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The Serotonin Link between Alcohol Use and Affective Disorders

Ariel Ketcherside[1]*, Ian Matthews[1,2] and Francesca Filbey[1]

[1]*Center for BrainHealth, University of Texas at Dallas, USA*
[2]*Lewis and Clark College, USA*

***Address for Correspondence**
Ariel Ketcherside, BA, Center for BrainHealth, University of Texas at Dallas, 2200 West Mockingbird Lane, Dallas, TX 75235, USA, Tel: 972-883-3315; E-mail: Ariel.Ketcherside@utdallas.edu

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Abstract

Serotonin is imperative for the normal operations in the central nervous system. The serotonergic circuitry is implicated in many neuronal processes, and, especially so in mechanisms of emotional regulation and reward. Although function in the serotonergic circuitry has been shown to be abnormal in many pathological states like depression, anxiety, and addiction, its ubiquitous nature complicates efforts to pinpoint the exact loci of pathology. This becomes especially relevant when these conditions occur together, which they do frequently. In this review, we examine the literature on the role of serotonin in depression, anxiety, and addiction, identifying commonalities between these disorders to elucidate the mechanisms at work when they are comorbid. Specifically, we examine the role of serotonergic receptors, transporters, and networks in incidences of alcohol dependence that is comorbid with depression to facilitate a deeper understanding of these mechanisms necessary for the development of more effective and personalized treatments.

Introduction

Addiction is characterized by chronic relapsing, inability to control drug or alcohol intake or compulsive use, and negative affect in the absence of the drug or alcohol. Of all addiction, alcohol use disorders (AUDs; alcohol dependence or abuse) comprise the majority, affecting 16.7 million persons aged 12 or older (6.5% of US population) in 2011 [1]. AUDs are one of the leading preventable causes of death, and, the fourth leading cause of disability in the United States [2]. Treatment efforts leave much to be desired as individuals who have been treated for alcohol–related problems demonstrate <40% success rate within 1 year following treatment [3]. One potential limitation to the efficacy of treatment strategies may be due to the multiple etiologies that lead to AUDs.

For instance, the widely known self-medication hypothesis of drug and alcohol use is based on the fact that 24.1% of people with depression or anxiety use alcohol or drugs to mitigate their symptoms [4]. The comorbidity of AUDs, depression, and anxiety is widely established in the literature. Further, when AUDs are present with depression or anxiety, the severity of both are positively correlated [5]. These relationships suggest common mechanisms, pathways, and environmental conditions. In this review, we focus on serotonergic function and signaling pathways implicated in AUDs to highlight mechanisms of comorbidity between AUDs, and, depression and anxiety (heretofore referred to affective disorders). If we know how addiction works on all these fronts, we will be more equipped to identify and develop more effective treatments. In other words, if we know how AUDs and affective disorders interact with each other, we will be better able to treat both.

Serotonin

Serotonin is a monoamine hormone/neurotransmitter with a complex circuitry comprising ubiquitous projections with more than 14 different types of receptors (pre- or post-synaptic, excitatory or inhibitory) [6]. Peripherally, it plays critical roles in digestion, pain sensation, and vasoconstriction in the event of an injury [7,8]. In the central nervous system, serotonin is known for its roles in feelings of well-being, appetite control, learning, and memory [9,10]. Serotonin in the brain is synthesized in the dorsal raphe nuclei (DRN) with tryptophan hydroxylase (TRH) as its principle and rate-limiting enzyme for synthesis [11]. It is subsequently dispersed throughout the rest of the brain, most notably to the mesolimbic and frontal cortices.

In the frontal cortex, serotonin (5-HT) primarily contributes to the inhibition of pyramidal cells, thus, providing prefrontal inhibition of potentially detrimental behavior. However, 5-HT can exert both excitatory and inhibitory transmission depending on the receptor being activated (i.e. the serotonin 1A receptor ($5HT_{1A}$) is inhibitory and the serotonin receptor 2A ($5HT_{2A}$) is excitatory on apical dendrites) [12,13].

In limbic regions, 5-HT plays an important role in the regulation of dopamine and norepinephrine signaling [14]. Serotonin is also implicated in feelings of well-being, and, therefore, is important in regulating mood. Evidence for this includes genetic associations between serotonergic genes and depression. Specifically, the serotonin transporter polymorphic region gene (5HTTLPR) region has been highly implicated in depression, particularly the short allele that is less active than its longer counterpart [15]. Individuals with the short allele have reported greater depression and life stress, and in a landmark longitudinal study, this correlation increased when the individual endured traumatic events [5,16]. This suggests a gene x environment interaction such that it results in depression and anxiety in individuals who endure both environment stress and have this allele [15,16]. This may be due to down-regulation of serotonergic receptors, which could occur in the presence of the initial surplus of synaptic serotonin, which results from a hypoactive transporter [17]. Perhaps the most compelling evidence for the role of serotonin in depression is the number of people successfully being treated with drugs that target serotonergic circuitry [18]. An estimated ten percent of Americans are currently taking serotonergic medication for emotion-related disorders. Selective Serotonin Reuptake Inhibitors (SSRIs), specifically, were introduced in the 1980s, and were quickly preferred over other emotion-regulation medications because of their decreased side effects and toxicity [19,20]. However, several have questioned, the superiority of SSRIs, especially fluoxetine. For example, Cipriani et al. reviewed 132 randomly controlled trials (RCTs) regarding the efficacy and side effects of commonly

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prescribed SSRIs with other antidepressants including tricyclic antidepressants, heterocyclic antidepressants, and norepinephrine inhibitors. They concluded that the efficacy and side effects of each drug class varied within the class itself, according to which drugs were tested. There were significant differences between drug classes, but the only conclusion to be made with certainty was that the majority of the studies recruited less than 100 participants, so the implications of the results should be interpreted with caution [21].

With regards to alcohol, in general, ethanol elevates 5-HT levels in several brain regions, including the nucleus accumbens, ventral tegmental area (VTA), amygdala, and hippocampus – all regions associated with the reward circuitry. For example, in the VTA, self-administration of ethanol is prevented by the co-administration of $5HT_3$ receptor antagonists, indicating that the rewarding effects of ethanol in this region act through serotonin [22]. Furthermore, a review of the effects of serotonin on alcohol consumption in animal models expounds that increasing serotonin in the brain decreases alcohol intake [23]. The literature also supports the co-occurrence of AUD in individuals who have undergone abuse as children [24,25]. Both AUD and childhood maltreatment have been associated with decreased serotonergic neurotransmission in humans [26,27]. Berglund et al. found a highly significant difference in prolactin (PRL) response to citalopram, an SSRI, in adult male alcohol dependent individuals with and without childhood maltreatment [28].

Taken together, the clear connection between elevation of neuronal serotonin and decrease of negative affect and ethanol consumption provides a strong ground for the role of serotonin in the comorbidity of affective disorders and alcohol dependence.

Serotonin in Comorbid AUD and Affective Disorders

Implications for serotonergic dysfunction in both AUDs and affective disorders have been found at multiple levels of serotonergic functioning, from synthesis to terminal projections. For example, serotonin's rate limiting enzyme, TRH, demonstrates increased immunoreactivity in the dorsal raphe of alcohol dependent victims of depression and suicide compared to psychiatrically normal controls [29]. This implies an increase is the amount of global serotonin in the brains of these individuals, suggesting an over-compensatory mechanism for downstream network shortfalls.

The serotonin transporter

Alcohol triggers serotonin and dopamine release in the nucleus accumbens - a hallmark characteristic of drugs of abuse. In rodent models, the amount of alcohol consumed correlated negatively with basal levels of serotonin and dopamine, indicating that an inherent dearth of these neurotransmitters, due to an increase in 5-HT release rather than uptake, may prompt greater alcohol use in humans [12,30]. For example, human and animal studies demonstrate a relationship between 5-HT synaptic clearance and amount of alcohol consumed. In humans, individuals with the less active short allele of the 5HTTLPR consumed less alcohol than their long-allele carrier counterparts [31]. Similarly, in mice, variations in the serotonin transporter demonstrated variations in the amount of alcohol consumed [32]. Some hypothesize that increases in serotonin associated with the short allele for the 5-HT transporter gene prevents negative drinking habits attributable to impulsivity – so perhaps a more active serotonin transporter (SERT) would promote such behavior [33].

Interestingly, the mélange of data regarding the long and short alleles for 5HTTLPR suggests that increased negative affect is associated with the short allele of the gene. Some studies have found that the short allele is associated with neuroticism and anxiety, although this finding has been inconsistent [34]. In alcohol dependent suicide victims diagnosed with anxiety disorders, there was less expression of SERT mRNA in the anterior cingulate gyrus/BA 24 compared to healthy matched controls [35]. Others have observed a decrease in binding affinity of SERT among alcohol dependent suicide victims in contrast to alcohol dependent non-suicide victims, suggesting decreased binding of SERT is involved in suicide [36]. Another study found an association between the 5-HTTLPR short allele and alcohol-dependence and suicidality in men [37].

A less prevalent (encoded by the short allele) protein would result in increased serotonin in the synapse. But specifically in alcohol dependent individuals with anxiety, the short allele for SERT correlated with decreased $5\text{-}HT_1$ receptor density in the caudate nucleus [38]. This suggests a model in which increased synaptic serotonin down-regulates $5\text{-}HT_{1B}$receptor density specifically in the basal ganglia, which, in turn, leads to alcohol seeking behavior. This mechanism is distinct from impulsivity-related alcohol disorders, as an increase in prefrontal cortex (PFC) synaptic serotonin has been shown to inhibit impulsive alcohol-related behaviors [39,40].

Serotonergic receptors

Serotonergic receptors are numerous, and, many have been associated with pathological conditions, including the comorbidity of alcohol dependence and affective disorders. The modulation of 5-HT receptors by chronic alcohol exposure has been widely described. For example, in a review by Renoir et al. of hypothalamic pituitary adrenal (HPA) axis regulation of serotonergic circuitry, connections between increased stress, increased alcohol consumption, and decreased BDNF (define) (which is downstream of and regulated by serotonergic circuitry) were identified [41]. Associations between serotonergic receptor function and behavioral symptoms of alcohol use have also been reported such as with post-serotonergic ($5\text{-}HT_2$) signal transduction and etoh withdrawal [42] and several serotonergic receptors and alcohol use patterns [33].

In terms of anxiety, there is comorbidity with alcohol dependence is accompanied by alterations in serotonergic receptor and transporter binding affinity. For example, $5HT_{2C}$ receptors in the amygdala mediate increases in anxiety resulting from repeated ethanol exposure and withdrawal, indicating sensitization of these receptors in a state of withdrawal [43]. Anxiety is a primary behavioral symptom of alcohol withdrawal, and has been attenuated through 5-HT circuitry such that $5\text{-}HT_{2C}$ receptor antagonists (SB242084, flumazenil, and CRA1000) effectively reduced anxious behavior in withdrawing rats [44].

In the perigenual anterior cingulate cortex (ACC), a positive correlation was observed between the binding affinity of SERT and postsynaptic serotonin receptor $5\text{-}HT_{1A}$ as well as an overall decrease in $5\text{-}HT_{1A}$ receptor density in Clonginger type 1 alcohol dependents[1] [45]. The ACC is known for its role in emotion regulation and

[1]In 1987, Robert Cloninger characterized two categories of alcohol dependence: "Type 1 Alcoholics" demonstrate low novelty-seeking behavior, higher age of onset of alcohol dependence, and are more likely to experience feelings of guilt about their alcohol dependence. "Type 2 Alcoholics" are more likely to manifest their disorder before the age of 25, be male, and are more prone to novelty-seeking behaviors, as well as aggressive behavior associated with drinking [48].

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behavioral planning [46]. Thus, this relationship suggests that an overall decrease in serotonergic circuitry is present in individuals with alcohol dependence that is related to increased anxiety.

A decrease in the binding affinity of 5-HT_{1A} was also found in a separate study of depressive alcohol dependent suicide victims, in Brodmann's area 9/dorsolateral prefrontal cortex (dlPFC) [35]. This region is associated with decision-making and reward processing, which have been shown to be impaired in individuals with alcohol dependence [47]. Another study by Underwood et al. also showed decreased binding affinity of 5-HT_{1A} in both alcohol dependent suicide victims and non-suicide victims [36]. This study also found greater binding affinity of 5-HT_{1A} receptor in the ventral prefrontal cortex of non-alcohol dependent suicide victims than in alcohol dependent suicide victims, as well as a decreased binding affinity of 5-HT_{1D} receptor related to alcohol dependence [36].

Similar correlations have also been reported in the caudate nucleus. Specifically, Storvik et al. reported a direct relationship between SERT and 5-HT_{1B}receptor binding affinity in the caudate of patients who were diagnosed with anxiety prone type one alcohol dependence [38]. Further, an indirect relationship between serotonin 5-HT_{1B}receptordensity and age was observed. This suggests that if age serves as a proxy for duration of alcohol dependence, that a longer duration of alcohol dependence correlates with less SERT binding. These studies together suggest that victims of alcohol dependence experience a decrease in serotonergic signaling in several areas associated with reward processing and decision-making.

Serotonergic projections

Bed nucleus of the stria terminalis: The bed nucleus of the stria terminalis (BNST), has been implicated with increased alcohol consumption after exposure and withdrawal [33]. The BNST is a hub of stimulatory input from cortical and limbic regions, as well as feedback from several including the hippocampus, PFC, paraventricular nucleus of the hypothalamus, ventral tegmental area, locus coeruleus, and dorsal raphe nuclei. Serotonergic signaling is prominent in the BNST, and has been shown to mediate stress and anxiety-like behavior [49]. One hypothesis suggests that pathologic serotonergic circuitry in this region results in a stress-response-positive-feedback-mechanism. In a long-term state of imbalance, this may produce excessive and pathological anxiety [33]. Further, exposure to alcohol has been shown to increase extracellular dopamine in the BNST [50].

Basal ganglia: As demonstrated by the research mentioned above, the serotonergic circuitry in the basal ganglia appears to be integral for the tendency towards and the development of alcohol dependence. Huggins et al. measured this directly in a macaque model of early childhood stress, and, found that monkeys who were raised in a stressful (nursery- reared) environment drank more alcohol in adulthood than monkeys raised in their normal (mother-reared) environment [51]. The stress-model monkeys also demonstrated lower concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in their cerebral spinal fluid (CSF) and putamen. Contrarily, 5-HIAA concentrations in the caudate, substantia nigra, or hippocampus of experimental animals were not significantly different than in control monkeys. However, 5-HT gets recycled, so serotonin metabolism is not directly a function of serotonergic activity. Because of this, they measured the 5-HIAA/5-HT ratio, and found an overall decrease in turnover of 5-HT in stress-model animals than in controls. By region, this was only significant in the hippocampus [51]. In humans, magnetic resonance imaging (MRI) revealed 10% smaller right caudate nuclei and 19% smaller globus pallidi in participants who attempted suicide when compared with healthy controls.

Prefrontal cortex: The role of the prefrontal cortex (PFC) particularly in terms of higher-order processing in the co-morbidity between affective disorders and alcohol dependence has also been suggested. For example, in a cohort of 374 females, Jacobs et al. demonstrated that indeed, the short5-HTTLPRallelewas associated with depression [52]. However, this effect disappeared when symptoms of neuroticism were taken into account implicating a role of higher-order processing, like perception of self and environment, in the pathology associated with this allele [52]. Taken together, perhaps in addition to its role in limbic and reward regulation, serotonergic inhibition of rumination prevents negative affect attributed to depression and anxiety.

Selective Serotonin Reuptake Inhibitors

As described above, SERT has been a therapeutic target for affective disorders since the 1950s [53]. To date, inhibitors of SERT, specifically selective serotonin reuptake inhibitors (SSRIs), are some of the most widely prescribed pharmacotherapy on the market, used to treat conditions ranging from depression and anxiety to anorexia nervosa [54,55]. Because serotonergic projections include the mesolimbic dopamine circuitry (reward centers) and the forebrain (decision-making centers) [56], which are highly implicated in both addiction and affective disorders, SSRIs have also been explored as a treatment for addictive disorders [57]. Interestingly, outcomes vary in accordance with alcohol dependence subtype. In early onset alcohol dependence patients with greater problems associated with use, treatment with fluoxetine (Prozac) resulted in worse outcomes than placebo [58]. In a separate study, treatment with sertraline (Zoloft) resulted in greater abstinence from alcohol than a placebo in late onset alcohol-dependent patients with fewer problems associated with use [59].

Xie et al. found that H-HTTLPR genotype modulated risk for developing PTSD in European Americans: Individuals with the LL allele had less development of PTSD after childhood maltreat than their SS and SL counterparts [60]. This gene x environment interaction, in conjunction with Seretti et al.'s meta-analysis of the effect o 5-HTTLPR genotype on SSRI treatment outcome indicate that individual differences are present and have important implications for therapeutic interventions [61]. However, further studies are necessary.

Other studies have been inconclusive, which may arise from several factors. First, study exclusion criteria often eliminate participants with a comorbid affective disorder from treatment studies to minimize variance in results [62]. While alcohol-dependent individuals may benefit from serotonergic medication even without having a comorbid affective disorder, such criteria eliminates a population that could provide valuable information about the comorbidity between AUDs and affective disorders. Moreover, SSRIs can take up to six weeks to be fully "active" [63], whereas treatment, like in the Garbutt et al. Study, often lasts for less time (e.g., 4 weeks) [57]. As a result, the trial may be over before the medication canbegin to counteract the patient's current symptoms, thus promoting relapse before the therapy was even effective.

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SSRIs may only help alcohol addiction when the addiction has roots in emotional dysregulation. As has been shown in animal models of AUDs, fluoxetine attenuates the reinstatement of alcohol self-administration after a stressful stimulus, but was unable to consistently prevent reinstatement of alcohol self-administration after priming with alcohol [64]. Nunes and Levin performed a meta-analysis including 14 studies that examined the effect of antidepressant treatments in comorbid depression and substance dependence [65]. While the involved studies collectively found that antidepressants were effective for treatment in their samples, the effect of antidepressants on substance dependence was less clear with large variation present because of patients' responses to placebos. Six of the studies had a high response to their respective placebos, but even with these considered, the overall effect size was still modest (0.38). Overall, these studies supported the hypothesis that medication treating depression also reduces substance use [66].

Conclusions

Our review of the literature shows that serotonin is highly implicated in brain networks most relevant to addiction: prefrontal cortex for higher-order processing and the mesolimbic reward circuitry. Serotonin in the reward network is especially relevant to emotional regulation disorders, and logically so, as the keynote of both disorders is dysregulation of hedonic homeostasis, which is partially attributed to serotonergic function [17,66]. Because of serotonin's regulatory roles in the prefrontal regulatory circuitry, and in mesolimbic reward circuitry, it is a prime candidate for therapeutic targets – on the condition that it is targeted in relevant patients with these comorbid disorders. As outlined, genetic variations in the 5HTTLPR region and in specific 5HT receptors provide a starting point from which to identify this unique pattern of negative affect in comorbid AUDs and emotional regulation disorders that could lead to more targeted treatment.

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