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Review
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A Pathological Study of Major Depressive Disorder Related to Amygdala Structure

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ABSTRACT

Major depressive disorder (MDD) has severe consequences that extend beyond mental health, affecting physical health and quality of life, and raising mortality risk. The pathophysiology of MDD is still poorly understood, and current antidepressants are not completely effective. Current research identifies several key hypotheses and biochemical mechanisms involved in the pathogenesis of MDD, demonstrating that no single theory can fully explain its complexities. Recent research on MDD therapies indicates that they alter the amygdala, causing changes that can serve as markers for recovery in MDD treatment. Observations suggest that selective serotonin reuptake inhibitors, which are routinely used to treat depression, alter amygdala anatomy and function. This study used a narrative and descriptive review methodology. This review aimed to update structural and functional alterations in the amygdala that are strongly associated with MDD and its clinical symptoms. Also, some possibilities about the role of key endogenous substances were discussed, such as cortisol, epinephrine, and norepinephrine, as well as receptors for hormones and neurotransmitters in the amygdala, providing evidence and molecular mechanisms that emphasize the amygdala's central role in MDD and its therapy.

Keywords: Major depressive disorder, amygdala, dysfunctional amygdalae, monoamines and receptors.

OVERVIEW OF MAJOR DEPRESSIVE DISORDER WITH CHANGES IN THE AMYGDALA

Updating the Basic Knowledge of Major Depressive Disorder: General Information, Prevalence, and Etiology

Depression is a mental illness affecting over 5% of the global population, with an estimated 700 000 suicides occurring per year (according to the World Health Organization (WHO)).[1] It has a lengthy history in terms of disease recognition, before being identified and acknowledged as a distinct medical condition necessitating treatment. In 1621, Richard Burton published "The Anatomy of Melancholy," gradually reshaping prior concepts that were rooted in causal theories. By the late 19th century, Kraepelin proposed that depression had a psychogenic etiology. A severe form of depression is major depressive disorder (MDD), which requires comprehensive treatment. Major depressive disorder patients do not exhibit physical phenotypes but instead present with mood, emotional, and cognitive manifestations, making classification and diagnosis intricate. The ICD-11 (International Classification of Diseases, 11th edition) in 2018 and the DSM-5 in 2013 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) documented and classified depression based on pathological standards of clinical features, incorporating both psychological and biological causative factors. Major depressive

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disorder symptoms include depressed mood, diminished interest or pleasure in activities, significant weight changes, sleep disturbances, fatigue, feelings of worthlessness or guilt, concentration difficulties, and suicidal thoughts. These symptoms must persist for at least 2 weeks and cause impairment in daily functioning to meet the diagnostic criteria.[2] The current diagnosis of MDD primarily relies on checklist tools rather than specific tests.

According to the WHO's 2023 fact sheet on depression and the 2024 fact sheet on adolescent and young adult health, depression affects people of all ages. However, older adults are at particular risk due to factors such as chronic illness and social isolation. At the same time, adolescents and young adults are also highly vulnerable, with depression being a major contributor to the overall global burden of disease in this age group. Studies on the epidemiology of diseases by gender show that females have a higher prevalence of elevated depressive symptoms and MDD compared to males.[3,4] MDD typically emerges in the mid-twenties, but it can appear at any age, from childhood to old age. Its clinical manifestations and comorbidities often include anxiety disorders and substance misuse.[5,6] In patients with other comorbid conditions, depressive symptoms can arise suddenly and persist for extended periods. Patients have poor outcomes and face challenges in treatment when other physical diseases are present.

The etiology of MDD is multifaceted and involves various factors such as (epi)genetics, stress, monoamine deficiency, inflammatory processes, hormonal imbalances, neurotransmission disorders, and the microbiome-gut-brain axis, as well as the hypothalamic–pituitary–adrenal (HPA) axis.[7,8] Related to brain structure, the amygdala is one of the most intensely studied regions in relation to depression, with its abnormalities being closely linked with other MDD etiological factors such as HPA axis hyperactivity and neurotransmission imbalances.

The Alteration of the Amygdala in Patients with Major Depressive Disorder

Researchers continue to deepen studies into the differences in various brain regions between depressed patients and healthy individuals, ranging from overall spatial structure to molecular mechanisms. The altered structural and functional characteristics of the amygdala in patients play a crucial role in MDD, particularly through amygdala dysfunction, which significantly affects emotional processing. First, the role of the amygdala, its clinical manifestation, and why its structure and function impact depression pathogenesis will be clarified. Further, at the molecular mechanism level, the focus will be on analyzing the 3 hormones cortisol, epinephrine, and norepinephrine, and their effects on the amygdala.

The amygdala was identified by the physiologist Karl Friedrich Burdach in 1822. It is part of a complex brain structure located in the temporal lobe.[9] It consists of heterogeneous nuclei, including basolateral, centromedial, and cortical complexes, with extensive connections to various cortical and subcortical regions. The amygdala is involved in emotional recognition, behavior, and decision-making, responding differentially to stimuli. It plays a functional role in emotional processing through facial expressions. The amygdala is also hypothesized to process emotional value, importance, social status, and moral features, contributing to behaviors and social cognition. Additionally, it manages emotional information, fear responses, and socio-sexual behaviors.[9]

To date, research has documented inconsistent findings regarding structural changes in the amygdala in depression. In 1 study, Chinese patients with severe MDD who had a history of suicide attempts exhibited reduced gray matter volume (GMV) in both the right and left amygdala.[10] In contrast, Taha et al[11] (2021) described depressed patients in Sudan as having increased GMV of the amygdala. Even more complicated, other research reported no significant differences in GMV and amygdala volumes between MDD patients and healthy controls.[12,13] The differences in results among these studies might be explained by the differences in the severity of clinical features and the age range of the patients. In connective regions, studies have shown that MDD patients exhibit atypical topological characteristics within the hippocampus-amygdala complex, with shortened mean characteristic path length, reduced modularity, and a reduced small-worldness index.[14] Overall, these studies reveal that there is no general pattern of amygdala structural changes in MDD.

In contrast to structural changes, functional changes in the amygdala in MDD patients are fairly consistent across studies. Quantitative evaluations of amygdala function in depressed patients have shown increased amygdala activation, reduced intrinsic connectivity, and hyperreactivity, which have a negligible impact on emotion processing and stress response. Individuals with MDD exhibit greater amygdala activation in response to threats compared to healthy controls,[15] contributing to anxious arousal. Children with MDD show heightened negative affective reactivity, increased amygdala response to negative stimuli, and a decreased response to positive emotional stimuli.[16] Major depressive disorder is associated with amygdala-based network dysfunction, including hypoconnectivity between amygdala subregions like the amygdalostriatal transition area (AStr) and basolateral amygdala (BLA) with the orbitofrontal cortex (OFC), and hyperconnectivity between the left AStr/BLA and the fusiform gyrus. Additionally, individuals with childhood maltreatment exhibit impaired regulation of the amygdala by the medial prefrontal cortex, leading to amygdala hyperactivity. Research suggests that altered brain connectivity and amygdala structure may mediate the effects of prenatal maternal depressive symptoms on child behavior, highlighting the impact of maternal mental health on children's development.[17,18] Moreover, MDD is associated with decreased functional connectivity between the amygdala and prefrontal cortex regions, linked to volumetric reductions in these brain regions, correlating with severe depressive symptoms.[10,19]

Correlation Between Changes in the Amygdala and Major Depressive Disorder Clinical Manifestations: Direct Observations

The amygdala is altered in patients with MDD, and these alterations lead to clinical symptoms. Research from multiple studies provides insights into the hyperactivity and reduced intrinsic connectivity in the amygdala of MDD patients. Neuroimaging has highlighted the involvement of the amygdala in depression, showing hyperreactivity in response to negative stimuli, particularly in the left amygdala.[20] This heightened amygdala reactivity is associated with biased emotional processing risk and mood and anxiety symptoms in young adults when exposed to negative life events in the future.[20] The amygdala plays a pivotal role in processing negative facial expressions in individuals with MDD. They exhibit altered amygdala responses to emotional stimuli, showing increased reactivity to negative faces (referred to as sad faces) and reduced responsiveness to positive ones.[21] Abnormalities in amygdala activity associated with threat-related facial expressions are also observed in early-onset MDD patients. All of these abnormalities in amygdala activity suggest disruptions in fronto-limbic pathways. This is because the limbic system comprises brain structures like the hippocampus, amygdala, nucleus accumbens, and cingulate gyrus, which are responsible

for emotional processing, memory, and spatial coding. Specifically, depressed individuals tend to display enhanced amygdala activation in response to sad facial expressions. This contrasts with the responses observed in healthy individuals. Adolescents with MDD show altered functional coupling in a network involving the subgenual anterior cingulate cortex (sgACC)-amygdala pathway during emotional face processing, leading to errors in assessing the condition and inappropriate emotional responses.[21,22] In summary, the dysfunctional amygdala contributes to the processing of negative facial expressions in MDD patients. They potentially lead to symptoms like anhedonia and altered emotional processing.

Amygdala Changes During Major Depressive Disorder Treatment with Selective Serotonin Reuptake Inhibitors and Others

The FDA (Food and Drug Administration) has approved several treatments for MDD, reflecting a range of pharmacological strategies. These treatments include antidepressant medications and non-medication therapies targeting different mechanisms. Antidepressant medications include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, serotonin modulators, atypical antidepressants, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), esketamine, and other medications such as mood stabilizers and antipsychotics. Non-medication therapies include psychotherapy, electroconvulsive therapy (ECT), transcranial magnetic stimulation, vagus nerve stimulation, and Cognitive Behavioral Therapy (CBT). Among these therapies, SSRIs are the most common treatments for MDD in both adults and children. Research suggests that response rates of fluoxetine and escitalopram in adolescents range from 56% to 63.6%.[23] Treatment of MDD patients with fluoxetine can induce changes in amygdala activity and improve emotional processing.[24] This can be involved with alterations in the central amygdala (CeA); fluoxetine has been linked to changes in endocannabinoid signaling and glutamatergic receptor function, potentially influencing behaviors related to alcohol relapse.[25] Short-term escitalopram (10 mg daily) treatment in depressed patients has been found to readjust amygdala hyperactivity in response to negative emotional stimuli, even before significant clinical improvement.[26] Additionally, acute administration of fluoxetine has been found to enhance fear memory by affecting specific amygdalar circuits, particularly the bed nucleus of the stria terminalis.[27] Studies on MDD in adult patients aged 25 to 55 years treated with paroxetine also demonstrate changes in amygdala activation, particularly in responders compared to nonresponders.[28] Higher amygdala serotonin transporter occupancy by paroxetine correlates with greater attenuation of amygdala activation in response to negative facial expressions in MDD patients.[29] This provides insights into the working mechanism of SSRIs in modulating amygdala activity. Besides SSRIs, ketamine and ECT treatment also result in decreases in amygdala reactivity during the processing of positive and negative stimuli, relating to their fast-acting antidepressant response. In medication-naive MDD patients, the amygdala's connectivity with the left medial superior frontal gyrus (mSFG) significantly enhances after ketamine treatment, correlating with a reduction in depressive symptoms.[30] Additionally, in 2024, the FDA approved CBT as a non-medication treatment in MDD. Cognitive Behavioral Therapy can lead to significant changes in brain activity, which may contribute to symptom improvement in MDD, as well as serve as predictive markers for treatment response. Moreover, there have been studies exploring the use of Deep Brain Stimulation of the ventral anterior limb of the internal capsule (vALIC) to modulate amygdala responsivity and connectivity. Although this method has not yet been approved by the FDA for the treatment of depression, research has shown that it can normalize amygdala responsivity, improve behavioral vigilance, and potentially contribute to the antidepressant effects in patients with treatment-resistant depression. Additionally, extremely selective laser ablation of the amygdala-hippocampal unit has been proposed as a successful surgical intervention for medically unresponsive post-traumatic stress disorder (PTSD), hinting at the potential for amygdala-targeted interventions in psychiatric disorders like MDD. Furthermore, in several studies, altering gene expression in the amygdala through lifestyle interventions may modulate amygdala activity, implying it to be a promising non-invasive treatment approach for MDD. While understanding the changes in amygdala activity during MDD treatment with SSRIs and others provides crucial insights into therapeutic mechanisms, it is also important to consider the underlying molecular and neurobiological alterations that may drive these observed effects. In this context, the abnormal expression of receptors in the amygdala, particularly those related to neurotransmitter systems, might play a significant role in the pathophysiology of MDD.

STRESS HORMONES AND THEIR EFFECTS ON THE AMYGDALA IN MAJOR DEPRESSIVE DISORDER

The Involvement of Cortisol in Depression: the Relationship Between the Hypothalamic-Pituitary-Adrenal Axis and the Amygdala

The HPA axis is a major neuroendocrine system that controls stress responses and regulates various other bodily processes. Activation of the HPA axis results in the secretion of glucocorticoids from the adrenal cortex, with cortisol being the primary glucocorticoid in humans. Cortisol produced in the adrenal cortex, in turn, has a negative feedback action on both the hypothalamic release of corticotropin-releasing hormone (CRH) and the pituitary release of adrenocorticotropic hormone (ACTH). To date, the hyperactivity of the HPA axis and dysfunctional negative feedback of the HPA axis have been consistently reported in MDD, with the cortisol level seeming to be chronically elevated in depressive patients. Cortisol has been widely been used in the laboratory to create animal models exhibiting depressive-like characteristics. Although more research is needed, there are accumulated data supporting that the dysregulation of the HPA axis and the abnormal cortisol level in MDD are associated with changes in the amygdala.[31] In 1 study, patients with recurrent depressive episodes had larger left and right amygdala volumes correlated with a more pronounced reduction of HPA activity measured by cortisol secretion during antidepressant therapy.[32] In another study, stress-induced cortisol response was associated with right amygdala volume in early childhood.[33] A recently published study on adolescent patients showed that greater activation of the amygdala in response to social distress and ambiguity may be related to the hyper-reactivity of the HPA axis and a greater cortisol activation slope.[34] Also, cortisol administration has been shown to alter resting-state functional connectivity (rsFC) in the amygdala, particularly reducing connectivity with regions like the dorsomedial prefrontal cortex in individuals with a history of depression.[35] Understanding the effects of cortisol on amygdala connectivity and structure may inform therapeutic strategies targeting the HPA axis and stress response systems in MDD.

The Role of Epinephrine and Norepinephrine in Memory and Emotional Processing in Major Depressive Disorder and the Involvement of the Amygdala

Epinephrine and norepinephrine are critical catecholamines involved in various physiological processes, especially the

mechanism of the "fight or flight" response and memory processing, which are indeed critical components in understanding MDD. Low levels of epinephrine and norepinephrine have been implicated in various physical and mental symptoms, including MDD. Notably, epinephrine and norepinephrine molecules participate in memory processes and emotional processes. In thalamo-amygdala synapses, norepinephrine is released during emotional stimulation, which helps to strengthen memories by facilitating long-term potentiation (LTP). In the amygdala, norepinephrine mechanisms mediate memory storage while glucocorticoids further enhance this process. Research suggests that the induction of LTP contributes to fear memory formation as norepinephrine suppresses GABAergic inhibition of projection neurons in the lateral amygdala (LA). Both epinephrine and norepinephrine are involved in selecting main information through interactions with glutamatergic activity in the amygdala. Besides, the interaction between norepinephrine and dopamine is also significant in MDD. Converting dopamine to norepinephrine is catalyzed by β-hydroxylase, and disruptions in these neurotransmitter systems contribute to the pathophysiology of the disorder and potentially influence treatment strategies.

It has been found that dysregulation of the HPA axis and the noradrenergic system often occur together in depressed patients, with correlations between noradrenergic activity and cortisol levels. Specifically, research since the 1980s suggests that cortisol levels can negatively impact norepinephrine activity, contributing to the neurochemical imbalance seen in depression. Conversely, the imbalance of norepinephrine can affect the regulation of cortisol. It has also been reported that beta-adrenergic activity in the BLA was essential in enabling the modulation of memory consolidation via hippocampal glucocorticoid receptor (GR) activation.[36] Also, epinephrine may activate noradrenergic receptors in the amygdala, enhancing memory formation. These understandings highlight the intricate balance and interplay of cortisol and epinephrine-norepinephrine in the amygdala, which is crucial for cognitive and emotional functions. Figure 1 summarizes the role of the HPA axis in depression, with important involvement of glucocorticoids (cortisol), epinephrine, and the amygdala.

ABNORMAL EXPRESSION OF RECEPTORS FOR VARIOUS HORMONES AND NEUROTRANSMITTERS IN THE AMYGDALA MAY BE LINKED TO MAJOR DEPRESSIVE DISORDER

The abnormal neurotransmitter hypothesis has long been an important theory in understanding MDD, and the receptors that receive them are equally important. Different subregions of the amygdala express various receptors. Types of receptors expressed in the amygdala, and their functions are shown in Table 1. Recent studies indicate that there is an abnormal expression of receptors for various hormones and neurotransmitters in the amygdala, providing strong evidence of their relationship with depressive symptoms.

GABAergic, glutamatergic systems, and α1-adrenergic receptors have abundant expression in the amygdala. Gamma-aminobutyric acid (GABA) plays a primary inhibitory role, while glutamate is crucial for primary excitatory signaling. Glutamatergic inputs in the lateral and CeA activate different types of receptors. Metabotropic glutamate receptors (mGluRs) are significant in regulating emotional-affective behaviors. They impact fear learning, extinction, and pain processing in the pathology of MDD. The thalamic afferents to the amygdala play a crucial role in modulating synaptic transmission through various glutamate receptor subtypes, particularly N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Several postmortem studies have indicated that glutamate receptor subunits were reduced in patients with major depression.[36] Furthermore, studies have shown that changes in the expression of α1-adrenoceptors, mGluRs, κ opioid receptors, and cholecystokinin B receptors (CCKBR) play a crucial role in the pathophysiology of depression.[37-39] Additionally, the dysregulation of neurotransmitter pathways and receptors, including monoaminergic, GABAergic, histaminergic, and cholinergic systems, has been implicated in depressive symptoms.[40] Research in both male and female mice revealed that the ratio of GABAergic neurons in the basal amygdala is significantly higher (22%) than in the LA (16%).[41] Chronic stress has been reported to regulate the expression of several gamma-aminobutyric acid type A receptor (GABAAR) subunits in the amygdala in rats.[42] Dysfunction of inhibitory GABA function across corticolimbic brain regions, including the BLA, has been observed in depressed

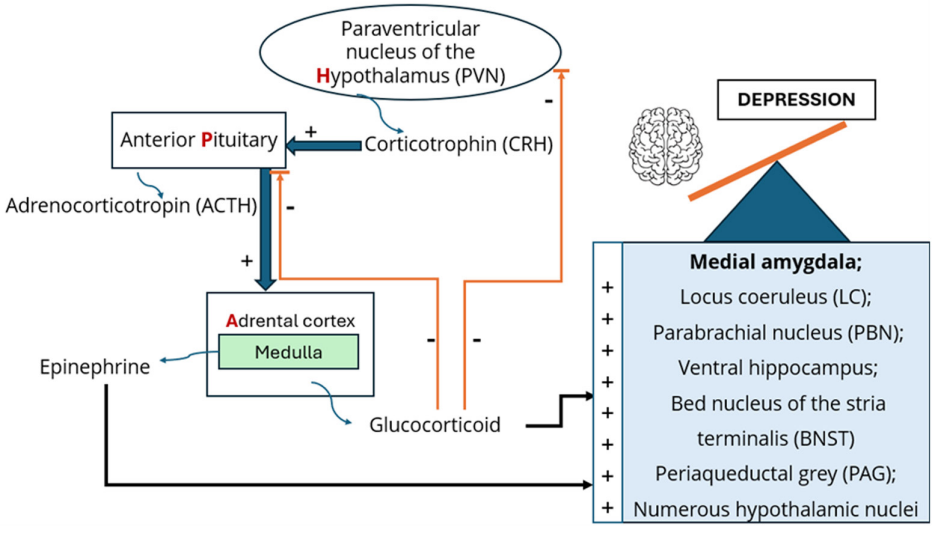

Figure 1. The involvement of the hypothalamic–pituitary–adrenal (HPA) axis and the amygdala in depression, with central roles of glucocorticoids (cortisol) and epinephrine, are shown. Cortisol and epinephrine, produced by the HPA axis, affect subregions of the limbic system, including the amygdala. + indicates activated signal; - indicates inhibited signal.

Table 1. Receptor Types for Monoamine Neurotransmitters on Cells in the Amygdala Region and Their Role

The Amygdala's Subregions	Types of Neurocells/ Afferents	Receptors	Ligands	Consequences
In the basolateral nucleus	Glutamatergic afferents	mGluR2	Glutamate	- Modulating anxiety-related behaviors - Stress responses - Fear memory - Sleep alterations - Pain behavior - Induce LTD (long-term depression) when selectively activated
		mGluR3		- Inducing LTD of excitatory transmission - Fear-related processes - Pain behavior - Regulated emotional-affective behaviors and fear learning - Linked to depressive-like behaviors
	Pyramidal neuron (CaMK+)	GluR1, GluR2, GluR3	Glutamate	- Fear processing
		Leptin R	Leptin	- Reduction in food intake - Anxiety expression - Regulating synaptic plasticity related to emotional processing
		GABAAR (α3)	GABA	- Modulating anxiety response
		GABABR1, GABABR2	GABA	
	GABAergic neuron (Cholecystokinin+)	mGluR3,	Glutamate	- Regulate emotions
		GABAAR (α3)	GABA	
	β-adrenergic	Adrb1 and Adrb2	Catecholamines	- Processing emotionally salient stimuli
In the lateral nucleus	Dopaminergic afferent from the ventral tegmental area	dopamine transporter	Dopamine	- Regulating dopamine transmission
	Glutamatergic afferent	GABABR1, GABABR2	GABA	- Modulating anxiety response
		Cannabinoid Receptor 1	Cannabinoids	- Impacting anxiety, stress responses, and ethanol consumption behaviors - Essential for synaptic plasticity and behaviors
	Pyramidal neuron	GABAAR (α1, β2+3)	GABA	- Gating of GABAAR
		GluR (2,3)	Glutamate	- Memory processing
		NMDAR (NR1, NR2B)	Glutamate and co-agonist (glycine or D-serine)	- Regulate emotional-affective behaviors - Facilitate fear extinction - Inhibit the metabolic effects of acute stress
	GABAergic neuron (Parvalbumin+)	mGluR1a	Glutamate	- Behavioral hypersensitivity - Influencing fear learning, extinction, and affective aspects of pain processing
		mGluR5	Glutamate	- Fear memory generalization
		NMDAR (NR2C), NMDAR (NR1, NR2C)	Glutamate and co-agonist (glycine or D-serine)	- Induced psychosis - Extinguish glucocorticoids modulation
In the medial nucleus	Pyramidal neuron (CaMK+)	Corticotropin-releasing Hormone Receptor 1	Corticotropin-Releasing Hormone (CRH)	- Modulate neuronal activity and synaptic transmission - Anxiety-like behaviors and nocifensive responses
		NMDAR (NR1, NR2A)	Glutamate and co-agonist (glycine or D-serine)	- Increase in excitatory neurons
		Somatostatin Receptor 2	Somatostatin	- Induces anxiety-like behavior
		GABAAR (α2)	GABA	- Affecting alcohol's anxiolytic effects
		GABAAR (β1)	GABA	- Fear acquisition and extinction processes
	GABAergic projection neuron (Vasointestinal Peptide +, Somatostatin*)	Vasointestinal Peptide Receptor 2	Vasoactive Intestinal Peptide (VIP)	- Regulating principal cell activity and are associated with anxiety and depression symptoms
		TrkB	Brain-Derived Neurotrophic Factor (BDNF)	- Related to depressive behaviors - Fear learning, memory extinction - Learning of aversive and appetitive emotional memories

(*Continued*)

Table 1. Receptor Types for Monoamine Neurotransmitters on Cells in the Amygdala Region and Their Role (Continued)

The Amygdala's Subregions	Types of Neurocells/ Afferents	Receptors	Ligands	Consequences
		mGluR1a	Glutamate	
		mGluR5		
In the periamygdaloid cortex	Accessory olfactory bulb glutamatergic afferent	mGluR8		- Modulate pain processing - Fear learning and extinction processes
		mGluR7		- Extinction of aversive memories
		mGluR2		
		mGluR2/R3		
		GABArgic Neuron : Parvalbumin+	Calcium	- Modulate synaptic activity - Fear learning
		GABArgic Neuron : Estrogen receptor β+	Estrogen	- Regulating stress and anxiety
	Pyramidal neuron (CaMK+)			- Fear learning

patients, with more pronounced deficits in women with depression.[43] Reduced expression of GABA may explain the hyperactivity of the amygdala. Research indicates that somatostatin (SST) can inhibit GABAergic transmission, affecting synaptic plasticity and neuronal communication. Reduction of SST levels in the amygdala of MDD females indicates a change in the SST cell phenotype rather than cell death.[44] Input from SST+ interneurons to pyramidal cells is enhanced into GABAergic inhibitory synapses, demonstrating an antidepressant-like effect. These actions mimic the effects of anxiolytic and antidepressant drugs.[45] Furthermore, targeting specific GABA interneurons and their receptors, such as the α5-GABA-A receptor, has shown promise as a potential therapeutic strategy for MDD, rescuing behavioral deficits when SST+ cell function is low.[46] Besides, activated BLA GABA can lead to the inhibition of BLA CAMKII neuronal activity, decreasing depressive-like behavior in mice.[47]

Various hormone receptors are present in the amygdala, including estrogen receptors, GRs, orexin receptors, melanin-concentrating hormone (MCH) receptors, and CRH receptors. Glucocorticoid receptors are expressed in the amygdala and are implicated in MDD. Moreover, increased GR expression in the amygdala of depressed patients indicates heightened sensitivity to cortisol.[48] Specifically, chronic stress can lead to alterations in the expression of GRs in the amygdala, resulting in increased levels observed in depressed individuals.[49] Orexin and MCH receptors in the BLA could impact brain regions such as the ventral hippocampus, CeA, and nucleus accumbens. Orexin receptors play a role in the regulation of reward, anxiety, stress response, and sleep-wake cycles. It has been demonstrated that alterations in orexin levels and related metabolic pathways in the brain contribute to cognitive deficits observed in depression.[50]

CONCLUSION

The fundamental causes of depressive illnesses are still not fully understood, making them complicated problems. Changes in the volume of parts of the amygdala are 1 identified mechanism that affects mood and emotional processing, including suicidal thoughts, in patients suffering from severe depression. A range of depressive behaviors, from mild to severe depression, has been found to be associated with changes in the molecular expression of GRs on the amygdala surface. The pathway involving cortisol, along with epinephrine and norepinephrine, warrants further exploration and study within the amygdala region. Moreover, abnormal activity patterns of the amygdala may serve as promising markers for depression diagnosis. Consequently, this exploration may lead to the development of effective medications and treatment methods to improve the condition and management of patients in the future.

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