Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/45/20240681

Cellular nature of major depressive disorder and alcohol use disorder comorbidity: An overview

Humiao Dong[1,6,†], Ziao Zhang[2,5,7,†], Yutong Chen[3,8,†], Yuhan Shao[3,9,†], Ziqi Huang[4,10]

[1]Department of basic medical science , Fudan University, Shanghai, 200032, China
[2]Department of Life Science and Technology, Shanghai Jiaotong University, Shanghai,200240, China
[3]Department of psychology, University of Warwick, Coventry,CV4 7AL, UK
[4]Grade 13, Wellington college international Tianjin, Tianjin, 300120, China,
[5]Corresponding author

[6]2464278627@qq.com
[7]zhangziying00000@163.com
[8]1264628652@qq.com
[9]shaoyuhan_zjgivy@163.com
[10]3503554904@qq.com
[†]These authors are co-first authors

Abstract. The co-occurrence of alcohol use disorders and depression is increasing in our society due to their wide prevalence. Both alcohol use disorders (AUD) and depression increase susceptibility to disability and mortality, and their symptoms are closely linked to the brain's reward circuits. While the pathogenesis of AUD and depression is well-researched, the mechanism of comorbidities remains a challenge. Individuals with depression may use alcohol for self-medication, leading to the formation of AUD over time. Abrupt cessation of alcohol consumption in individuals with long-term AUD can result in neurotransmitter abnormalities and an elevated risk of depression or relapse. This review primarily focuses on basic research and summarizes neurotransmitters such as GABA, glutamate, dopamine, norepinephrine, and 5-HT in relation to Major Depressive Disorder and AUD. Currently, the effectiveness of treatment for comorbidities is not clearly evident. Our goal is to comprehensively explore the cellular attributes associated with these comorbidities in order to identify new avenues for therapeutic interventions.

Keywords: AUD, MDD, Cellular Nature, Comorbidity

1. Introduction

Depression is a mood disorder characterized by avolition, low mood, and anhedonia, and it is a significant global mental health issue [1], affecting around 4.4% of the global population. This category encompasses bipolar disorder and major depressive disorder (MDD), with MDD being the primary psychiatric condition worldwide.

DOI: 10.54254/2753-8818/45/20240681

Alcohol Use Disorder (AUD) is also a leading cause of preventable deaths worldwide. Both MDD and AUD are top risk factors for disability and premature death, causing substantial suffering to affected individuals and imposing significant societal and economic burdens [2].

Comorbidity between MDD and AUD is common and is associated with more severe clinical presentations and reduced quality of life greatly.

Various hypotheses have been proposed regarding the mechanisms of MDD and AUD. MDD is considered a neuro network disorder involving changes across widely distributed brain areas [3]. The detrimental effects of stress on a physiological level are also discussed, considering its association with other risk factors influencing synaptic connectivity in neural circuits. In AUD, reinforcement mechanisms play a crucial role in individual drinking behavior. Cessation of alcohol consumption leads to withdrawal symptoms characterized by irregular nervous system hyperactivity and dysfunction [4].

However, the neuropsychological nature of this comorbidity has not been elucidated, and treatment to this combination has long been a problem.In this review, evidence will be presented to support the hypothesis that MDD mechanism overlap with AUD in someway. We aim to get a view of the neurotransmitters and neuro circuit, with a special emphasis on the stress system . By discussing this overlap, we aim to further understand the correlation between AUD and MDD. The way we understand this comorbidity may well define the way we treat our patient, and they deserve a more effective treatment.

2. Neurotransmitter and neuro circuits involved in depression.

Depression, the most prevalent psychiatric disorder, continues to be a puzzle when it comes to understanding its underlying mechanisms. However, gaining insights into the neurobiological factors behind its symptoms can potentially lead to the development of a biological model of depression. Research suggests that five neurotransmitter systems, namely 5-HT, GABA, glutamate, and the HPA axis, play significant roles in depression.

2.1. Dysfunction of GABA and glutamate

The dysfunction of GABA and glutamate is implicated in the manifestation of depressive symptoms. Within the central nervous system (CNS), glutamate serves as an excitatory neurotransmitter and GABA as an inhibitory neurotransmitter. Studies have shown that people with depression have changes to the way their brains are wired and operate, including a shrinkage of the hippocampus and prefrontal cortex. Furthermore, markers for GABA and glutamate neurons, as well as vesicular GABA transporters, are found to be decreased. These changes disrupt the delicate balance between excitatory and inhibitory neurotransmission, which is a defining characteristic of depression.

2.2. Dysfunction of 5-HT

The dysfunction of the neurotransmitter 5-HT, also known as serotonin, is strongly associated with depression. Serotonin plays a critical role in regulating mood, and disruptions in its activity are linked to emotional, cognitive, and endocrine disturbances in individuals with depression. Multiple factors can contribute to damage within the 5-HT system, including genetic predisposition, personality traits, societal influences, and stress. Stress, in particular, has a significant impact on the excitability of 5-HT neurons. In response to stress, the brain modulates the activity of the 5-HT system to prompt defensive behaviors. Prolonged exposure to negative effects and the utilization of avoidance coping strategies can lead to reduced levels of serotonin neurotransmitters, impairing mood regulation and increasing sensitivity to stress. Consequently, the risk of developing depression and experiencing suicidal thoughts is heightened [5].

2.3. Dysfunction of Hypothalamic-pituitary-adrenal axis (HPA)

The hypothalamic-pituitary-adrenal (HPA) axis, which involves the paraventricular nucleus (PVN), pituitary frontal lobe, and adrenal cortex, is responsible for connecting peripheral organs to the central nervous system (CNS). It primarily functions as a stress-regulating system and plays a crucial role in

DOI: 10.54254/2753-8818/45/20240681

maintaining internal homeostasis, as well as influencing mood, cognitive disorders, and various physiological processes [6]. Numerous studies have observed hyperactivity within the hypothalamic-pituitary-adrenal axis in individuals with depression [7]. This hyperactivity can result in an excessive exposure to glucocorticoids, which inhibits glucocorticoid receptors and is associated with depression [8].

3. Cellular Nature of AUD

Freud's concept of "Profound Dissatisfaction with Civilization" (1923/1961) highlights the close relationsship between alcohol use disorder (AUD) and other mental health conditions. Co-occurrence of AUD and depression is frequently observed, with high prevalence and low remission rates. Regular alcohol consumption increases the risk of developing depression. Excessive and prolonged alcohol consumption can lead to addictive behavior and irreversible brain damage.

3.1. Alcohol Elevation of GABA Levels in the Brain

Alcohol consumption affects the neurotransmitter levels in the brain. Specifically, it increases the levels of GABA, which is an inhibitory neurotransmitter, while decreasing the levels of glutamate, an excitatory neurotransmitter. The binding of GABA to its receptors on the cell surface reduces neuronal activity, leading to inhibitory effects. This amplifies the inhibitory activity of GABA and enhances the functioning of its receptors, resulting in a decrease in neuronal excitability. As a consequence, overall brain function slows down, producing anesthetic and sedative effects. The reduced excitability may cause mood fluctuations, compromised attention spans, and cognitive impairments, reinforcing the dependence on alcohol to maintain a stable brain excitability level.

3.2. Dopamine system in euphoria and withdrawal

In controlling alcohol addiction, the dopamine system is crucial. During alcohol consumption at lower doses, dopamine levels may exhibit an increase. Alcohol consumption triggers the release or activation of dopamine in the brain's reward system, leading to pleasurable sensations. The rapid fluctuations in hormone levels, particularly the sudden surge in dopamine, can contribute to the development of alcohol addiction. These pleasurable associations formed and the heightened motivation to continue alcohol use become reinforcing factors. Long-term alcoholism leads to adaptive alterations in the dopamine system, resulting in a notable reduction in dopamine levels during withdrawal. This decline in dopamine levels contributes to the emergence of withdrawal symptoms, including anxiety, depression, and intense cravings [4]. These withdrawal symptoms pose significant challenges for individuals seeking to overcome alcohol use disorder (AUD) and can hinder the recovery process.

4. The Comorbidity of MDD and AUD

Numerous studies consistently demonstrate a high rate of comorbidity between major depressive disorder (MDD) and alcohol use disorder (AUD), with rates as high as 21%. This comorbidity tends to increase from 2% in adolescence to 17% in adulthood. Regardless of the directionality, recent research indicates that the involvement of the stress system in both disorders may contribute to comorbidity.

In humans, the stress system comprises the corticotropin-releasing factor (CRF)-dependent hypothalamic-pituitary-adrenal (HPA) axis, the noradrenergic system, and the activation of the extended amygdala. Stress triggers the activation of the HPA axis, and serotonin (5-hydroxytryptamine, 5-HT) has been implicated in stress regulation [9].

In a state of chronic stress, continuous activation of the HPA axis impairs the negative feedback mechanism, leading to an overactive HPA axis and increasing the risk of developing MDD. Dysregulation of the 5-HT system further contributes to the loss of control over the stress response, thus amplifying the symptoms of MDD [9]. Consequently, medications targeting the 5-HT system, such as selective serotonin reuptake inhibitors (SSRIs), and stimulation of the parasympathetic system are therapeutic strategies for alleviating MDD symptoms.

DOI: 10.54254/2753-8818/45/20240681

Likewise, in line with the perspective of Koob and colleagues, AUD is considered a disorder associated with excessive stress. Stress-induced glucocorticoid hormones from the HPA axis interact with the brain's limbic system, leading to increased dopamine release and reinforcing alcohol-seeking and consumption [10]. This dysregulation in the motivation system contributes to the development of AUD and increases susceptibility to its occurrence.

Based on these studies, we propose that the stress system may mediate the connection between MDD and AUD. Impaired response to glucocorticoids caused by chronic stress may damage the central nervous system and contribute to depression. Additionally, stress-induced release of neurotransmitters, including serotonin, may play a role in promoting AUD development and maintenance. However, further research is needed to confirm these hypotheses.

5. Discussion

The co-occurrence of Alcohol Use Disorder (AUD) and Major Depressive Disorder (MDD) has been extensively documented in the literature, underscoring the involvement of the brain's stress system in this comorbidity. It is well-established that chronic stress triggers the activation of the hypothalamic-pituitary-adrenal (HPA) axis, initiating a cascade of events that result in the increased release of neurotransmitters like serotonin and dopamine in the brain. These alterations in the brain's motivational system are believed to contribute to the transition from stress-induced drinking behavior to compulsive alcohol consumption, ultimately culminating in the development of AUD [10]. Additionally, elevated levels of serotonin may serve to reinforce and exacerbate AUD.

On the other hand, chronic activation of the HPA axis due to stress leads to prolonged secretion of glucocorticoids, which can eventually desensitize the brain to these hormones [11]. This desensitization disrupts the regulation of neurotransmitters and synaptic plasticity, potentially precipitating the onset of severe depression. Thus, it is plausible to propose that the co-occurrence of AUD and MDD can be attributed, at least in part, to dysregulation of the stress system.

By considering the existing body of literature, our hypothesis offers a fresh perspective for comprehending the co-occurrence of AUD and MDD. It posits that this comorbidity is not merely a product of the unique pathological mechanisms underlying each disorder, but is also influenced by the impact of the stress system. Therefore, it is imperative for future research to not only delve into unraveling the individual pathological mechanisms of AUD and MDD, but also to incorporate investigations into the intricate workings of the stress system. Exploring how the stress system influences both disorders is pivotal in unraveling the mechanisms underpinning their comorbidity.

Moreover, the elucidation of the interplay between the stress system, AUD, and MDD may have important implications for the development of targeted treatments. If we can understand the pathways through which chronic stress affects both disorders, researchers as well as clinicians may be better equipped to devise more effective therapeutic approaches that address the comorbidity as a whole.

In conclusion, the co-occurrence of AUD and MDD is likely to emerge from the dysregulation of the brain's stress system, in addition to the interaction of their specific pathological mechanisms. This hypothesis highlights the crucial role of the stress system and calls for a comprehensive investigation into its influence on both disorders. Advancing our understanding of the intricate relationship between stress, AUD, and MDD will not only broaden our knowledge of these disorders but also pave the way for the development of novel treatment strategies.

6. Conclusion

In conclusion, our synthesis of the existing literature has highlighted the involvement of neurotransmitters in the pathogenesis of both Major Depressive Disorder (MDD) and Alcohol Use Disorder (AUD). By examining the role of the stress system in both disorders, we have proposed a novel hypothesis that implicates the dysregulation of the stress system as a mediator of comorbidity between MDD and AUD. This comprehensive approach not only enhances our understanding of the complex relationship between these disorders but also opens up new avenues for developing targeted therapeutic interventions.

DOI: 10.54254/2753-8818/45/20240681

Acknowledgement

Humiao Dong, Ziao Zhang, Yutong Chen, Yuhan Shao and Ziqi Huang contributed equally to this work and should be considered co-first authors.

References

[1] Herrman, H., Patel, V., Kieling, C., Berk, M., Buchweitz, C., Cuijpers, P., Furukawa, T. A., Kessler, R. C., Kohrt, B. A., Maj, M., McGorry, P., Reynolds, C. F., Weissman, M. M., Chibanda, D., Dowrick, C., Howard, L. M., Hoven, C. W., Knapp, M., Mayberg, H. S., … Wolpert, M. (2022). Time for united action on depression: A Lancet–World Psychiatric Association Commission. The Lancet, 399(10328), 957–1022.

[2] Sacks, J. J., Gonzales, K. R., Bouchery, E. E., Tomedi, L. E., & Brewer, R. D. (2015). 2010 National and State Costs of Excessive Alcohol Consumption. American Journal of Preventive Medicine, 49(5), e73–e79.

[3] Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of Mood Disorders. Neuropsychopharmacology, 35(1), 192–216.

[4] Koob, G. F. (2003). Alcoholism: Allostasis and beyond. Alcoholism, Clinical and Experimental Research, 27(2), 232–243.

[5] Mahar, I., Bambico, F. R., Mechawar, N., & Nobrega, J. N. (2014). Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. Neuroscience & Biobehavioral Reviews, 38, 173–192.

[6] El Husseini, N., & Laskowitz, D. T. (2014). The role of neuroendocrine pathways in prognosis after stroke. Expert Review of Neurotherapeutics, 14(2), 217–232.

[7] Grundmann, O., Lv, Y., Kelber, O., & Butterweck, V. (2010). Mechanism of St. John's wort extract (STW3-VI) during chronic restraint stress is mediated by the interrelationship of the immune, oxidative defense, and neuroendocrine system. Neuropharmacology, 58(4–5), 767–773.

[8] Castrén, E., & Rantamäki, T. (2010). The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. Developmental Neurobiology, 70(5), 289–297.

[9] Chen, G.-L., & Miller, G. M. (2012). Advances in Tryptophan Hydroxylase-2 Gene Expression Regulation: New Insights into Serotonin-Stress Interaction and Clinical Implications. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics, 159B(2), 152–171.

[10] Rougé-Pont, F., Deroche, V., Moal, M. L., & Piazza, P. V. (1998). Individual differences in stressinduced dopamine release in the nucleus accumbens are influenced by corticosterone. European Journal of Neuroscience, 10(12), 3903–3907.

[11] McEwen, B. S., & Morrison, J. H. (2013). Brain On Stress: Vulnerability and Plasticity of the Prefrontal Cortex Over the Life Course. Neuron, 79(1), 16–29.