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EC PSYCHOLOGY AND PSYCHIATRY
Research Article

Modifications on Histone Tails in Psychiatric Disorders

Qiao Mao[1]#, Zhixiong Luo[2]#, Zongyang Yu[3]#, Bin Chen[4], Kesheng Wang[5], Yuping Cao[6], Jiawu Ji[7], Fan Wang[8], Lingjun Zuo[9], Chiang-Shan Li[9], Xiaoping Wang[10]*, Yong Zhang[11]* and Xingguang Luo[9]*

[1]Department of Psychosomatic Medicine, People's Hospital of Deyang City, Deyang, Sichuan, China

[2]College of Integrative Medicine, Fujian University of Traditional Medicine, Fuzhou, China

[3]Department of Pulmonary and Critical Care Medicine, Fuzhou General Hospital of Fujian Medical University, Fuzhou, China

[4]Shengli Clinical Medical College of Fujian Medical University and Department of Cardiovascular Medicine, Fujian Provincial Hospital, Fuzhou, Fujian, China

[5]Department of Family and Community Health, School of Nursing, Health Sciences Center, West Virginia University, Morgantown, WV, USA

[6]Department of psychiatry, China National Clinical Research Center on Mental Disorders (Xiangya), the Second Xiangya Hospital of Central South University, ChangSha, China

[7]Department of Psychiatry, Fujian Medical University Affiliated Fuzhou Neuropsychiatric Hospital, Fuzhou, Fujian, China

[8]Beijing Huilongguan Hospital, Peking University Huilongguan Clinical School of Medicine, Beijing, China

[9]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

[10]Department of Neurology, Shanghai Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

[11]Institute of Mental Health, Tianjin Anding Hospital, Mental Health Center of Tianjin Medical University, Tianjin, China

***Corresponding Author:** Xiaoping Wang, Department of Neurology, Shanghai Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China and Yong Zhang, Institute of Mental Health, Tianjin Anding Hospital, Mental Health Center of Tianjin Medical University, Tianjin, China and Xingguang Luo, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA.

Received: March 25, 2025; **Published:** February 11, 2026

Abstract

The present study provides a comprehensive introduction to the features of histone tails, including their length, subtypes, nomenclature, biological functions, and regulation, and systematically reviews their roles in psychiatric disorders. A literature search was conducted, covering over 200 common histone modifications and the top 20 common psychiatric disorders. The results indicate that 26 histone tail modifications are positively associated with ten psychiatric disorders, with most located at H3 and H4 tails, and only one at the H2AX tail. All modifications occur at lysines (K), except for two at arginine (R) or serine (S). The top five modifications associated with psychiatric disorders are H3K9ac, H3K4me3, H3K27ac, H3K9me2, and γH2AX. The majority of the studies (92%) report substance use disorders, Alzheimer's disease, major depressive disorder, schizophrenia, and autism spectrum disorders as the top five psychiatric disorders associated with histone tail modifications. In conclusion, histone tail modifications play crucial roles in various psychiatric disorders, and targeting them and associated epigenetic regulators may offer potential therapeutic strategies for treating psychiatric disorders by providing new insights into the molecular mechanisms underlying abnormal gene expression.

Keywords: *Histone Tail; Histone Modification; Psychiatric Disorder; Methylation; Acetylation; Epigenetic Regulation; Gene Expression*

Introduction

Histones act as spools for DNA to form nucleosomes. The nucleosome core is an octameric structure made up of two H2A-H2B dimers and one H3-H4 tetramer. Nucleosomes are then packed into 30-nanometer fibers that form chromatin, which are further packaged into chromosomes. Additionally, in the core of nucleosomes, there are unstructured N-terminal or C-terminal tails of histone proteins called histone tails, which are flexible regions flanking both ends of the histone fold.

Histones play important roles in gene regulation, DNA replication, and protecting DNA from tangling and damage. Different histone variants control chromatin architecture, nucleosomal positioning, and DNA access. Histone positive charge, particularly in the tails, stabilizes nucleosomes by neutralizing DNA's negative charge. The histone tails are the most common sites of post-translational histone modifications, and they play a critical role in nucleosome structure and dynamics. These modifications disrupt condensed chromatin structure, allowing for gene access and higher-order chromatin formation. The present study comprehensively introduces the features of histone tails and systematically reviews the role of histone tail modifications in psychiatric disorders.

Length of histone tails: The lengths of histone tails in humans vary with the specific isoforms, post-translational modifications, and definitions. In general, the N-terminal tails of histones H2A, H2B, H3, and H4 consist of about 15-23, 30-35, 25-40 and 25 amino acid residues, respectively. Similarly, the C-terminal tails of histones H2A, H2AX (a variant H2A), and H2B consist of about 30, 43, and 18 amino acid residues, respectively (Figure 1).

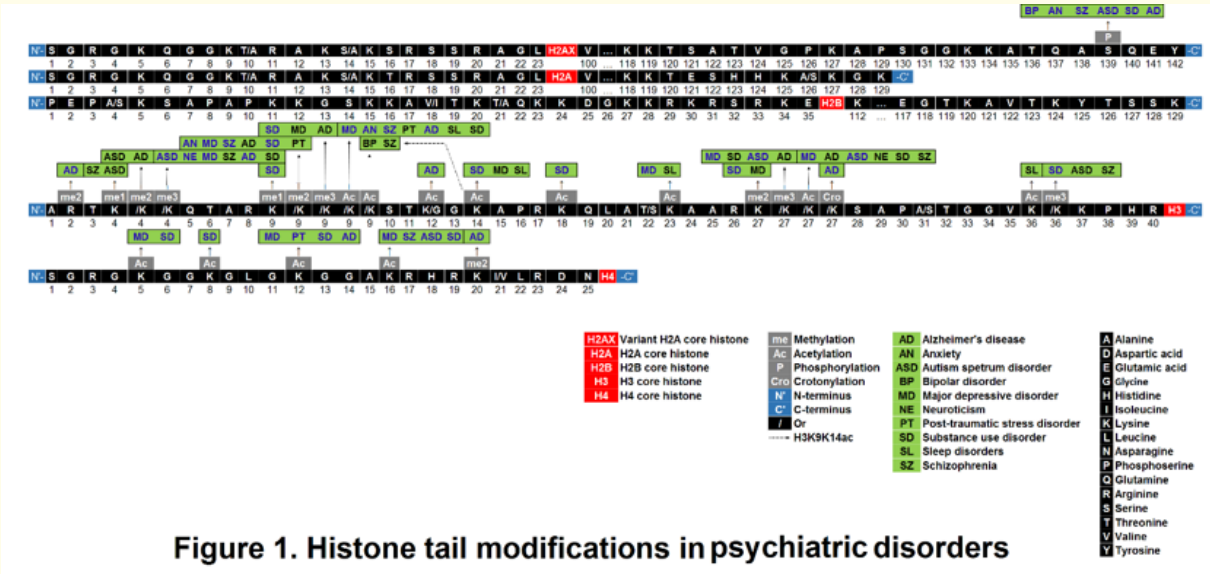

Figure 1. Histone tail modifications in psychiatric disorders

Subtypes of histone tail modifications: At least nine different types of histone tail modifications have been discovered, with well-understood methylation, acetylation, phosphorylation, and ubiquitylation, and less-understood GlcNAcylation, citrullination, crotonylation, sumoylation, and ADP-ribosylation:

- Methylation (me): Addition of one (me1), two (me2), or three (me3) methyl groups from S-adenosyl-L-methionine to a lysine (K) or arginine (R) residue on the histone tail.
- Acetylation (ac): Addition of one acetyl group to a lysine (K) residue.
- Phosphorylation (Ph): Addition of a phosphate group to a serine (S), threonine (T) or tyrosine (Y) residue.

- Ubiquitination (ub): Addition of a ubiquitin protein to lysine (K) residues.
- Glycosylation (GlcNAc): Addition of a carbohydrate group to serine (S) or threonine (T) residues.
- Citrullination (cit): Addition of a deimination group to arginine (R) residues.
- Crotonylation (cro): Addition of a crotonyl group to lysine (K) residues.
- Sumoylation (su): Addition of a small ubiquitin-like modifier (SUMO) protein to lysine (K) residues.
- ADP-ribosylation (ADPr): Addition of an ADP-ribose molecule to glutamic acid (E) or aspartic acid (D) residues.

Nomenclature of histone tail modification: Histone modifications are named using a common nomenclature that follows a specific format. This format includes the histone type (H2A, H2B, H3, and H4), the single-letter abbreviation of the modified amino acid residue (K, R, S, T, Y, E, and D) and its position in the protein, the type of modification (ac, me, Ph, ub, GlcNAc, cit, cro, su, and ADPr), and the number of modifications (illustrated in table 1). Methylation can be mono-, di-, or tri- (me1, me2, or me3), with methylation being the only modification that can occur in multiple copies. For instance, H3K4me3 indicates the trimethylation of the 4th lysine residue from the N-terminal of the H3 protein.

H3K4me3	=	**H3**	+	**K**	+	**4**	+	**me**	+	**3**
↓		↓		↓		↓		↓		↓
Name of histone modification		Histone type		Symbol of residue		Position of residue		Type of modification		Number of modifications

Table 1: *Nomenclature of histone modifications.*

Most common subtypes of histone tail modifications: In most species, common histone modifications include H3K9ac, H3K14ac, H3K18ac, H3K23ac, H3R2me, H3K4me, H3K9me, H3K27me, H3K36me, H3S10Ph, H3S28Ph, H3T11Ph, H4K5ac, H4K8ac, H4K12ac, H4K16ac, H4R3me, H4K20me and H4S1Ph, with the top three being H3K4me3, H3K9me3, and H3K27me3. In general, the most common modifications are the methylation of lysine (K) or arginine (R) residues or the acetylation of lysine (K).

Biological functions of histone tail modification: Histone tail post-translational modifications regulate biological processes such as transcription, histone code forming, chromosome packaging, and DNA damage/repair, which alters chromatin structure, recruits histone modifiers, affects transcriptional state and impacts gene expression. Some modifications disrupt histone-DNA interactions, unwinding nucleosomes and creating euchromatin (i.e. open chromatin conformation) that facilitates transcriptional machinery binding to DNA for gene activation. In contrast, other modifications strengthen histone-DNA interactions to form heterochromatin, which tightly packs DNA and results in gene silencing. Therefore, different types of histone modifications correspond to different biological functions:

- Methylation (me): Methylation can affect how other protein such as transcription factors interact with the nucleosomes and activate or silence specific genes, with lysine (K) methylation being the most dominant. Although the addition of one, two, or many methyl groups to lysine has little effect on the chemistry of the histone, it can be recognized with exquisite sensitivity by some proteins differentially, which makes lysine methylation a very informative histone modification mark.
- Acetylation (ac): Histone acetylation is consistently related to transcriptional activation, affecting many cellular processes [1]. Lysine (K) acetylation could eliminate a positive charge on lysine, thereby eliminating the electrostatic attraction between histone and DNA, and making DNA more accessible for gene expression by partially unwinding it. Highly acetylated histones are linked to active transcription and form more accessible chromatin. Unlike methylation, lysine acetylation is less precise in meaning since histone acetyltransferases tend to modify multiple lysines, which is necessary to have a significant effect on chromatin structure.

- Phosphorylation (Ph): Histone phosphorylation has clear functions as a post-translational modification. Serine (S), threonine (T) or tyrosine (Y) phosphorylation can lead to major changes in protein structure, leading to the well-characterized role of phosphorylation in controlling protein function.

Specifically, (I) some common modifications on the histone tails associated with transcriptional activation, their locations in associated genes, and their biological functions are listed in table 3 or described below:

- H3K4me1 marks active enhancers.
- H3K4me2 marks active promoters.
- H3K4me3 is an excellent mark of active promoters.
- H3K36me3 occurs in actively transcribed gene bodies, regulating transcription and playing a critical role in maintaining genome stability.
- H3K9ac marks active enhancers and promoters.
- H3K27ac marks active enhancers and promoters.
- H3S10Ph, H3S28Ph and H2AT120Ph mark active enhancers and promoters. They are involved in chromatin compaction and regulation of chromatin structure and function during mitosis. They are important markers of cell cycle and cell growth that are conserved throughout eukaryotes.
- γH2AX is a phosphorylated H2AX, a variant H2A, at serine 139. It serves as an early marker for DNA double-strand breaks (DSB), which can cause cell death if unrepaired [2]. γH2AX forms a domain extending many kilobases on either side of the damage, recruits DNA damage repair proteins [3,4] and facilitates chromatin decondensation after DNA double-strand breaks. Overall, γH2AX plays a vital role in maintaining genome stability.
- H2A.z, a variant H2A, is required for mitosis and enriched in nucleosomes surrounding the transcription start site of active promoters, playing critical roles in chromatin structure and epigenetic regulation.

(II) The common modifications on the histone tails associated with transcriptional repression, their locations in associated genes, and their biological functions are listed in table 3 or described below:

- H3K9me2/3 is a well-characterized marker for heterochromatin and satellite repeats, therefore, strongly associated with gene repression.
- H3K27me2/3 is a marker of inactive genes, specifically marking promoters in gene-rich regions to exert a repressive function.
- H4K20me3 is tightly associated with heterochromatin and represses transcription, particularly when present at promoters of genes that are repressed.

Regulation of histone tail modifications: Table 2 shows the specific enzymes, known as writers and erasers, responsible for dynamically adding and removing histone modifications on specific amino acid residues. Histone methyltransferases (HMTs) regulate DNA methylation via transcriptional repression or activation through controlling histone methylation. Inhibition of histone demethylases (KDMs) can lead to histone re-methylation, affecting chromatin dynamics and gene expression. Histone acetyltransferases (HATs) control histone acetylation, and more than 20 HATs have been identified. Histone deacetylases (HDACs) catalyze the removal of acetyl groups from histone lysine residues and have been classified into four classes. HDAC inhibition can increase histone acetylation, whereas HAT inhibition decreases it.

Types of modifications	Writers	Erasers
Methylation	Histone methyltransferases (HMTs/KMTs) and protein arginine methyltransferases (PRMTs)	Lysine demethylases (KDMs)
Acetylation	Histone acetyltransferases (HATs)	Histone deacetylases (HDACs)
Phosphorylation	Kinases	Phosphatases

Table 2: *Histone erasers and writers. Source: (https://www.abcam.com/epigenetics/histone-modifications).*

Significance of histone modification detection in neuropsychiatric disorders: Epigenetic modifications, including histone modifications, are crucial for neuronal development and function, neural stem cell fate determination, and have been implicated in psychiatric disorders such as bipolar disorder and major depressive disorder. An imbalance in histone acetylation has been associated with pathological processes in psychiatric disorders, with increased global H3K27me methylation found in some cases. Detection of various histone modifications, particularly histone H3 acetylation at lysine residues, can provide useful information for a better understanding of epigenetic regulation and the development of histone modifying enzyme-targeted drugs. The dysfunction of epigenetic regulation has been closely linked to neurodegenerative diseases such as Alzheimer's, Parkinson's [5] and Huntington's, suggesting potential therapeutic targets for these diseases.

Methodology

A systematic literature search was conducted using the PubMed database to identify papers published up to March 2023, with the search terms "H2A* OR H2B* OR H3* OR H4*" and "psychiatric disorders." The study examined over 200 common histone modifications and the top 20 common psychiatric disorders, including major depressive disorder (MDD), bipolar disorder, anxiety disorders (such as generalized anxiety disorder, panic disorder, and phobias), schizophrenia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), attention-deficit/hyperactivity disorder (ADHD), borderline personality disorder, eating disorders (such as anorexia nervosa and bulimia nervosa), autism spectrum disorder (ASD), substance use disorders (including alcohol and drug abuse/dependence), insomnia and other sleep disorders, dissociative disorders (including dissociative identity disorder), Alzheimer's disease, personality disorders (such as antisocial personality disorder and narcissistic personality disorder), schizoaffective disorder, adjustment disorder, delusional disorder, conduct disorder, and depersonalization/derealization disorder. The present study reviewed, extracted, summarized, illustrated, and discussed the positive findings between histone modifications and psychiatric disorders.

Results

A total of 26 histone tail modifications are positively associated with a total of ten psychiatric disorders. Most of them are located at H3 tail, and then H4 tail; only one is at H2A tail, i.e. γH2AX; but none at H2B tail. All of these modifications occur at lysines (K), but two at arginine (R) (i.e. H3R2me2) or serine (S) (i.e. γH2AX). The five disease-associated histone tail modifications reported by highest numbers (65%) of studies are H3K4me3, H3K9ac, H3K27ac, H3K9me2 and H3K27me3. The five modifications associated with highest numbers of psychiatric disorders are H3K9ac, H3K4me3, H3K27ac, H3K9me2 and γH2AX; each of them is associated with ≥6 different psychiatric disorders; and 100% of the total ten psychiatric disorders are positively associated with these five modifications (Table 3 and figure 1).

Modification	Associated diseases	#	Functions	Location
H3K4me3	MDD, SZ, PD, ASD, SD, AD	31	Activation	Promoter, bivalent domains
H3K9ac	MDD, AN, SZ, PT, SD, AD, SL	30	Activation	Enhancers, promoters
H3K27ac	MDD, SZ, PD, ASD, SD, AD	21	Activation	Enhancers, promoters
H3K9me2	MDD, AN, SZ, PT, SD, AD	19	Repression	Satellite repeats, telomeres, pericentromeres
H3K27me3	MDD, ASD, SD, AD	15	Repression	Promoters in gene-rich regions, developmental regulators, bivalent domains
H4K12ac	MDD, PT, SD, AD	8	Activation	Promoters
H3K14ac	MDD, SD, SL	8	Activation	Promoters
H3K9me3	MDD, SD, AD	7	Repression	Satellite repeats, telomeres, pericentromeres
γH2AX	BP, AN, SZ, ASD, SD, AD	6	DNA damage	DNA double-strand breaks
H4K16ac	MDD, SZ, ASD, SD	5	Activation	Repetitive sequences
H3K36me3	SZ, ASD, SD	4	Activation	Gene bodies
H3K27me2	MDD, SD	3	Repression	Promoters in gene-rich regions, developmental regulators, bivalent domains
H4K5ac	MDD, SD	3	Activation	Enhancers
H4K8ac	SD	3	Activation	Enhancers
H3K4me1	SZ, ASD	2	Activation	Enhancers
H3K4me2	ASD, AD	2	Activation	Promoter
H3K9K14ac	BP, SZ	2	Activation	Enhancers, promoters
H3K18ac	SD	2	Activation	Enhancers
H3K9me1	SD	1	Activation	Enhancers
H3K12ac	AD	1	Activation	Promoter
H3K23ac	SL	1	Activation	Promoter
H3K27Cro	AD	1	Activation	Promoter
H3K36Ac	SL	1	Activation	Enhancers, promoters, gene bodies
H3R2me2	AD	1	Activation	Enhancers, promoters
H4K20me2	AD	1	Activation	Enhancers, promoters
Crotonylation	MDD	1	Activation	Promoter
H3S10P	-	-	DNA replication	Mitotic chromosomes, enhancers, promoters
H3S28Ph	-	-	Activation	Enhancers, promoters
H4K20me3	-	-	Repression	Promoter
H2A.Z	-	-	Activation	Promoter
H2AT120Ph	-	-	Activation	Enhancers, promoters

Table 3: *Associated psychiatric disorders, functions and locations for histone modifications.*

#: Total number of studies for each disease. SD: Substance Use Disorders; AD: Alzheimer's Disease; MDD: Major Depressive Disorders; SZ: Schizophrenia; ASD: Autism Spectrum Disorders; SL: Sleep Disorders; AN: Anxiety; PT: Post-Traumatic Stress Disorder; BP: Bipolar Disorder; PD: Personality Disorder (Neuroticism, NE). γH2AX = pS139H2AX. "-", missing.

Disease	Histone modifications (in an order of numbers of studies)	#
SD	H3K9ac, H3K9me2, H3K4me3, H3K27me3, H3K14ac, H3K27ac, H4K12ac, H4K8ac, H3K36me3, H3K9me3, H3K27me2, H4K5ac, H3K18ac, H4K16ac, γH2AX (pS139H2AX) and H3K9me1	67
AD	H3K27ac, H3K9ac, H3K27me3, H3K4me3, H3K9me2, H3K9me3, H4K12ac, γH2AX (pS139H2AX), H3K4me2, H3K12ac, H3K27Cro, H3R2me2 and H4K20me2	45
MDD	H3K9ac, H3K4me3, H3K27me3, H4K12ac, H3K9me3, H3K27ac, H3K9me2, H3K14ac, H4K16ac, H3K27me2, H4K5ac, H3K23ac and histone crotonylation	21
SZ	H3K4me3, H3K27ac, H3K9me2, γH2AX (pS139H2AX), H3K9ac, H3K9K14ac, H4K16ac, H3K36me3 and H3K4me1	18
ASD	H3K4me3, H3K27ac, H4K16ac, γH2AX (pS139H2AX), H3K36me3, H3K4me1, H3K27me3 and H3K4me2	15
SL	H3K9ac, H3K14ac, H3K23ac and H3K36Ac	4
AN	γH2AX (pS139H2AX), H3K9ac and H3K9me2	3
PT	H3K9me2, H3K9ac and H4K12ac	3
BP	H3K9K14ac and γH2AX (pS139H2AX)	2
PD	H3K4me3 and H3K27ac	2

Table 4: *The histone tail modifications associated with various psychiatric disorders.*

#: Total number of studies for each disease. SD: Substance Use Disorders; AD: Alzheimer's Disease; MDD: Major Depressive Disorders; SZ: Schizophrenia; ASD: Autism Spectrum Disorders; SL: Sleep Disorders; AN: Anxiety; PT: Post-Traumatic Stress Disorder; BP: Bipolar Disorder; PD: Personality Disorder (Neuroticism, NE).

The majority (92%) of the studies report five psychiatric disorders that are positively associated with histone tail modifications, including SD, AD, MDD, SZ and ASD each of which is associated with ≥8 different modifications; and 84% of the total 26 histone modifications are positively associated with these five disorders (Table 4 and figure 1). The findings regarding the specific roles of various histone modifications in distinct disorders are described below.

Substance use disorders (SD) [6-45]: Acute or chronic alcohol exposure induces neurodegeneration and chromatin modifications in the brain, including histone tail methylation and acetylation. It affects H3K18ac levels in the cerebral cortex and alters genes involved in histone demethylation at H3K36me3 and H3K9me3. Alcohol exposure decreases histone acetylation levels, such as H3K27ac, H4K12ac, and H4K16ac, particularly at the Slc23a2 gene, and leads to a global increase in γH2AX levels and H3K27me3 enrichment in IL-6 signaling pathway genes. Alcohol exposure also increases H3K9me2 levels and HTR3A mRNA levels through mechanisms involving H3K9ac, and enhances G9a, causing caspase-3-mediated degradation of H3K9me2. Furthermore, it significantly increases H3K9ac levels in the NAc, prefrontal cortex, and dentate gyrus, and may modify H3K9ac in the NR2B gene promoter in the hippocampus. Finally, alcohol exposure can increase the expression of prefrontal cortex GABA-Aα5 through H3K4me3 induction. These changes could be hereditary, potentially increasing vulnerability to alcohol addiction in offspring.

Numerous studies have demonstrated that histone tail modifications contribute to the development of alcohol use disorders. Fetal Alcohol Spectrum Disorders (FASD) are characterized by enrichment of H3K27me2, H3K27me3, H3K9me2, and increased expression of histone acetyltransferases and methyltransferases. Additionally, the adult hippocampus in alcohol use disorder exhibits a novel interface between H3K27me3, H3K4me3, and oxidative stress mechanisms. In the prefrontal cortex, alcohol-dependent patients have significantly higher H3K9ac levels than the saline group, and HTR3A mRNA expression levels are positively correlated with H3K9ac levels in the HTR3A promoter region. Histone demethylase KDM6B is upregulated in alcohol-dependent rats, leading to decreased H3K27me3 levels. Higher HDAC2 expression-related deficits in global H3K9ac may be involved in controlling alcohol drinking behaviors. Alcohol dependence is also

associated with H3K9me1 levels, and changes in H3K9ac modifications in the local chromatin of the NR2B gene underlie alcohol-induced neuroadaptation. Lastly, amygdaloid G9a-mediated H3K9me2 mechanisms regulate rapid tolerance to the anxiolytic effects of alcohol via neuropeptide Y expression regulation. These histone modifications, e.g. H3K9ac in the HTR3A promoter region, and related enzymes, e.g. G9a, could be potential therapeutic targets for alcohol dependence. Inhibiting G9a pharmacologically may provide a novel approach to treating stress-induced alcohol drinking, a major trigger of relapse in alcohol-dependent individuals.

Studies have also found alterations in histone modifications and related enzymes in response to cocaine exposure, including global reduction of H3K9me2 in the nucleus accumbens by cocaine-induced repression of G9a through ΔFosB, which enhanced dendritic spine plasticity and preference for cocaine, implicating the crucial role of H3K9me2 in the long-term effects of cocaine. Additionally, cocaine decreased H3K9me3 at specific genomic repeats and showed similar effects on H3K4me3 with alcohol. Finally, cocaine-induced alterations in gene expression may cause changes in neuronal morphology and behavior underlying cocaine addiction, highlighting the potential of histone modifications and related enzymes as therapeutic targets for treating cocaine addiction.

During reinstatement from heroin use, the increased levels of H3K18ac, H4K8ac, and H4K5ac in the accumbens nucleus core and shell are further strengthened by intracerebroventricular injection of sodium butyrate (NaB), which reduces heroin-seeking behaviors. Heroin-related H3K27ac contributes to glutamatergic transcriptional changes underlying heroin-seeking behaviors. The increased BRG1 expression in the mPFC after heroin self-administration suggests an essential and novel role for BRG1 and its H3K9ac-mediated regulation in epigenetically modulating the activation of neuroplasticity-associated genes. Bromodomain inhibitor JQ1, which blocks the functional readout of acetylated lysines, is a promising candidate for targeted clinical interventions in heroin-seeking behaviors. Additionally, chronic morphine exposure regulates H3K9me2 and H3K14ac in basolateral amygdala (BLA) which are associated with the formation of morphine memory in rats. Inhibition of histone deacetylases activity in BLA can promote cue-associated memory induced by morphine, and histone acetylation may regulate the involvement of BDNF in BLA.

Finally, histone tail modifications may contribute to more other substance use disorders. In the adult nucleus accumbens (NAc), G9a regulates multiple behaviors associated with substance use disorder by dimethylating H3K9me2. METH-associated memory development and expression are regulated by H3K4me2/3 levels via MLL1 and KDM5C, respectively, in the NAc. Acute METH injections increase gene expression of genes with increased H4K5ac binding near their transcription start sites. THC exposure disrupts the normal developmental pattern of H3K9me2 or H3K9me3 methylation, mediating Penk upregulation in the NAcsh.

Alzheimer's disease (AD) [46-70]: Histone acetylation plays a role in aging, with H3K27ac hypoacetylated at the 5htr2a and Drd2 promoters in aged mice, resulting in reduced expression of key atypical antipsychotic drug targets. H3K9ac is increased in the promoter region of Bdnf exon IV in aged mice, leading to improved memory through increased BDNF expression in the hippocampus. Histone methylations, including H3K27me3, H3K79me3, H3R2me2, and H4K20me2, tend to decrease with age in brain tissues. Histone phosphorylation, including γH2AX, linearly increases with age and may serve as a biomarker for human morbidity in age-related diseases.

Alzheimer's disease involves epigenome reconfiguration that dysregulates transcription and chromatin-gene feedback loops, resulting in increased H3K27ac and H3K9ac histone modifications in the brain of AD patients. Diabetes may promote AD development by hyperacetylating H3K9 histone on the CDK5 promoter. Some risk loci associated with differentially acetylated risk genes have H3K27ac peaks enriched in oligodendrocyte-enriched glial (OEG). Curcumin (CUR) at moderate and high doses regulates AD progression via MSR JMJD3-H3K27me3-BDNF axis. H3K4me3 is lower, and H3K27me3 is higher in AD patients' entorhinal cortices, particularly in males. H3K4me3 in healthy and AD samples involves promoter regions of genes in AD-related pathways like glutamate receptor signaling. Age-related changes in H3K27ac and H3K27me3 are detected in NF-labeled pyramidal neurons and calretinin-positive interneurons, respectively. Increasing genome-wide H3K27ac or H3K9ac exacerbates amyloid-β42-driven neurodegeneration, while decreased H3K27Ac and/or increased H3K27Cro reduces the expression of multiple related genes in the early stage of AD. Studies suggest that

histone modification transcriptionally regulates most lncRNA genes in AD as 8 differential H3K27me3 peaks are found upstream of 7 lncRNA genes. The ANK1 gene in entorhinal cortex with high or low AD pathology has decreased H3K4me3 levels, a marker of active gene transcription, and altered epigenetic marks indicative of reduced gene activation in Alzheimer's disease.

Major depressive disorder (MDD) [71-83]: Stress, whether early in life (ELS) or chronic, can bring about changes in gene expression and epigenetic modifications in the brain, affecting histone acetylation and methylation. ELS, in particular, is associated with altered BDNF expression and H3K9me2, while decreased levels of H3K9ac and H4K12ac have been linked to stress-induced depressive-like behaviors. In depression, numerous studies have reported changes in histone methylation and acetylation, with suicides exhibiting significant increases in H3K4me3 and H3K27me2 levels and risk variants for depressive symptoms being over-represented in neuronal H3K4me3 and H3K27ac landscapes. The coupling of epigenetic histone acetylation with 5-HT1A receptor activity may play a role in depression's pathophysiology and treatment, as selective agonists for 5-HT1A receptors can increase H3K9ac, H4K5ac, and H4K12ac levels. Enriched environments can prevent depression-like behaviors caused by chronic unpredictable stress (CUS) by preventing changes in H3K4me3 and H3K27me3 caused by CUS. Histone modifications can also regulate specific genes implicated in depression, such as the Crhr1 gene in the hypothalamus of rats exposed to chronic unpredictable mild stress (CUMS). Jumonji domain containing demethylases (Jmjd2) have been identified as critical epigenetic regulators involved in depression's etiopathology and related disorders, with chronic administration of inhibitors targeting these demethylases resulting in depression-like phenotypes. Therefore, activating these demethylases may represent a potential strategy for treating mood disorders. Finally, chromodomain Y-like protein (CDYL) inhibits structural synaptic plasticity by transcriptional repression of neuropeptide VGF nerve growth factor inducible, and its activity as a key regulator of depression-like behaviors induced by chronic social defeat stress is dependent on its dual effect on histone crotonylation and H3K27me3 on the VGF promoter.

Schizophrenia (SZ) [81,84-95]: Histone modifications play a role in the pathogenesis of schizophrenia, with H3K4me3 dysregulation identified as a mechanism contributing to the disease's development. Schizophrenia is associated with H3K4me3 changes in a subject-specific manner, and risk variants for the disease are found in neuronal H3K4me3 and H3K27ac landscapes. Next-generation sequencing has identified H3K4me3 regulators mutated in neurodevelopmental disorders, including schizophrenia. Increased H3K9me2 levels are observed in schizophrenia patients, while a restrictive chromatin state is associated with the disease and is less modifiable using HDAC inhibitors. Enrichment of H3K4me1 and H3K36me3 is related to the development of schizophrenia, and enriched environment exposure during early adolescence can inhibit the disease's symptoms by regulating epigenetic mechanisms. Understanding the role of histone modifications in schizophrenia can provide insights into the disease's risk architecture and may contribute to the development of improved prevention and treatment strategies for schizophrenia.

Autism spectrum disorder (ASD) [28,85,88,96-105]: Next-generation sequencing has found mutations in H3K4me regulators associated with neurodevelopmental disorders like intellectual disabilities and autism spectrum disorders. These mutations affect proteins that play a central role in epigenetic regulation and have been identified in genes associated with autism spectrum disorders and Rett syndrome. Dysregulated H3K4me3 is observed in neuronal chromatin from autism spectrum disorder cases, and an excess of H3K4me3 spreading is observed into downstream gene bodies and upstream promoters. The mean level of H3K4me3 is elevated in the autism spectrum disorder cerebellar samples, and genes related to ion channels, synaptic function, and epilepsy/neuronal excitability are strongly enriched among loci with increased H3K27ac, which have been previously shown to be dysregulated in autism spectrum disorders. Loci with decreased H3K27ac in autism spectrum disorders also converge on shared functional categories such as digestive tract morphogenesis, chemokine signaling, HDAC activity, and immune processes related to microglia. H3K4 demethylases play a role in brain development, and when these enzymes are mutated, brain development is altered. The RAI1-containing H3K4me3 writer complex counterbalances the LSD1-containing H3K4me3 eraser complex to ensure normal brain development. Environmental determinants such as maternal immune activation, parental care, and monoaminergic drugs are identified as influencing brain-specific H3K4me3.

Furthermore, vigilin (Vgl1) plays an essential role in heterochromatin formation, chromosome segregation, and mRNA stability and is associated with autism spectrum disorders. Vigilin depletion delays dephosphorylation of ionizing radiation (IR)-induced γ-H2AX, impairing their recruitment to double-strand break (DSB) sites. H4K16ac promotes vigilin recruitment to DSBs preferentially in the transcriptionally active genome, and there is a novel vigilin role in DNA damage repair with implications for autism spectrum disorders. Abnormal H3K4me2 is associated with downregulated genes in synaptic signaling and developmental processes in autism spectrum disorders. Human-specific regulatory changes of H3K27ac are uncovered in genes associated with autism spectrum disorders. There is preferential evolutionary divergence in neuron subtype-specific regulatory elements H3K27ac, showing that a substantial fraction of pan-neuronal regulatory elements H3K27ac undergoes subtype-specific evolutionary changes. H3K27me3 in the engrailed-2 (EN-2) promoter is significantly decreased in autism spectrum disorder samples. H3K36me3 is associated with alternative pre-RNA processing, which occurs in an FMRP-dependent manner on transcripts linked to neural function and autism spectrum disorders. The downregulation of TGIF2, possibly regulated by H3K4me1, is correlated with neuronal apoptosis and development of autism spectrum disorders through the inactivation of the Wnt/β-catenin pathway.

Sleep disorders (SL) [106,107]: Sleep disorders are associated with changes in H3K9ac and H3K14ac, which are increased in the hippocampus and hypothalamus but decreased in the prefrontal cortex and raphe nucleus. Meanwhile, obstructive sleep apnea (OSA) patients show decreased global expression of H3K23ac and H3K36ac. It is suggested that H3K23ac and H3K36ac may influence the severity of sleep-disordered breathing through up-regulation of HDAC1. Specifically, decreased H3K36ac, including HIF-1α gene promoter-specific enrichment, is associated with disease severity in OSA patients.

Anxiety disorders (AN) [108-110]: Adolescent intermittent ethanol (AIE) exposure increases HDACs and decreases CBP levels, potentially decreasing H3K9ac and BDNF expression, inhibiting neurogenesis, and inducing anxiety-related behavioral abnormalities in adulthood. AIE also specifically modulates epizymes involved in H3K9me2 in the amygdala, possibly contributing to AIE-induced chromatin remodeling and adult anxiety. Additionally, stress exposure alters anxiety-like behavior in male C57BL/6J mice by increasing γH2AX levels in the bed nucleus of the stria terminalis (BNST).

Post-traumatic stress disorders (PT) [111,112]: Traumatic stress in adolescence and the inescapable foot shock (IFS) procedure induce H3K9me2 levels in the hippocampus (HIP) and prefrontal cortex (PFC), suggesting that H3K9me2 dysfunction plays a key role in the pathogenesis of PTSD. However, environmental enrichment (EE) has been shown to regulate H3K9ac and H4K12ac in the hippocampus and amygdala. This regulation can ameliorate Early life stress (ELS)-induced PTSD-like behaviors and reduce susceptibility to PTSD in adulthood.

Bipolar disorder (BP) [86,113]: Lithium salt treatment in bipolar disorder affects DNA integrity by accumulating p53 and γH2AX, important markers of genome damage, which initiates a chromatin-based signaling cascade and activates DNA damage response proteins at the lesion site. In addition, several bipolar disorder-related genes, such as GAD1, HTR2C, TOMM70A, and PPM1E, have promoter-associated H3K9K14ac levels correlated with gene expression levels. Notably, the H3K9K14ac levels of some of these genes are significantly negatively associated with bipolar disorder.

Personality disorder (PD) [81]: Neuronal H3K4me3 and H3K27ac landscapes are significantly enriched with risk variants for neuroticism (NE).

Discussion

The findings presented in the Results above indicate that epigenetic mechanisms play a critical role in alcohol dependence by regulating gene expression through histone modifications at gene promoters that are up- and down-regulated by alcohol [32]. Alcohol's effects on histone methylation may trigger future transcriptional changes, leading to behavioral changes that last into adulthood [11]. Higher HDAC2

expression-related deficits in global histone acetylation may contribute to lower NPY expression in the amygdala, controlling alcohol-drinking behaviors [19]. Epigenetic alterations also contribute to low-dose alcohol-induced neurodegeneration in the developing brain and alcohol withdrawal-induced depression [36]. The use of an HDAC inhibitor can correct the altered epigenetic state caused by alcohol withdrawal and alleviate depression-like symptoms [36]. Targeting histone acetylation and permissive histone methylation, along with the associated epigenetic writers and erasers, represent potential targets for treating alcohol dependence. Individual variability in acute alcohol-induced epigenetic response may contribute to vulnerability to alcohol dependence and relapse [114], while the consistency of epigenetic alterations may implicate them as key mechanisms underlying fetal alcohol spectrum disorders (FASD) [38]. Epigenetic mechanisms also underlie behavioral deficits after adolescent intermittent alcohol exposure and contrasted behavioral response to alcohol challenge. Moreover, the findings presented in the Results also indicate that permissive histone modifications, such as acetylation, and associated epigenetic writers and erasers are also potential therapeutic targets for heroin-induced behaviors, cocaine addiction, and marijuana dependence. The epigenetic alterations in prefrontal cortex after repeated cocaine administration support the epigenetic basis of cocaine addiction, and the epigenetic dysregulation of Penk in NAcsh induced by THC underlies the long-term effects of THC [12].

Moreover, the findings support that histone modifications play a role in brain aging, age-related neurodegenerations, and AD pathogenesis, and the signatures of these modifications in AD patients validate their role in epigenetic chromatin remodeling and highlight the genomic adaptive mechanisms in AD. AD involves early epigenetic changes that may result in increasing severity of typical antipsychotic haloperidol-induced side effects in the elderly and dementia patients, causing lower efficacy [70]. These changes are attributed to the involvement of a broad spectrum of histone modifications in brain aging and neurodegenerations. In particular, oligodendrocyte gene regulation is suggested as a potential mechanism by which early and late onset risk genes mediate their effects and deregulate myelinating processes in AD [53]. Epigenetic modifiers may mediate latent increases in AD-related proteins in the brain [66] and histone modifications may transcriptionally regulate many lncRNAs in AD [49]. These findings also suggest that histone modifications could be potential therapeutic targets for AD.

Finally, the findings indicate that histone modifications, including CDYL-mediated histone crotonylation, contribute to depression, particularly stress-induced depression and suicidal behavior [76,77]. They are a crucial mechanism in the pathogenesis of schizophrenia too, supporting the hypothesis of a restrictive epigenome in this disease. Furthermore, dysregulation of histone modifications is a significant driver of autism spectrum disorders [104]. The epigenetic risk architectures may also provide potential prevention and therapeutic targets for these disorders.

Summary

Environmental factors, such as adolescent ethanol exposure and traumatic stress, as well as genetic factors, can affect histone modifications that contribute to alterations in human behaviors. For example, positive early-life experiences may enhance coping with stress in adulthood through stable and long-lasting histone modifications. Histone tail modifications regulate genes and contribute to psychiatric and neurological processes. Dysregulated histone methylation causes neurodevelopmental disorders, while histone acetylation contributes to drug-induced behaviors and neuroplasticity impairment. Histone tail modifications and dysregulation of histone-modifying enzymes and chromatin regulators have been associated with psychiatric disorders, including substance use disorders, aging-related diseases such as Alzheimer's disease, depression, intellectual disabilities, autism spectrum disorders, schizophrenia, bipolar disorders, sleep disorders, anxiety, PTSD, and personality disorders.

Significance

Epigenetic alterations in the brain, including histone tail modifications, histone-modifying enzymes, and chromatin regulators, are potential therapeutic targets for psychiatric disorders. Studies on these alterations can provide insights into the molecular mechanisms underlying abnormal gene expression in these disorders, leading to new therapeutic pathways. By understanding the dysregulation of epigenetic alterations, prevention and treatment of psychiatric disorders can be improved.

Conclusion

Histone tail modifications play crucial roles in regulating genes in both normal and pathological psychiatric processes, and their dysregulation can lead to various psychiatric disorders. Certain brain regions utilize histone modifications to interact with environmental and genetic factors, contributing to the development of these disorders. Targeting histone tail modifications and associated epigenetic regulators may provide new insights into the molecular mechanisms underlying abnormal gene expression and offer potential therapeutic strategies for treating psychiatric disorders.

Future Directions

Histone tail modifications do not exist in isolation but rather engage in complex interplay, often referred to as crosstalk, forming intricate regulatory networks. Understanding this interconnectedness is crucial for comprehending the dynamic regulation of gene expression, thus forming a significant future research direction.

These histone modifications are not spontaneous events but are tightly regulated by specific enzymes, also known as writer and reader proteins, such as histone methyltransferases, demethylases, acetyltransferases, and deacetylases. Reader proteins recognize and bind to specific histone tail modifications, recruiting other effector molecules to further modulate gene expression. Investigating the modification effects of these enzymes represents another important research direction.

In-depth analysis of the specific roles and regulatory networks of these enzymes in the context of psychiatric disorders is crucial for a comprehensive understanding of the multifaceted nature of histone tail modification regulation, forming yet another future research direction.

Other research directions include identifying specific histone tail modifications or regulatory mechanisms and exploring how these modifications can be targeted to develop novel therapeutic strategies for psychiatric disorders.

Disclosure

#Qiao Mao, Zhixiong Luo and Zongyang Yu all authors contributed equally.

Authors Contribution

Q.M., Z.L. and Z.Y. wrote this article. Q.M., Z.L. and XG.L. did the data analysis. B.C., K.W., Y.C., J.J., F.W., L.Z., CS.L., X.W., Y.Z. and XG.L. edited this article.

Conflict of Interest

There is no conflict of interest to declare.

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