mood) of an individual may be influenced by external stimuli but responses are diminished or exaggerated. During mood episodes, individuals with MDD or BPD often experience cognitive dysfunction, particularly individuals with BPD who may experience residual cognitive symptoms between episodes even in the absence of other prominent mood symptoms (Zarate et al., 2000; Baune et al., 2010). Other psychiatric disorders, including anxiety disorders and substance use disorders, commonly co-occur with mood disorders and contribute to their morbidity.

Despite intensive basic research and clinical studies, our understanding of the etiology and pathophysiology of mood disorders is severely limited (Manji and Duman, 2001; Quiroz and Manji, 2002; Krishnan and Nestler, 2008; Pittenger and Duman, 2008). Consequently, mood disorders remain one of the leading causes of disability worldwide, with the World Health Organization projecting that depressive disorders will be the leading cause of disease burden by 2030 (World Health Organization, 2004). While defined by an episodic course, MDD and BPD symptoms may be chronic, and while periods of recovery are common, rates of recurrence remain high even with appropriate treatment (Rush et al., 2008; Bowden et al., 2012). In fact, such treatments may themselves be associated with significant adverse effects and safety concerns. Consequences of these disorders include functional impairment and poorer general health outcomes; it has been estimated that the economic burden of these disorders in the United States alone stretches into tens of billions of dollars each year (Greenberg et al., 1993).

In the case of MDD, there exists substantial experimental and clinical evidence dating back six decades implicating alterations in 5-hydroxytryptamine (serotonin) and catecholamines such as dopamine and norepinephrine in pathophysiology as well as treatment, giving rise to the ''monoamine theory'' of MDD. However, despite the wealth of data supporting the role of the aberrant monoaminergic system in the pathophysiology of MDD, directly targeting these mechanisms of synaptic transmission is neither necessary nor sufficient for clinical efficacy, as shown by the effectiveness of electroconvulsive therapy (Dierckx et al., 2012), the effects of glutamatergic antidepressants such as ketamine (Zarate et al., 2010), and the repeated observation that more than a third of individuals with MDD do not achieve symptomatic remission with monoaminergic antidepressants (Rush et al., 2009).

In the case of BPD, which involves both manic and depressive episodes, longitudinal studies indicate that patients with BPD I and II are burdened by significant depressive symptoms for much of their course despite standard treatments (Judd et al., 2002, 2003). These symptoms contribute to the substantial morbidity and mortality observed in bipolar disorder, including persistent functional impairment (Tohen et al., 2000) as well as suicide (Osby et al., 2001). National and international treatment guidelines recognize the challenges in treating bipolar depression (Hirschfeld et al., 2002; Keck et al., 2004). Specifically, standard antidepressants have repeatedly failed to show benefit in randomized, controlled trials (Nemeroff et al., 2001; Sachs et al., 2007). Lithium, considered a gold standard treatment in preventing recurrence by *all* major guidelines, nonetheless does not consistently show superiority to placebo for the treatment of depression.