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Behavioral and Neurobiological Consequences of Hedonic Feeding on Alcohol Drinking

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Abstract

A complex interplay of peripheral and central signaling mechanisms within the body of an organism maintains energy homeostasis. In addition, energy/food intake is modified by various external factors (*e.g.*, palatability, food availability, social and environmental triggers). Highly palatable foods can provoke maladaptive feeding behavior, which in turn disrupts normal homeostatic regulation resulting in numerous health consequences. Furthermore, neuroendocrine peptides, traditionally considered to regulate appetite and energy homeostasis, also control the intake and reinforcing properties of alcohol and drugs of abuse. Therefore, dysregulated eating as a result of a hedonic/binge-like intake of hyper-palatable food may impact alcohol drinking behavior. Relevant in this case is the fact that eating disorders are highly comorbid with several neuropsychiatric conditions, including alcohol use disorder. The present review is intended to summarize the neurobiological and functional consequences of hedonic feeding on alcohol intake.

Keywords

high-fat diet; alcohol; nutritional contingency; palatable diet; alcohol use disorder

1. INTRODUCTION

Food intake, a behavior necessary to fuel basic biological function and survival, is under control of a complex interplay between peripheral and central signaling mechanisms. Several coordinated interactions between peripheral key feeding players (*e.g.*, ghrelin, leptin, insulin, *etc.*) and central appetite control center (*e.g.*, hypothalamus) regulate when and how much to eat, which is critical for maintaining energy balance and homeostasis [1, 2]. However, food intake can also be modified by various external factors (*e.g.*, palatability,

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food availability, sensory cues, social and environmental triggers) [3–6]. For example, palatability, which is a hedonic evaluation of several oro-sensory food-related factors (*e.g.*, taste, texture, odor and presentation, *etc.*), can greatly influence food preference and consumption [6–8]. Altering the macronutrient composition may further enhance palatability as foods rich in sugar and fat are highly palatable and largely over-consumed during binge-episodes in human and laboratory animals [7, 9, 10]. This hedonic eating, not driven by homeostatic needs, could contribute to the development of eating disorders, metabolic complications, and related pathology.

Eating disorders (EDs) currently recognized by DSM-5 criteria include anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED) and are a significant health concern to the modern society [11, 12]. Eating disorders are highly comorbid with substance use disorders (SUDs) and other neuropsychiatric conditions [12–16]. Approximately half of the individuals diagnosed with EDs also struggle with SUDs, including alcohol use disorder (AUD) [17,18]. Recent work from Udo and Grilo examined the comorbidity prevalence rate for EDs and AUD in a large epidemiological study using data from a nationally representative clinical subsample, including 36,309 participants of all genders, racial groups, and ages. The study's findings reported that 49% of patients with AN, 61% of patients with BN, and 52.0% of BED patients met the criteria for alcohol use disorder compared to 28.7% of those with no-specific EDs [16]. These data suggest that eating disorders, especially those with a strong hedonic component (binge-like eating), are more frequently associated with AUDs.

While both clinical and pre-clinical studies have shown an association between EDs and AUD, the behavioral and neurobiological consequences of hedonic eating on AUD are poorly understood. Understanding this relationship is critically important considering that hyper-palatable foods, consumed during binge-episodes in humans, activate similar brain reward circuitry as of drugs of abuse [19–22] and common neurobiological mechanisms regulate energy homeostasis and reinforcing properties of alcohol and drugs of abuse [23–25]. The present review is intended to summarize the functional consequences of hedonic eating on alcohol intake and potential neurobiological mechanisms.

2. HUMAN STUDIES

Although the co-existence of EDs and AUD is well-documented in the scientific literature, several complex biological and environmental factors that could trigger maladaptive alcohol drinking in response to dysregulated eating are poorly understood. For example, there appears to be a shared familial risk for BN and AUD in both male and female youth [26], and this familial relationship significantly lowered the age of binge eating onset, quickly advancing to BED diagnosis, and significantly increased the likelihood of psychiatric comorbidities [27]. There could also be gender-specific differences in how certain eating disorders are impacted by alcohol drinking behavior as a recent study found that alcohol-related compensatory bulimic behavior selectively worsened ED pathology in females [28]. It has also been suggested that shared genetic factors could influence the comorbidity between BN and SUD [29]. On the contrary, evidence supporting the independent genesis of EDs and alcohol use disorder also exists [30,31]. For example, Walter H. Kaye and

colleagues suggested no shared familial link between BN and alcohol use/substance abuse disorders [30]. Earlier studies focused on the chronological evaluation of these disorders have suggested a bi-directional association [17], whereas relatively recent reports indicate that BN typically manifests before SUDs [32,33]. Furthermore, the binge-eating aspect of disordered eating is strongly correlated with AUD [17,34]. While these data may suggest that eating disorders with a prominent hedonic aspect precede or trigger AUD, it could be that the manifestation of BN occurs at an earlier age, thereby preceding the onset of SUDs. On the other hand, a recent study which examined emotional overeating, drinking pattern, substance abuse and suspected eating disorders in female university students found a negative correlation between intermittent emotional eating episodes and moderate to excessive alcohol drinking [35].

A handful of studies have also examined the macronutrient specific impact of palatable diets on alcohol drinking. For example, a study examining the macronutrient composition of dietary intake in 64 newly sober alcoholic patients found significantly escalated sugar and carbohydrate intake in those who stayed sober longer [36]. Similar alterations in the nutrition-related behavior were also recently reported by a study in which abstainers in an outpatient alcohol detoxification program consumed 3 times more chocolate compared to nonabstainers [37]. While these data may demonstrate a protective effect of excessive intake of palatable food on alcohol consumptions, it is unclear if sugar decreased alcohol drinking or alcohol withdrawal increased sugar consumption triggered by a coping mechanism or gateway drug effect. Interestingly, these studies also align with the Alcoholics Anonymous movement, which recommends eating sweets to curb alcohol craving [38]. The relationship between high-calorie food and alcohol consumption could also be influenced by certain cultural/racial differences. For example, a study recruited students using multiple modes of communications and based on self-reported data documented that calories obtained from fat and sugar-sweetened beverages were much higher in African Americans compared to the white students and opposite was true in the case of calories obtained from alcohol [39]. While these studies collectively suggest a reduction in alcohol drinking behavior following overconsumption of palatable food, it remains unclear whether the effect on alcohol drinking is macronutrient specific.

While similar neural pathways could be involved in mediating the reinforced behavior, hedonic intake of fat and sugar has been suggested to produce distinct behavioral states [21]. However, assessing the macronutrient specific effects on alcohol drinking in the human population could be inherently challenging as palatable diets consumed during human binging could be rich in fat and sugar or a diet high in fat would be automatically low in carbohydrates and vice versa. In the past several years, a strong association between eating disorders and substance abuse disorders (SUDs), most notably alcohol, has emerged in the scientific literature, which has sparked the interest of clinicians and basic researchers to understand the etiology and development of these two families of disorders. However, the precise contribution of dysregulated eating behavior on the development of alcohol use disorder remains poorly understood, and future well-controlled empirical studies are needed to advance our understanding in this regard.

3. NON-HUMAN STUDIES

The availability of certain purified diets for laboratory animals with selective alteration in any macronutrient content could overcome several limitations, which could make assessing the macronutrient specific effects on alcohol drinking difficult in a clinical setting. A greater body of work examining the impact of hyper-palatable food (*e.g.*, high-fat and/or high-sugar diets) intake on alcohol drinking comes from non-human studies. Several studies have evaluated alcohol drinking following various high-fat diet exposure conditions; however, a clear picture has yet to come out.

For example, an earlier study examined the acute effects of high-fat exposure on oral ethanol intake (2–9% v/v) in Sprague-Dawley rats. In this study, a separate group of rats received fat emulsion (20% fat, 5.0 ml) injections, 1-hr or 7 days of HFD (50% fat) exposure, and then switched to standard chow while alcohol testing occurred. Ethanol intake under all conditions escalated in the HFD exposed group of rats compared to the controls [40]. Another study which examined the impact of relatively longer dietary exposure duration (4 weeks) on oral alcohol drinking (10% v/v) in male Sprague-Dawley rats found that rats on a high-fat diet (65%) drank significantly higher amount of ethanol compared to the low-fat diet (15%) controls [41]. Furthermore, when male Sprague-Dawley rats were grouped based on their fat (~81%) and carbohydrate (~90% with 12% sucrose) preferences, fat-preferring rats consumed more alcohol orally compared to the carbohydrate-preferring rats [42]. In addition, alcohol preference was higher in the fat-preferring rats, whereas no such effect was evident in carbohydrate-preferring rats [42].

While the studies mentioned above suggest a positive relationship between fat and alcohol intake, other studies have suggested no such relationship or blunted/reduced alcohol drinking following high-fat diet exposure [43–48]. For example, Takase *et al.* examined ethanol preference using a two-bottle choice paradigm in male C57BL/6J mice following 5-weeks of control (low-fat diet: 13% calories from fat), HFD-induced obese (ad-libitum HFD 45% calories from fat) and HFD-fed nonobese exposure conditions. Mice receiving a low-fat diet showed a significant preference for 10% ethanol, whereas no such effect was observed in either HFD-exposed groups of mice [43]. Another study evaluating oral alcohol intake in male and female B6 mice following 3-weeks of low-fat (10.2%) and HFD (60%) exposure also found reduced alcohol drinking in the HFD-exposed group of mice. While females drank more ethanol, HFD-induced reduction in alcohol drinking was observed in both male and female groups of mice [45]. Cook *et al.* evaluated home-cage oral ethanol drinking in male Wistar rats following 4 weeks of cafeteria diet consisting of high-calorie junk food (42% fat) and compared it to the chow (14% fat). While there were no baseline differences, alcohol drinking was significantly reduced in the cafeteria-diet group of rats [47]. Interestingly, reduced oral alcohol drinking has also been documented in golden hamsters maintained on a high-fat diet (72.6% calories from fat) compared to normal chow (12% calories from fat) [46].

It is important to note that the abovementioned studies provided HFD under acute or chronic ad libitum conditions. Fewer studies have assessed the effects of binge-like HFD intake on alcohol drinking. For example, our lab demonstrated for the first time that binge-like HFD

intake reduced alcohol drinking in rats [49]. In this study, adult male Long Evans rats received acute intermittent HFD (40% calories from fat) access for 2hrs every day (HFD-ED) or every third day (HFD-3D) and 5-weeks later in cage oral alcohol drinking (2hr) was evaluated on the following days of HFD binge-episodes while the rats were still on the acute intermittent HFD binge cycling. We found that alcohol drinking was significantly attenuated in both HFD-3D and HFD-ED group of rats compared to the chow controls [49]. While HFD binge episodes in our study were initiated in adult rats, a recent study examining the impact of binge eating of HFD (45% calories from fat) during adolescence found escalation of alcohol reward and oral self-administration in mice [50]. Adolescence is a critical period of maturation and imparts greater vulnerability to individuals for engaging in risk-taking behavior, which has consequences in later life. This study not only highlights the danger of binge-like eating during this critical period in terms of developing alcohol use disorder but also suggests that the age of HFD exposure (adolescent vs. adult) might impact alcohol reward differentially. On the other hand, Pain *et al.* found that sweetened milk consumption during adolescence decreased oral alcohol drinking in adult rats [51]. As mentioned above that the length and exposure duration of high-calorie foods can produce fundamentally different behavioral states [52,53], we also examined the impact of extended intermittent HFD access (24 hr, Tuesday and Thursdays) for six-weeks on alcohol drinking in rats. Again alcohol drinking was significantly reduced in the intermittent HFD exposed group of rats compared to the chow controls [54]. Using the similar paradigm, a more recent study from our lab has identified that intermittent HFD pre-exposure is critical to reducing alcohol drinking [55]. It is important to mention here that our studies utilized male adult rats, and it is unclear if similar results could be obtained in female rats. A recent study reported a negative correlation between intermittent emotional eating episodes and alcohol drinking in female students, suggesting that the impact of intermittent palatable diets exposure could impact females in a similar manner, at least in case of alcohol drinking [35].

While several studies have examined the impact of a high-fat diet on alcohol drinking, fewer have evaluated alcohol drinking following carbohydrate and/or protein manipulations. For example, Forsander and Sinclair examined voluntary alcohol drinking in alcohol-preferring (AA) female rats following various dietary exposure conditions and found that carbohydrate intake negatively impacted whereas protein intake positively impacted alcohol drinking [56]. A similar relationship between carbohydrates, proteins, and alcohol was documented by another study [41]. Furthermore, chronic protein restriction was shown to significantly reduce free-choice oral alcohol drinking in rats [57]. Avena *et al.* reported that intermittent exposure to sugar (10% sucrose) solution enhanced voluntary ethanol intake in male Sprague-Dawley rats [58]. In this study, rats in the intermittent access groups received 12 hr deprivation followed by 12 hr exposure to sucrose+chow (Int-S+C) or chow (Int-C) only. Ad libitum chow (Ad-C) and sugar+chow (Ad-S+C) groups were also included. It was shown that oral alcohol intake in both intermittent groups was significantly increased compared to the ad libitum conditions and there was no difference in alcohol intake between Int-S+C and Int-C group of rats, suggesting that intermittent food availability/deprivation, instead of sugar exposure, could have contributed to escalated alcohol intake. To support this, studies have shown that alcohol drinking in food-deprived rats is significantly increased compared to sated conditions, irrespective of the alcohol concentration [59]. Interestingly, an earlier

empirical study demonstrated a decrease in alcohol (5% v/v) responding when paired with sucrose solution (3–5%) [60].

Although mixed results have been obtained following HFD exposure on alcohol drinking, the majority of reports indicate a negative relationship between palatable diets (high in fat/sugar) exposure and alcohol drinking [35, 41,43, 45–47, 49, 54–56]. Inconsistencies obtained in the outcomes could be attributed to experimental/procedural differences among these studies. For example, HFD-induced escalated alcohol drinking by Krahn and Gosnell was evaluated in rats selected based on their natural preference for dietary fat [42]. It is possible that selecting rats based on their inherent dietary choices had isolated a phenotype naturally prone to consume more calories irrespective of the source. Furthermore, it has been argued that the macronutrient preference profile may not be a reliable predictor of voluntary ethanol intake [44]. Furthermore, fat content in the HFD was generally higher and the duration of dietary exposure prior to alcohol testing was relatively shorter in studies reporting increased alcohol drinking. It is important to mention here that length and exposure conditions of high-calorie food can produce fundamentally different behavioral states [52,53,61], which could explain the surprising difference in alcohol drinking following HFD exposure conditions and needs further investigation. Furthermore, the relationship between HFD consumption and alcohol intake could be dependent on the presence or absence of dietary manipulations while alcohol testing occurred [62], raising the necessity of testing alcohol drinking at multiple times following palatable diets exposure. A relatively recent study showed that alcohol drinking behavior in rodents could be differentially impacted in mice maintained on various standard rodents chows [63]. This study not only helps to address some of the discrepancies in the HFD-induced alterations in alcohol drinking mentioned above but also raises an important point on experimental design while assessing the impact of various dietary manipulations.

4. POTENTIAL NEUROBIOLOGICAL MECHANISMS

High-calorie hyper-palatable foods can independently interact with brain reward circuitry [19–22], and common neurobiological mechanisms are implicated in energy homeostasis and reinforcing properties of alcohol and drugs of abuse [23–25]. A detailed account of all these changes is reviewed recently [64–66] and is beyond the scope of the present paper. Here we offer conjecture on potential mechanisms that could underlie reduced alcohol intake in binge-exposed rodents. It is important to mention here that multiple mechanisms could explain reduced alcohol intake in binge-exposed rats, and future studies are needed to validate underlying mechanisms scientifically.

Prolonged consumption of western diets (high in sugar and fat) reduces dopamine (DA) concentrations in both patients and rodents [67–69]. Mesolimbic dopamine release is a well-known regulator of motivation for both food and alcohol intake. In this context, an increase in extracellular mesolimbic dopamine is associated with an enhanced motivational drive to obtain either food or chemical drugs [70,71]. Activation of VTA DA neurons and accumbens neurons have been reported following binge-eating on HFD [72] and mutations in the dopamine receptor-2 have been linked to binge eating pathology clinically [73]. Another rodent study that examined the impact of adolescent binge-like eating of HFD on alcohol

drinking reported decreased tyrosine hydroxylase (an enzyme involved in DA synthesis) gene expression in HFD exposed group [50]. We did not measure changes in mesolimbic dopamine in our previous study, demonstrating reduced alcohol drinking behavior following binge-like eating of HFD; thus, we cannot rule out its contribution to reduced alcohol intake observed in binge-exposed rats [49].

Neurotensin is a peptide produced in both peripheral site and central nervous system that regulates alcohol intake. Mice that lack the neurotensin-1 receptor (NRT1R) are resistant to the intoxicating effects of alcohol and consume more ethanol relative to control mice [74]. In addition, neurotensin-2 receptor (NRT2R) knock out mice display enhanced preference and consumption of ethanol relative to controls, and a brain permeable neurotensin analog (NT69L) treatment was shown to reduce alcohol drinking [75]. We observed increases in NRT1R mRNA expression in the medial prefrontal cortex (mPFC) in HFD-3D rats relative to HFD-ED and controls rats. In contrast, we found that HFD-ED rats displayed reduced NRT2R expression in the mPFC [49]. The mPFC is a structure that regulates executive control over the brain. In this context, the maladaptive mPFC function is hypothesized to underlie the loss of control for food and chemical drugs [76]. Thus, the observed changes in neurotensin expression in the mPFC could contribute to the reduced alcohol consumption following binge HFD exposure.

A growing body of pre-clinical and clinical work has elucidated the reinforcing role of endogenous neuroendocrine signals in the reward-dependency aspect of hedonic eating [77–79]. In this context, it is well established that levels of the predominant orexigenic neuroendocrine signal, ghrelin, are environmentally influenced and are differentially modulated in clinically obese and underweight populations [80]. Likewise, ghrelin levels change in eating disordered populations. It is known that those presenting with AN have increased total plasma ghrelin levels, while those presenting with BN display increased and/or unchanged total plasma ghrelin levels relative to healthy controls [81,82]. Certain studies suggest that obese BED patients have lower plasma ghrelin levels [77], whereas other studies suggest that ghrelin levels in obese BED patients are unremarkable relative to controls [78]. Furthermore, recent clinical work from Landgren *et al.* suggests a genetic basis between ghrelin and ghrelin receptor (GHSR-1a) gene variation, body mass, and alcohol use [79]. Ghrelin is also heavily implicated in alcohol use disorder [83–85]. It is interesting to note that a positive relationship between ghrelin and alcohol drinking has been suggested and ghrelin levels are elevated in the abstinent alcoholics [83–85]. However, we found elevated plasma ghrelin levels in a group of rats displaying reduced alcohol drinking behavior following binge-like HFD exposure [49]. A recent study argued that the activity of central ghrelin receptor (GHSR) could be an important regulator of alcohol intake, instead of peripheral ghrelin levels [83]. However, we did not detect alterations in the GHSR expression in the ventral striatum in the rats receiving binge-like exposure of HFD [54]. In short, the data on ghrelin secretion under hedonic eating conditions are conflicting.

It is well known that the ingestion of food stimulates the secretion of neuroendocrine factors such as glucagon-like peptide-1 (GLP-1) that target the brain to reduce the reinforcing properties of food and chemical drugs, including alcohol [25, 86–88]. Notably, GLP-1 signaling has been shown to control alcohol intake in models of elevated alcohol

consumption [89]. To understand if GLP-1 could contribute to reduced alcohol intake observed in our model, we measured circulating levels of GLP-1 in binge-exposed rats. However, plasma GLP-1 levels in HFD-3D and HFD-ED rats did not differ from chow-fed controls [49]. This observation suggests that changes in plasma GLP-1 likely do not contribute to the reduced alcohol intake observed in binge-exposed rats. However, GLP-1 is also produced in the hindbrain neurons that project to mesolimbic structures to regulate food and drug intake [87]. We did not evaluate changes in central GLP-1 activity in this model, thus cannot entirely rule out its potential role in reducing alcohol intake following binge HFD exposure.

To summarize, reduced alcohol intake in binge-exposed rats could derive from multiple mechanisms, including physiological and neurobiological processes linked to control both food and alcohol intake. A recent study found no differences in the plasma feeding peptides in rats displaying reduced alcohol drinking phenotype following a binge/compensate HFD feeding [55]. In addition, gene expression of several neurotransmitter receptors was significantly altered in the striatum and VTA of rats displaying binge/compensate HFD feeding compared to the chow controls, whereas no such changes were observed in the amygdala and hypothalamus [55]. These data collectively argue against the involvement of peripheral systems and point towards central mechanisms, particularly brain reward regions, in mediating reduced alcohol drinking following binge-like HFD intake. Ongoing studies in our laboratory are aimed at determining the significance of these central alterations in reduced alcohol intake following binge HFD exposure. These possibilities have yet to be studied in hedonic ED/AUD populations, but future work in this realm may inform the basis for the neurobiological regulation of comorbid hedonic EDs and AUD.

5. FUTURE DIRECTIONS

As we begin to understand the relationship between hedonic eating and alcohol drinking, it is becoming clear that several complex variables could modify this relationship and account for observed variabilities in the outcomes of clinical and pre-clinical studies in this regard. Nevertheless, a majority of studies suggest a negative relationship between hedonic eating behavior and alcohol intake. However, several questions remain unaddressed. For example, we observed a reduction in alcohol drinking behavior following binge-like HFD intake. It is unknown how binge-like intake of a diet high in sugar or both fat and sugar would impact alcohol drinking. It would also be interesting to know how binge-like eating behavior impact alcohol drinking in alcohol-preferring and non-preferring rats. Since the length and exposure conditions of high-calorie food can produce fundamentally different behavioral states [52,53,61], future studies assessing the effects of the long-term binge-like intake of palatable diets on alcohol drinking are also needed.

Alcohol provides more calories than carbohydrates and proteins per gm, and some individuals may engage in inappropriate compensatory activities or limit food intake to avoid body weight gain as a result of alcoholic caloric overload – a term referred to as “Drunkorexia” [90,91]. This bi-directional relationship between restricted eating and alcohol drinking could increase the risk of eating and substance use disorder-related pathology later in life, reviewed elsewhere [92]. Furthermore, nutrient intake and absorption are negatively

hampered by problematic alcohol use, which could manifest as poor nutritional status and lower body weight in patients with AUD [93–95]. Since neuroendocrine peptides that regulate energy metabolism can also influence emotional states and reinforcing properties of alcohol [23], a compromised nutritional status may further exacerbate various behavioral impairments observed in alcoholics and could substantially contribute to this chronic relapsing disorder [94, 96]. Importantly, increased intake of highly palatable food has been documented in human alcoholics during recovery [36, 37], suggesting that palatable food consumption might be protective during the early stages of alcohol detoxification process to maintain sobriety. On a similar note, the propensity to consume highly palatable food could compete with the propensity of alcohol drinking, as shown in a large sample of adolescent girls further supports this idea [97]. In addition to the poor nutritional status, impaired physiological and emotional states observed in the alcoholic patients could contribute to AUD and adversely affect treatment outcomes. In this regard, alcohol dependence-induced negative emotional states have been shown to contribute to excessive alcohol drinking [98,99]. Sufficient intake of palatable food has been shown to reduce anxiety and ameliorate the negative emotional states [100, 101]. Pertinent to this, our studies also show anxiolytic effects following intermittent HFD exposure in rodents in which the same treatment reduces alcohol drinking behavior [49, 54]. This raises the possibility that improving nutritional status during abstinence could not only correct nutritional deficiencies as a result of prolonged alcohol drinking but also could ameliorate some of the adverse symptoms observed in alcohol withdrawal, thereby enhancing prospects of recovery. Interestingly, a very recent study reported suppression of alcohol withdrawal syndrome following a high fat/ketogenic diet intake [102], which warrants future studies to address these possibilities.

CONCLUSION

While epidemiological studies have found a strong relationship between alcohol drinking behavior and eating disorders with a binge-eating component, the precise nature of this relationship remains unclear. Mixed results have been obtained in studies assessing macronutrient specific effects of hedonic eating of palatable diets on alcohol drinking and future well-controlled studies are needed to address these discrepancies. Nevertheless, hedonic eating of hyper-palatable food could compete for the tendency to drink alcohol and thereby reducing alcohol drinking, which has important clinical implications in the management of AUD.

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