Neurocircuitry of the PTSD-AUD Comorbidity

Subjects: Neurosciences

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Post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) are prevalent neuropsychiatric disorders and frequently co-occur concomitantly. Individuals suffering from this dual diagnosis often exhibit increased symptom severity and poorer treatment outcomes than those with only one of these diseases. The ventral tegmental area (VTA), hippocampus, amygdala, prefrontal cortex (PFC), paraventricular nuclei (PVN), and locus coeruleus (LC), are well-associated with processing fear, anxiety, stress, and rewards.

comorbid PTSD and AUD | ventral tegmental area | amygdala

1. VTA

The VTA in the midbrain is enriched with dopaminergic (DA) neurons that project to limbic regions through the mesolimbic pathway [1]. The limbic system, comprised of the VTA, the nucleus accumbens (NAc), and the hippocampus, is responsible for incentive salience, decision-making, working memory, reward, and aversion [2].

Since stress or traumatic experiences are necessary to induce PTSD, various paradigms are used to precipitate the disorder by applying physical, social, and psychological stressors individually or collectively. Stress affects DA neuron activity and elevates dopamine levels in the mesolimbic system. Acute stressful situations have a stimulating effect on VTA-DA neurons. At the same time, chronic stress exerts an allostatic shift in the mesolimbic DA system to be hypoactive and hyporesponsive in the long term [3]. Alterations in mesolimbic DA neurotransmission allow behavioral adaptations in response to various environmental stimuli. They, thus, are essential for stress coping.

The effect of acute stress on the VTA-DA neurons is short lasting and characterized by initial transient activation. Acute stress can expedite the initial stage of AUD. Stressful stimuli could increase the baseline VTA dopamine level, sensitize the rewarding circuits, and potentially enhances VTA-DA neuron burst firings. Thus, acute stress can enhance ethanol's rewarding property and facilitate binge drinking behavior [4]. In addition, acute psychological stressors can increase extracellular dopamine levels in regions innervated by VTA neuronal projections, such as NAc [5][6]. It is well accepted that the mesolimbic DA system can become hyper-reactive in response to drug reward, which is one of the characteristics of drug abuse, including alcohol addiction [7][8].

There are several reasons accounting for the phenomenon mentioned above. Specifically, acute stress can produce excitatory synapse proliferation in VTA, broadly promoting the DA output. For example, glutamatergic receptors, including α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs) and N-methyl D-

aspartate receptors (NMDARs), are ubiquitously expressed in the area receiving inputs from VTA-DA neurons. Besides, inhibitory synaptic transmission in the VTA is also susceptible to undergoing plastic changes during acute stress [3]. Such cellular configuration can stimulate mesolimbic DA release in the VTA. In conclusion, with the effect of stress, the sensitized VTA DA neurons significantly increase the rewarding property of alcohol, which increases the propensity to develop alcohol abuse.

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Morphological changes in VTA DA neurons are associated with depressive symptoms. Moreover, anhedonia, one of the core features of depression [9], contributes to problematic alcohol use [10]. Anhedonia prompts PTSD patients to self-medicate alcohol to alleviate negative moods, probably by compensating for low dopamine levels. It is well-accepted that anhedonia can significantly increase relapse drinking and reduce treatment efficacy [11].

VTA Gamma-aminobutyric acid (GABA) neuron activation has been suggested to contribute to chronic stress-induced DA neuron hypofunction. VTA GABAergic neurons and their afferent inputs from diverse brain regions are highly responsive to stressful stimuli.

A concurrent decrease in inhibition and increased excitation from the regions targeting VTA GABAergic neurons in stress can increase VTA GABAergic neuron firing [12]. Consequently, the exciting local VTA GABAergic interneurons could inhibit DA neurons through $GABA_A$ receptor activation [13]. To observe the influence of stress on alcohol consumption, Alexey Ostroumov et al. used a single episode of restraint as a stressor and the ethanol self-management program. They noted the increase in extracellular dopamine concentration after alcohol intake in stressed mice was lower than that in the control group. Reduced mesolimbic dopamine release in response to alcohol diminishes the reward circuit [14]. Therefore, alcohol abusers require more alcohol to experience salience, promoting the development of dependence [15].

VTA GABAergic neurons can also be excited by aversive stimuli and functionally elicits negative emotions [12]. Negative moods lead PTSD patients to consume alcohol to relieve PTSD symptoms [16]. Notably, during the alcohol withdrawal period, PTSD-associated psychological symptoms such as anxiety and depression are persistent, which indicates that alcohol itself can provoke a stress response [17]. Thus, VTA GABAergic cells may be a potential target of PTSD and AUD comorbidity treatment.

There is a strong association between alcohol addiction and the midbrain DA system. During the commencement of alcohol addiction, the VTA-DA neurons are activated, reflected by an increased in tonic and burst firings [18]. Whereas ablation of VTA GABAergic neurons increased ethanol intake [19], systemic administration of dopamine receptor antagonists can reduce cravings for alcohol in AUD patients [20]. The functional and structural changes of the VTA DA system promote/drive the VTA of AUD patients in a euphoric state and increases the risk of facing trauma. Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) is the most

extensively studied neurotrophins in the VTA [21]. Short-term exposure to drug abuse increases BDNF levels in VTA neurons, promoting local DA neuron activity and positively reinforcing acute alcohol intake [22]. Likewise, GDNF is upregulated during short-term alcohol intake and exerts acute inhibitory effects on reducing alcohol consumption [23].

Chronic ethanol exposure produces neuroadaptations in DA circuits within VTA. These alterations, such as reduced dopamine receptors in NAc, remarkably decrease dopamine neuro-transmission in NAc and other related regions, suggesting that chronic ethanol consumption leads to DA hypofunction [24]. The above changes indicate the alterations drive excessive ethanol drinking [25]. The low VTA DAergic activity may impede the formation of fear-extinction memories [26], and fear and avoidance are core symptoms of PTSD. During alcohol withdrawal, profound decrement of VTA DAergic neuronal activity contributes to aversive or stress-like states [15], which can aggravate the negative mood and cognition symptoms in PTSD. Overall, alcohol addiction increases the possibility of being faced with trauma and may exacerbate PTSD symptoms.

2. Hippocampus

Hippocampus is characterized by its trisynaptic circuit architecture and is essentially involved in learning and memory, navigation, and cognition. Hippocampal dysfunction can lead to memory deficits, depression, epilepsy, and schizophrenia. PTSD and AUD are associated with profound changes in memory function and neuronal signaling related to the hippocampus.

PTSD alters hippocampal neurons' synaptic plasticity and firing properties, induces morphological atrophy, inhibits neuronal proliferation, and reduces hippocampal volume [3]. It impairs the function of the hippocampus and produces solid and long-lasting nociceptive memories. In addition, phosphorylation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) in the hippocampus has been proven to mediate the extinction of contextual freezing behavior, which is one of the main risk factors for PTSD [27].

Certain neuroimaging studies documented that acute alcohol exposure affects the episodic memory encoding function of the hippocampus [28]. Following the binge pattern of ethanol consumption, anaplastic lymphoma kinase signaling has been activated, and the transcription factor STAT3 level is increased in the brain [29]. There is also substantial evidence showing that AUD may be related to reduced hippocampal volume [30], decreased hippocampal neurogenesis [31][32], and downregulated mRNA expression levels [33].

Accumulating evidence has demonstrated that PTSD-AUD comorbidity is related to hypoxia, inflammation, and excessive cortisol secretion in the hippocampus [34][35]. Altered GABAergic receptor expression and reduced allopregnanolone levels have been identified in the comorbid mice compared to their littermates [36][37]. The above comorbid mice were induced by maternal separation or social isolation stress paradigm. Stress is one of the most commonly used methods to establish comorbidity models. Most recently, changes in the cannabinoid system enriched in the hippocampus are also reported to be implicated in comorbidity [38][39]. In this study, Veronica M. Piggott used chronic intermittent ethanol vapor exposure to increase the body ethanol concentration in mice, and

weekly plasma samples were collected. The mice were intoxicated if the plasma ethanol concentration was above 175 mg/dL.

3. Amygdala

The amygdala has been proven involved in multiple physiological and behavioral responses to fear, stress, and substance use disorders [40][41]. Dysregulation of neuroplasticity in the amygdala has been recognized as one of the mechanisms in the pathophysiology of several mental illnesses, such as depressive and anxiety disorders [42].

As neuroimaging findings revealed, PTSD patients often display structural changes in the amygdala. For example, teenage or adult patients with relevant psychological symptoms both company with significantly lower amygdala volume, especially volumetric reductions of grey matter [43]. In addition, PTSD patients also suffer regional malfunction, which may depend upon different molecular mediators of plasticity, including glutamatergic NMDA-dependent mechanisms, BDNF, calcium-dependent mechanisms, and so on. Compared to healthy people, the amygdala of trauma patients shows more substantial activity [44]. This amygdala hyperactivity predicts blocked fear extinction in the brain, while low amygdala activity predicts impaired response to fear restimulation [45]. Therefore, the hyperactivity of the amygdala elicited by negative stimuli may be indicative of trauma pre-traumatic events.

AUD patients had smaller amygdala volumes, which were positively associated with anxiety and negative urgency in AUD [46]. In particular, the GABAergic neurotransmitter system and adrenergic receptors in the central amygdala (CeA) have been implicated in regulating acute and chronic drinking behaviors [47]. Specifically, acute ethanol exposure activates α1 receptors and potentiates CeA GABAergic transmission, while chronic alcohol consumption activates β receptors and disinhibits a subpopulation of CeA neurons leading to their sustained hyperactivity [48][49]. The action of CRHR1 in the CeA was enhanced by ethanol exposure, suggesting that the CRH signaling pathway affects both the pre and postsynaptic transmission of GABA. Mineralocorticoid receptors (MR) in the CeA have been found to modulate alcohol self-administration and showed inverse correlations between its expression and measures of alcohol drinking [50][51].

In terms of the comorbidity, a 2-hit model was proposed to examine increased GABAergic transmission, and expressions of different neuroinflammatory factors, including G-CSF, and IL-13, were profiled in the amygdala [52] [53]. Clinical studies have also demonstrated higher amygdala blood flow in AUD and PTSD patients than in healthy controls [54]. Despite the significantly lower hippocampal volume observed in PTSD and AUD patients, other brain areas appear not to be different by volumetric analysis [55].

4. PFC

The PFC is a portion of the cerebral cortex covering the major part of the frontal lobe. The ventromedial prefrontal cortex (vmPFC) and dorsolateral prefrontal cortex (dlPFC) are closely associated with social, cognitive, and affective functions.

PTSD patients often showed morphological defects, such as a lower volume [43], especially in the gray matter [56] of the vmPFC, accompanied by reduced regional cerebral blood flow [57]. The interconnectivity between the PFC and the amygdala [58] suggests that the enhanced emotional memory traces in PTSD patients may result from an unbalanced interaction between two brain regions and PFC inhibition [59]. Additionally, reduced connectivity in dlPFC and medial PFC of PTSD cases have been uncovered through fMRI studies [60]. It has also been suggested that dephosphorylation of the mechanistic target of rapamycin (mTOR) and its upstream kinase, protein kinase B (Akt), in the PFC results in the disappearance of PTSD symptoms like fear extinction [61]. Thus, PTSD is associated with PFC hypofunction.

Structural and functional MRI studies suggest that disruption to the circuits originating from the PFC plays a crucial role in cognitive and motor impairments in AUD patients [62]. AUD is associated with reduced gray matter volume of corticostriatal and marginal circuit components such as dlPFC, which contributes to regional executive dysfunction. Reduced inhibition and enhanced excitatory synaptic activity of the PFC in addiction are well-documented in fMRI studies and are associated with increased adverse clinical outcomes [8][63]. In addition, the role and impact of the PFC-striatum circuit [64] and the PFC-amygdala circuit have been under intensive investigation recently [65].

Functional and structural alterations are observed in the prelimbic region of the PTSD and comorbid AUD patients' PFC, which is especially important due to its involvement in promoting and suppressing fear and ethanol-seeking behavior [66]. It is noted that these deficits could be treated by enhanced activity at metabotropic glutamate receptor 5 (mGluR5) in this region [67]. Using optogenetics to suppress prelimbic activity, it was found that fear memory reconsolidation and addiction behaviors were blocked [7]. Likely, PTSD patients with alcohol abuse showed lower blood flow in the PFC [54].

5. PVN

PVN is an integral part of the hypothalamic-pituitary-adrenal (HPA) axis, composed of three distinct anatomical loci: the PVN of the hypothalamus, the pituitary gland, and the adrenal cortices. The stress system, comprising of the HPA axis, and the locus (LC)/norepinephrine (NE)-autonomic nervous system, can be activated by stressful stimuli and initiates central and peripheral neuroendocrine responses to maintain regular homeostasis [68]. However, aberrant responses may lead to PTSD and AUD.

Trauma has been evidenced to contribute to HPA axis disturbances [69]. Glucocorticoids can easily cross the blood–brain barrier and produce negative feedback on the HPA axis, thereby reducing the secretion of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH). Under the circumstance of trauma, the secretion of hypothalamic CRH elevates rapidly, leading to enhanced release of ACTH [70]. The glucocorticoid secretion occurs more slowly [71]. The HPA axis activates the CeA, which generates negative emotions, such as fear and anger. The CeA stimulates the stress system, producing a positive regulatory feedback loop [72]. People with PTSD showed a flat distribution of cortisol levels throughout the day and night [73], which indicates that PTSD patients are more vulnerable to an arousal state.

AUD patients also show changes in HPA axis function, as the HPA axis has been suggested to play an essential role in drinking behavior [74]. Alcohol initially increases HPA axis activity leading to autonomic arousal, which further potentiates alcohol-related striatal transmission to promote motivation and rewarding properties of alcohol [75][76]. Alcohol also increases the NAc dopamine release [77], so glucocorticoids may regulate drinking behavior by acting on the reward system of the limbic brain, which expresses a large amount of GR [78]. However, heavy and excessive alcohol consumption leads to adaptations and debilitation to neuroendocrine regulation circuits and the reward system [79], which results in the transition from controlled to compulsive drinking behavior [80]. In the withdrawal of alcohol consumption, the negative reinforcement may drive AUD patients to intake more alcohol. Relapse-associated resumed consumption of alcohol would worsen the HPA axis and autonomic dysfunction, which hinders recovery from alcohol addiction [81].

6. LC

The LC in the central NE system plays an irreplaceable role in daily stress response and fear response. The LC is a cluster of NE-synthesizing neurons in the pontine brainstem adjacent to the fourth ventricle, which projects widely throughout the entire neuraxis [82]. LC-NE, along with other components, constitutes the stress system, which affects several psychological processes, including arousal, attention, and some control of fundamental physiological processes such as emotion regulation and cognition.

One of the significant symptoms of PTSD patients is flashing out, which is shown as cognition, memory, and arousal deficits. LC-NE is involved in stress responses and regulating cognitive function via PFC [83]. Acute stress increases tonic LC activity to facilitate alertness and scanning attention [83]. However, exposure to prolonged, chronic stress would cause LC-NE dysfunction [84], which can worsen PTSD symptoms. This statement is supported by a finding of aggravated core symptoms (including anxiety and avoidance) in people with PTSD using an α2-adrenergic receptor antagonist [85].

NE is involved in multiple aspects of motivation, including compulsive behaviors associated with alcohol abuse [86]. There is ample evidence that acute and chronic drinking can affect NE neuronal function and NE release [87]. Stressors have been documented to reinstate drug-seeking behavior [86][88], and the NE system is activated by stress and exerts robust arousal-promoting actions. The stress of withdrawal acts as a negative reward, encouraging AUD patients to relapse.

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