Proceedings of ICEGEE 2026 Symposium: AI-Based Medicine and Biological Data Analysis
DOI: 10.54254/2753-8818/2026.AU31842

Epigenetic Alterations of Brain Neurotransmitter Receptors of Patients with Anxiety Disorders

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Abstract. Anxiety disorders comprise a diverse set of psychiatric conditions. They do not arise from a single pathological pathway but from interactions among neurobiological susceptibility, environmental influences, and regulatory processes. Growing evidence indicates that traditional neurotransmitter-centered models cannot fully explain individual differences in disease risk, disease duration, or treatment response. Epigenetic regulation has thus emerged as a key mechanism linking environmental exposure to persistent alterations in gene expression without changing the DNA sequence. Through epigenetic modification, neurotransmitter receptor expression and function may be dysregulated within anxiety-related neural circuits. This review summarizes current findings on epigenetic modulation of neurotransmitter receptors in anxiety disorders, with particular emphasis on multigenic regulation, receptor-level mechanisms, and the unresolved barriers to clinical translation

Keywords: Anxiety disorders, Epigenetic regulation, Neurotransmitter receptors, Gene expression, Stress susceptibility

1. Introduction

1.1. General characteristics of anxiety disorders

From a functional perspective, anxiety represents an adaptive response to uncertain or distal threats, manifesting as coordinated changes in behavior, physiology, and cognition to enhance environmental vigilance [1]. These defensive responses are evolutionarily conserved, facilitating translational research into underlying neural circuits [1]. At the circuit level, the prefrontal cortex (PFC) plays a regulatory role in primates, potentially by predicting potential threats and modulating neural activity [1].

Epidemiologically, anxiety disorders affect roughly 25% of individuals globally, and approximately 34% of the U.S. population. It is often characterized by persistent worry and apprehension preceding actual threats, imposing lifelong impairments on functioning and quality of life [2,3]. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) categorizes anxiety disorders into generalized anxiety disorder (GAD), social anxiety disorder (SAD), specific phobias, panic disorder (PD), post-traumatic stress disorder (PTSD), adjustment disorder, selective mutism, and obsessive-compulsive disorder (OCD) [3]. Common symptoms of anxiety disorders in primary care include panic disorder (lifetime prevalence: 5.2%), generalized anxiety disorder (6.2%), and

DOI: 10.54254/2753-8818/2026.AU31842

social anxiety disorder (13%) [2]. Besides, sleep disturbances, such as insomnia, are frequently comorbid [3]. First-line treatments for patients with anxiety disorders typically include pharmacotherapy and psychological interventions. Medications such as selective serotonin reuptake inhibitors (SSRIs, e.g., sertraline) and serotonin-norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine) show modest to moderate efficacy over placebo [2].

1.2. Genetic mechanisms of pathogenesis

Neurobiologically, anxiety and fear are mediated by distinct circuits: the bed nucleus of the stria terminalis (BNST) is implicated in anxiety, whereas the central amygdala (CeA) primarily governs fear responses [4]. Notably, structural brain abnormalities are generally absent in individuals with anxiety disorders compared to healthy controls [4].

Genome-wide analyses of 1.2 million participants, including 97,383 anxiety cases, have identified 51 anxiety-related loci [5]. Heritability is enriched in genes expressed within the cerebral cortex, brainstem, limbic system, cerebellum, entorhinal cortex, and metencephalon [5]. Transcriptomic and proteomic studies further link 115 genes to anxiety, implicating both brain-specific and systemic pathways [5]. Anxiety also shows genetic overlap with depression, bipolar disorder, and schizophrenia, along with pleiotropic associations with various physical health domains [5].

In humans, anxiety disorders have been associated with SNPs such as rs1709393 (near LOC15225) and rs7528604 (near PDE4B) [6]. Animal models support a genetic basis. For instance, the C57BL/6J strain mice exhibit greater stress resilience compared to DBA/2J or BALB/cJ strains, with sex modulating anxiety-related phenotypes [6]. Phosphodiesterase 4 (PDE4), abundant in anxiety-related regions like the amygdala and prefrontal cortex, regulates cAMP signaling. PDE4B knockout significantly exacerbates anxiety-like behaviors in mice, underscoring its role in anxiety modulation [6].

1.3. Environmental and psychological factors

Variability in anxiety responses may lead to different coping strategies: problem-focused coping targets actionable stressors, while emotion-focused coping aims to regulate affective distress [7]. In a broader psychosocial context, demographic variables such as gender, age and even climate may also cause anxiety [7]. Individuals with pre-existing mental health conditions are more vulnerable to climate-related anxiety, which may exacerbate underlying distress [7].

Adverse childhood environments significantly elevate the risk of mood and anxiety disorders in adulthood [8]. Risk factors can be categorized into biological (e.g., genetics, health status, medication), social (e.g., social support, living conditions, stressful events), and psychological domains (e.g., personality traits, coping styles) [9].

2. Classification and functions of neurotransmitter receptors

2.1. Classification of neurotransmitter receptors

Neurotransmitters are endogenous chemicals that mediate neuronal communication, underpinning diverse brain functions [10]. They are released from presynaptic terminals and bind to postsynaptic receptors, enabling chemical synaptic transmission [10]. Imbalances in neurotransmitter systems are implicated in numerous neurological and psychiatric disorders, including Alzheimer's disease,

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Parkinson's disease, depression, and schizophrenia [10]. During development, neurotransmitters guide neuronal differentiation, growth, and circuit formation [10].

Neurotransmitters are broadly classified into amino acids (e.g., GABA, glutamate), amines (e.g., dopamine, serotonin), and other molecules (e.g., purines, gaseous transmitters) [11]. Based on the effects, neurotransmitters are further categorized into excitatory neurotransmitters, such as glutamate, and inhibitory ones, such as glycine and gamma-aminobutyric acid (GABA) [10]. The effect of a neuron on its targets depends on the neurotransmitter it released and the specific receptor on the postsynaptic cell [12]. Fast-acting transmitters like glutamate and GABA are stored in small clear vesicles, whereas monoamines (dopamine, serotonin) reside in small dense-core vesicles, and neuropeptides in larger dense-core vesicles [12].

2.2. Key neurotransmitter receptors involved in anxiety disorders

Neurotransmitter receptors and transporters govern synaptic signaling and contribute to regional brain specialization. However, only a subset of receptors (e.g., CB1, D2, 5-HT1A, MOR) exhibit strong correlations between density and gene expression, which should be a key focus in clinical translation [13]. Besides, studies showed that the distributions of neurotransmitter receptors also correlated with its functions. Positron emission tomography (PET) mapping of 19 receptors across over 1200 healthy individuals reveals that the neurotransmitter receptor similarity aligns with both structural and functional connectivity [14]. These neurotransmitter receptor distributions correlate with cortical abnormalities in 13 neuropsychiatric disorders, suggesting that chemoarchitectural patterns may underline neuropsychiatric disorder vulnerability [14].

Key neurotransmitters implicated in anxiety include GABA, glutamate, dopamine, serotonin, norepinephrine, and acetylcholine [10]. Glutamate drives excitatory transmission and synaptic plasticity, whereas GABA mediates approximately 40% of inhibitory signaling [10]. Dopamine modulates reward, emotion, and executive control; serotonin regulates diverse psychological processes and is a primary target of psychotropic drugs [10]. Norepinephrine influences attention, stress response, and autonomic regulation [10].

The GABA-A receptor, with its allosteric modulatory sites, is a major target of anxiolytic drugs [15]. Altered subunit composition or endogenous modulation may disrupt its inhibitory effect in anxiety disorders, with stress-sensitive neurosteroids offering therapeutic potential [15].

In animal studies, heat-killed Enterococcus faecalis (EC-12) alleviated anxiety-like behavior in mice and upregulated prefrontal cortex genes such as Adrb3, Avpr1a, and Drd5 [16].

3. Epigenetic regulation of neurotransmitter receptors in anxiety disorders

3.1. Overview of epigenetic modifications

The heritability of anxiety disorders is around 30%, yet GWAS have not identified definitive causal genes [17]. Stress exerts strong effects on stress-responsive brain regions and the HPA axis via epigenetic mechanisms. Neuroepigenetics may explain individual differences in stress susceptibility and anxiety behaviors [17].

Epigenetic regulation involves heritable changes in gene activity without DNA sequence alteration, including DNA methylation, RNA modifications, non-coding RNA (ncRNA) activity and histone modifications [17,18].

DNA methylation, catalyzed by DNMTs at CpG dinucleotides, typically represses transcription [18]. Early-life and adult stress differentially shape anxiety-related methylation patterns [17]. Key

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methylated loci associated with anxiety include promoters of GR, CRH, CRF, RELN, NR3C1, NTSR1, HDAC2, and DNMT3A [17]. Other genes with reported methylation changes in anxiety include BDNF, OXTR, GAD1, FKBP5, and POMC [18].

Reversible chemical modifications on RNA molecules-collectively termed the 'epigenetic transcriptome' or 'epitranscriptome'-have also emerged as a crucial layer of post-transcriptional regulation. These RNA modifications, including N6-methyladenosine (m6A), N1-methyladenosine (m1A), and 5-methylcytosine (m5C), dynamically fine-tune RNA metabolism, influencing RNA stability, splicing, nucleus export, and translation [19-21]. The m6A modification, the most abundant internal mark on eukaryotic mRNA, is installed by methyltransferase complexes (writers, e.g., METTL3/METTL14), removed by demethylases (erasers, e.g., FTO, ALKBH5), and recognized by binding proteins (readers, e.g., YTHDF family), creating a reversible and precise regulatory circuit [19-21].

Non-coding RNAs (miRNAs, lncRNAs, circRNAs) fine-tune gene expression by sequestering RNAs or regulating translation [18]. Several miRNAs are implicated in anxiety: anxiolytic miRNAs (e.g., Let-7d, miR-17, miR-92) and anxiogenic ones (e.g., miR-92a, miR-155) [18]. Patients with GAD show altered expression of miRNAs such as miR-501, miR-663, and miR-432 in peripheral blood mononuclear cells [22].

Beyond DNA methylation and RNA modifications, histone modifications also play a pivotal role in regulating gene expression at post-translational level. Histone modifications (e.g., acetylation, methylation) regulate chromatin accessibility. Histone acetyltransferases (HATs) promote gene expression, whereas histone deacetylases (HDACs) suppress it [18].

Studies have shown that dysregulated DNMT/HDAC activity can disrupt HPA axis function, stress pathways, and glutamate/GABA/BDNF signaling across the PFC, hypothalamus, amygdala, and hippocampus [23]. HDAC inhibitors can reverse anxiety-like behaviors and stress-induced molecular changes in preclinical models [23].

3.2. Epigenetic regulation of core neurotransmitter systems in anxiety

3.2.1. Glutamate and GABA: excitation/inhibition balance

The balance between glutamatergic (excitatory) and GABAergic (inhibitory) neurotransmitters in certain brain regions like the prefrontal cortex (PFC), amygdala, and hippocampus is fundamental to anxiety disorders.

The expression of glutamate receptor subunits is finely regulated by epigenetic mechanisms. Chronic stress models of anxiety often show promoter DNA hypermethylation and/or increased repressive histone marks (e.g., H3K27me3) on genes encoding glutamate receptor subunits (e.g., GRIN1, GRIN2A) in the PFC and hippocampus, leading lower expression levels [23]. This impairs synaptic transmission and neuroplasticity, correlating with deficits in fear extinction and cognitive flexibility. Besides, targeted epigenetic intervention can be therapeutic. Research showed that the inhibition of histone deacetylase 5 (HDAC5) increased histone acetylation, elevated the expression of the glutamate receptor delta-1 subunit (GRID1/GluD1), and resulted in anxiolytic and antidepressant effects [24]. Animal studies also showed that stress can downregulate endocannabinoid (CB1) receptor expression in the prefrontal-amygdala circuit via epigenetic mechanisms may impair the ability to suppress excessive glutamate release and lead to anxiety-like behaviors and fear extinction deficits [25].

Attenuated GABAergic signaling is also a hallmark of anxiety. Chronic stress can induce promoter hypermethylation of genes for GABA synthesis enzymes or receptor subunits in key brain

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regions [24]. Furthermore, enhanced activity of histone deacetylases (HDACs) reduces histone acetylation and suppresses GABA-related gene expression. Broad or specific HDAC inhibitors have been shown to restore GABAergic function and exert anxiolytic effects in animal models [23].

3.2.2. Monoaminergic systems

Monoamine neurotransmitters are the primary targets of classic anxiolytic and antidepressant drugs, and the monoamine neurotransmitters expression are greatly related to epigenetic control.

Serotonin (5-HT): Research has shown that the methylation status of the serotonin transporter SERT and receptor 5-HT1A is closely related to anxiety traits and stress reactivity. Early-life stress can induce lasting epigenetic changes in 5-HT related genes, increasing anxiety susceptibility in adulthood [23].

Dopamine: Dysregulated methylation level of dopamine system may also result in anxiety. A study of human saliva samples showed that the increased methylation of dopamine transporter DAT1 correlated with higher stress level in highly sensitive individuals [26]. Animal studies showed that the aberrant dopamine signaling led to widespread increase in repressive H3K9me2/3 modification, downregulating the expression of nearly 2000 genes in prefrontal cortex linked to psychotic-like behaviors [27].

3.2.3. The Hypothalamic-Pituitary-Adrenal (HPA) axis

Hyperactivity of the HPA axis is a core neuroendocrine feature of anxiety disorders. Epigenetic regulation of the glucocorticoid receptor, such as (GR, encoded by NR3C1) is pivotal.

Research indicated that the methylation level of the glucocorticoid receptor gene NR3C1 had strong correlation with depressive and anxious symptoms of young adults [28]. Besides, robust evidence confirmed that early-life adversity, such as childhood maltreatment, may lead to DNA hypermethylation of specific promoter regions (exon 1F) of the NR3C1 gene [28]. This hypermethylation suppresses GR expression, resulting in impaired negative feedback of the HPA axis, sustained cortisol elevation, and a significantly increased risk for anxiety and depression in adulthood [23,28].

4. Conclusion

Many psychiatric disorders, including anxiety, involve polygenic contributions, reflecting the 'one phenotype-many genes' dilemma. Despite advances in sequencing, identifying causative genes remains difficult, necessitating integrated genotype-phenotype and network analyses.

Although no single gene causally defines anxiety disorders, accumulating evidence highlights the role of epigenetic variation. However, most research has focused on early-life and acute stress, leaving the epigenetic impacts of chronic low-grade stress, metabolic factors, environmental toxins, and psychosocial variables underexplored. Reliance on animal models and peripheral tissues further limit direct translation to human brain pathophysiology.

Future progress will require integrative approaches that connect epigenomic profiles, neurotransmitter receptor biology, and systems neuroscience to elucidate how specific epigenetic modifications alter receptor function and drive anxiety phenotypes. Addressing these challenges is essential for developing epigenetically informed therapies for anxiety disorders.

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