Depressive and Alcohol Use Disorders

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Depressive disorders and alcohol use disorders are widespread among the general population and are significant public health and economic burdens. Alcohol use disorders often co-occur with other psychiatric conditions and this dual diagnosis is called comorbidity. Depressive disorders invariably contribute to the development and worsening of alcohol use disorders, and vice versa. The mechanisms underlying these disorders and their comorbidities remain unclear. Recently, interest in the lateral habenula, a small epithalamic brain structure, has increased because it becomes hyperactive in depression and alcohol use disorders, and can inhibit dopamine and serotonin neurons in the midbrain reward center, the hypofunction of which is believed to be a critical contributor to the etiology of depressive disorders and alcohol use disorders as well as their comorbidities. Additionally, calcium/calmodulin-dependent protein kinase II (CaMKII) in the lateral habenula has emerged as a critical player in the etiology of these comorbidities.

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1. Introduction

Alcohol use disorders (AUDs) is a medical diagnosis given to individuals who are suffering from severe problem drinking. AUDs are chronic relapsing brain disorders characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences. AUDs are a severe problem in the United States. According to the National Institute of Health Alcohol Facts and Statistics, in 2018, in the United States, AUDs affect an estimated 15 million people, 5.8 percent or 14.4 million adults (ages 18 and older). This includes 9.2 million men and 5.3 million women. AUDs also affect an estimated 401,000 adolescents between the ages of 12 and 17 (National Institute on Alcohol Abuse and Alcoholism (NIAAA): Understanding the impact of alcohol on human health and well-being).

In 2018, 26.45 percent and 6.6 percent of adults engaged in binge drinking or heavy drinking, respectively. An estimated 88,000 people (62,000 men and 26,000 women) die from alcohol-related causes each year, making alcohol the third leading preventable cause of death in the United States (Centers for Disease Control and Prevention. Alcohol and Public Health: Alcohol-Related Disease Impact). In 2014, 9967 deaths (31 percent of overall driving fatalities) were due to alcohol-impaired driving (Traffic Safety Facts CrashStats. Report No. DOT HS 812 219, Washington, DC: National Highway Traffic Safety Administration, 2015). AUDs are a severe economic burden on society. In 2010, alcohol misuse cost the United States $249 billion [1]. Three-quarters of the total cost of alcohol misuse is related to binge drinking [1]. AUDs seriously affect family life. According to a 2012 study, more than 10 percent of children in the U.S. live with a parent with alcohol struggles.

AUDs are also a severe problem worldwide. According to the World Health Organization (WHO), in 2012, the harmful use of alcohol caused 3.3 million deaths globally, or 5.9 percent of all global deaths (7.6 percent for men and 4.0 percent for women) (WHO Global status report on alcohol and health, 2018). In 2014, the WHO reported that alcohol contributed to more than 200 diseases and injury-related health conditions, most notably, the Diagnostic and Statistical Manual of Mental Disorders-4 (DSM-IV) alcohol dependence, liver cirrhosis, cancers, and injuries. In 2012, 5.1 percent of the burden of disease and injury worldwide (139 million disability-adjusted life years) was attributable to alcohol consumption (WHO Global status report on alcohol and health, 2018). Globally, alcohol misuse was the fifth leading risk factor for premature death and disability in 2010. It was the primary risk factor among people between the ages of 15 and 49 (WHO Global status report on alcohol and health, 2018). In the age group of 20–39 years, 25 percent of the total deaths were attributable to alcohol consumption (WHO Global status report on alcohol and health, 2018).

In the same vein, depressive disorders (DDs), including major depressive disorders, are among the most prevalent neuropsychiatric disorders that can interfere with patients' functioning [2][3]. DDs are mood disorders characterized by sadness severe enough or persistent enough to interfere with function and often decreased interest or pleasure in activities. Individuals who suffer from DDs may have trouble doing normal day-to-day activities, think their lives are meaningless, and even engage in suicide ideations or behaviors. The exact cause of DDs is unknown, but it may involve a combination of heredity, changes in neurotransmitter levels, altered neuroendocrine function, and psychosocial factors.

AUDs often occur with other psychiatric conditions and this dual diagnosis is called comorbidity. This pattern of comorbidity adversely affects the prognosis, course, and treatment of both DDs and AUDs. High severity in one of these disorders is associated with high severity in another condition. Alcohol dependence prolongs the course of depression and increases the risk of suicidal symptoms and behaviors. DDs invariably contribute to the development and worsening of AUDs [4]. Patients with depression and AUDs are at increased risk of relapse to heavy drinking. However, the mechanisms underlying this association are not fully understood. This gap in our knowledge prevents us to find out a better treatment strategy for these comorbidities. Professionals working with patients suffering from these comorbidities face unique and challenging dilemmas about providing the best treatment to address both conditions. Despite the growing interest in this issue, relatively few clinical studies have tested treatments for this patient population [5]. This highlights the need to understand the etiology of the disorders and develop an effective treatment regimen.

Although many factors can contribute to the comorbidity of AUDs and DDs [6], the molecular interplay will be discussed in depth. Recently, the lateral habenula (LHb) has emerged as a crucial brain region in the pathophysiology of DDs and AUDs. Fortunately, a detailed outline of the calcium/calmodulin-dependent protein kinase II (CaMKII) signaling pathway has emerged. The target of its signaling cascade in the LHb has proven beneficial for treating AUDs, especially for those with comorbid DDs [7].

2. The Role of CaMKII in Alcohol Use Disorders and Depressive Disorders

2.1. The Role of CaMKII in Alcohol Use Disorders

The role of CaMKII in AUDs has not been extensively studied. However, some evidence indicates that CaMKII contributes to several AUD-related behaviors. Alcohol self-administration increases phosphorylation of GluA1 at the CaMKIIα recognition site (pGluA1- Ser831) in the central amygdala (CeA) of selectively bred alcohol-preferring P-rats as compared to behavior-matched (non-drug) sucrose controls. Intra-CeA injection of the AMPAR-positive modulator aniracetam or the cell-permeable CaMKII peptide inhibitor myristolated autocamtide-2-related inhibitory peptide (m-AIP), respectively, facilitated or inhibited alcohol self-administration [8]. Interestingly, CaMKII plays a different role in the aberrant behaviors induced by different doses of alcohol. In αCaMKII autophosphorylation-deficient αCaMKII-T286A mice, acute and subchronic administration of a low dose of alcohol (2 g/kg, intraperitoneal injection, i.p.) failed to induce locomotion, but a high dose (3.5 g/kg, i.p.) caused sedation. In αCaMKII-T286A mice, acute or subchronic alcohol administration did not change dopamine (DA) levels, measured by in vivo microdialysis, in the NAc, but enhanced serotonin (5-HT) responses in the prefrontal cortex were observed. Thus, αCaMKII autophosphorylation and the change in the DA–5-HT balance contribute to the establishment of alcohol-drinking behavior [9]. CaMKII may also act as a primary molecular mechanism that regulates relapse in alcohol addiction and cue-induced reinstatement of alcohol-seeking behavior, a hallmark behavioral pathology of addiction. In male C57BL/6J mice, reinstatement was associated with increased pCaMKII-T286 immunofluorescence reactive in specific reward- and memory-related brain regions, including the amygdala, NAc, lateral septum, mediodorsal thalamus, and piriform cortex, as compared with extinction control [10].

2.2. The Role of CaMKII in Depressive Disorders

Depressive disorders (DDs) are one of the most widespread and incapacitating mental disorders, resulting in the loss of motivation and interest, feelings of despair, and the inability to feel pleasure [11]. Since LHb was recently discovered as the key brain region in the pathophysiology of depression, a surge in interest over CaMKII has uncovered its role in regulating several signal transduction pathways associated with learning and memory. Since it can remain activated beyond the timeframe of Ca^{2+} infiltration that initially stimulated the molecule, CaMKII is often dubbed a “memory molecule” [12]. Stress-induced elevations in bCaMKII signaling, in particular, are related to depression because they influence the formation and retention of aversive memories [13].

Through a combination of electrophysiological, behavioral, and molecular approaches, the bCaMKII was identified as the key contributor for habenular hyperactivity and, thus, depressive-like behaviors. Recent studies have shown that amplification of bCaMKII function mediates increased depolarization of LHb neurons. When tested in rats and mice, overexpression of bCaMKII, but not αCaMKII, in the LHb, using viral vectors (adeno-associated virus 2 (AAV2)) strongly enhanced the synaptic efficacy and spike output of LHb neurons and produced profound depressive symptoms, including anhedonia and behavioral despair, which were reversed by downregulation of βCaMKII levels, blocking its activity or its target molecule glutamate A1 (GluR1) [11]. In contrast to chronic stress, acute stress has been shown to increase both isoforms, αCaMKII, and bCaMKII [14]. Furthermore, an increase of bCaMKII enhanced the synaptic efficacy of LHb neurons, producing profound depressive-like symptoms. This could be because of elevated bCaMKII, strengthening AMPAR-mediated synaptic transmission and hyperactivity of

the LHb. On the other hand, blocking CaMKII activity, or its target molecule, GluA1, reversed depressive-like symptoms [11].

Additionally, bCaMKII may regulate other channels of LHb neurons that enhance spike output. An important question that has yet to be addressed is the feature that renders βCaMKII sensitive to depressive stimuli and antidepressants [11]. This leads to speculation that βCaMKII plays a significant role in LHb neuronal function and is a key determinant of depression [11]. That facilitation of glutamate transmission in the LHb may lead to depressive symptoms [7][15][16][17][18][19]. Further support of this idea is the finding that ketamine, an NMDAR antagonist, suppresses the depressive-like behaviors in rodent models of depression [15]. The discovery of ketamine's rapid antidepressant effects is perhaps the most critical advance in the psychiatry field in recent history [20]. To investigate the underlying mechanisms, in a recent study, ketamine was applied to the LHb in rats, which quickly rescued depression-like behaviors. In vivo and ex vivo, electrophysiological recording found that burst firing, which was increased in the LHb of depressive rodent models, was suppressed by ketamine [15].

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