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Behavioral, Neurobiological, and Neurochemical Mechanisms of Ethanol Self-Administration: A Translational Review

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Abstract

Alcohol use disorder has multiple characteristics including excessive ethanol consumption, impaired control over drinking behaviors, craving and withdrawal symptoms, compulsive seeking behaviors, and is considered a chronic condition. Relapse is common. Determining the neurobiological targets of ethanol and the adaptations induced by chronic ethanol exposure is critical to understanding the clinical manifestation of alcohol use disorders, the mechanisms underlying the various features of the disorder, and for informing medication development. In the present review, we discuss ethanol's interactions with a variety of neurotransmitter systems, summarizing findings from preclinical and translational studies to highlight recent progress in the field. We then describe animal models of ethanol self-administration, emphasizing the value, limitations, and validity of commonly used models. Lastly, we summarize the behavioral changes induced by chronic ethanol self-administration, with an emphasis on cue-elicited behavior, the role of ethanol-related memories, and the emergence of habitual ethanol seeking behavior.

Keywords: neuroimmune, adrenergic, opioid, habitual behavior, neuropeptide, microdialysis

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Abbreviations: AUD, alcohol use disorder; AVP, vasopressin; BEC, blood ethanol concentration; BLA, basolateral complex of the amygdala; BNST, bed nucleus of the stria terminalis; CRF, corticotropin releasing factor; DOR, delta opioid receptor; GABA, gamma-aminobutyric acid; i.p., intraperitoneal; KOR, kappa opioid receptor; LC, locus coeruleus; MCP-1, monocyte chemoattractant protein 1; MOR, mu opioid receptor; NPY, neuropeptide Y; pVTA, posterior ventral tegmental area; VTA, ventral tegmental area

1. Introduction

Ethanol is a simple two carbon molecule with a single hydroxyl group bound to one of the carbons, but this simple molecule has tremendous significance for society, medicine, and pharmacology. There is a long history of the consumption of ethanol containing beverages by humans as an agent to produce intoxication (Curry, 2017). The scientific study of ethanol and its effects on the human body has been largely driven by attempts to understand the pharmacological and toxicological effects of acute and chronic ethanol exposure. Ethanol consumption provides numerous desired effects on human consciousness and social interactions due to its intoxicating nature.

The medical and social problems that are caused by the prolonged excessive consumption of ethanol in humans, known collectively as alcohol use disorders (AUD), spans a spectrum of severity that can include impaired decision making, interpersonal problems, and serious physical consequences as ethanol can have toxic effects on the liver (Rehm et al., 2010), heart (Urbano-Marquez et al., 1989), and brain (NIAAA, 2001), among numerous organ systems.

A common thread for AUD is the loss of control over consumption of ethanol that eventually leads to gross intoxication of the individual and prominent behavioral problems. Since the brain ultimately controls complex behavior including self-administration of ethanol, the study of how ethanol alters brain function is critical to understanding the mechanisms of ethanol-induced behaviors. While animal models hold tremendous value for identifying these mechanisms, ultimately, the goal of such studies is to provide new knowledge that may be harnessed to reduce or reverse the harm caused by AUD. Currently, there are only three available pharmacotherapeutic agents approved by the Food and Drug Administration of the United States for

treatment of AUD (Akbar et al., 2018), and as these medications have modest efficacy, there is a critical need for new knowledge of neurobiological mechanisms of ethanol.

The present review covers the neurobiological and neurochemical substrates implicated in ethanol self-administration, summarizing findings from preclinical and translational studies to highlight recent progress in the field. We first describe animal models of ethanol self-administration, emphasizing the value, limitations, and validity of commonly used models. Next, we summarize the behavioral changes induced by chronic ethanol self-administration, with an emphasis on cue-elicited behavior, the role of ethanol-related memories, and the emergence of habitual ethanol seeking behavior. Lastly, we discuss ethanol's interactions with specific neurochemical systems and the proposed functional implications.

2. Animal models of ethanol self-administration

2.1. Two-bottle choice models of ethanol drinking initiation

Rodents can be forced to initiate ethanol drinking by depriving them of other fluids (Veale and Myers, 1969; Wise, 1973). However, the most valid non-human models of alcohol drinking initiation process are those that incorporate a free choice between ethanol containing fluids and fluids containing substances other than ethanol. The amount of alcohol consumed by rodents in free-choice (homecage) paradigms is a function of several factors such as the concentration of alcohol in the bottle (e.g., Veale and Myers, 1969), how many bottles are presented (e.g., Palm et al., 2011), for how long alcohol is available and when (Wayner et al., 1972; Wise, 1973), whether the alcohol is sweetened (Cox and Mertz, 1985; Samson and Falk, 1974), and what other fluids are available (Colombo et al., 1997; Cox and Mertz, 1985; Loi et al., 2010; Samson and Falk, 1974). Sensitivity to these factors is also a function of rodent species, strain, and sex as well as suppliers or housing conditions (Belknap et al., 1993;

Linseman, 1987; Melchior and Myers, 1976; Morales et al., 2015; Palm et al., 2011; Simms et al., 2008; Sparks et al., 2014; Wise, 1973; Yoneyama et al., 2008). The number of rodents that initiate and maintain alcohol drinking in these models may also be a function of the same factors. However, the latter is difficult to know because, as Carnicella et al. (2014) noted in a review of findings from the most popular variant of these models, researchers do not routinely report the number of rodents that they acquired vs used for their studies.

One of the mechanisms that may promote and/or maintain ethanol drinking in rodents during the initiation phase is habituation to the aversive taste of ethanol or conditioning of taste preference. Ethanol-naïve rodents initially respond to the taste of unsweetened ethanol solutions with orofacial gestures indicative of disgust (Kiefer et al., 1994; Kiefer et al., 1990; Kiefer and Dopp, 1989). These negative responses (“dislike”) decrease following repeated opportunities to consume ethanol while orofacial responses that indicate “liking” remain unchanged or increase in frequency. Both “like” and “dislike” reactions revert back to initial levels after sufficient time after cessation of access (Kiefer et al., 1994; Kiefer and Dopp, 1989). Indirect measures of preference such as relative fluid consumption (e.g., ratio of consumption from the ethanol bottle versus total fluid consumption) tend to be initially low and increase over time (e.g., Simms et al., 2008). Under typical conditions, most unselected rat strains fail to show a reliable preference for ethanol over alternative fluids. In contrast, several mouse strains (e.g., C57BL/6J) will show a reliable preference for 6-10% ethanol (v/v) over plain tap water (Yoneyama et al., 2008) consuming 60% or more of their total daily fluid from the ethanol bottle.

Support for the idea that homecage drinking paradigms allow for reinforcement of ethanol seeking and drinking by ethanol’s neuropharmacological properties comes from two lines of evidence. First, these paradigms allow voluntary exposure to a wide range

of blood alcohol concentrations (e.g., see Table 1 in Carnicella et al., 2014), with intermittent access protocols [i.e. alternating periods of free access to 2-bottle choice (water and ethanol) with periods during which ethanol is not available (for examples see Carnicella et al 2014; Holgate et al 2017)] generally yielding higher levels of ethanol intake than continuous access protocols (Carnicella et al, 2014). Second, the neurobiological correlates of ethanol seeking and drinking identified from analysis of rodent brains trained on the homecage paradigms overlap with the correlates identified in other paradigms (e.g., operant oral self-administration, Pavlovian conditioning). Specifically, the mesocorticolimbic systems are similarly involved in ethanol drinking across paradigms. For example, dopamine release can be observed in the ventral striatum of rats drinking ethanol in the homecage two-bottle paradigm (Ericson et al., 1998) just like it can be observed in the operant oral self-administration paradigm (see **Section 4.1**; Bassareo et al., 2017; Boyon et al., 2003, 2005; Howard et al., 2009; Robinson et al., 2009). Other neuromodulatory signals in the corticostriatal systems such as brain-derived neurotrophic factor are also similarly engaged by ethanol consumption in both paradigms (Jeanblanc et al., 2009, 2013; Logrip et al., 2009).

2.2. Operant self-administration in adult animals

2.2.1 Reinforcement schedules

Operant ethanol self-administration models, in which access to ethanol is contingent upon completion of a specific response or responses (i.e. lever pressing, nose-poking) (Skinner, 1938), are central to studying the behavioral pharmacology of ethanol. Preclinical operant models provide an opportunity to measure and experimentally manipulate the reinforcing effects of ethanol (or other drugs), as well as model human drug seeking.

Within an operant paradigm, appetitive/seeking and consummatory behaviors can be examined separately. The schedule of reinforcement determines the amount of work necessary to access alcohol, and different reinforcement schedules can produce different behavioral steady states (for complete review, see Panlilio and Goldberg, 2007; Cunningham et al., 2000; Leslie, 2003). The most commonly used schedules are fixed ratio, fixed interval, variable ratio, and variable interval. Ratio schedules are those in which a specified number of responses are required for access to the reinforcer and interval schedules are those in which a specified amount of time must pass before the response grants access to the reinforcer. Under fixed schedules, the response requirement remains constant throughout the operant session, while under variable schedules, the response requirement fluctuates within the operant session. Another schedule of reinforcement is the progressive ratio, in which the response requirement steadily increases for each subsequent reinforcer. The highest completed response requirement is termed the “break point” and represents the motivational salience or reinforcement efficacy of the drug (Czachowski and Samson, 1999). These fundamental schedules are frequently used to explore the neurobiological substrates and circuits involved in ethanol self-administration and in medications development for the treatment of AUD (Cunningham et al., 2000; June and Gilpin, 2010; Leslie, 2003; Panlilio and Goldberg, 2007; Samson and Czachowski, 2003).

A challenge encountered with the aforementioned reinforcement schedules is that ethanol seeking is conflated with ethanol consumption, and the rate of responding may be influenced by intoxication. Further, when operant paradigms are used in conjunction with neurochemical assays, such as *in vivo* voltammetry or microdialysis, it becomes impossible to distinguish the role of brain signaling molecules (i.e. neurotransmitters such as dopamine) in appetitive versus consummatory behaviors. To address this issue, Samson et al. (1998) established an appetitive-consummatory model in which a

single completion of the response requirement provides ad libitum access to ethanol for a finite time period (usually 20-30 minutes). Using this model concurrently with in vivo microdialysis to quantify extracellular dopamine and ethanol concentrations facilitated the discovery that a transient, but robust accumbal dopamine response occurs at the beginning of the oral consumption period, when brain concentrations of ethanol are very low (Carrillo and Gonzales, 2011; Doyon et al., 2003; Doyon et al., 2005). Interestingly, this response declines to baseline as brain ethanol concentrations increase, suggesting that, in experienced animals, the dopamine signal may not be due to ethanol's pharmacological actions, but instead may be an anticipatory response to the sensory cues associated with ethanol (Vena and Gonzales, 2015; Gonzales et al., 2004).

In sum, operant ethanol self-administration paradigms are excellent tools for examining and manipulating the behavioral pharmacology of alcohol in animal models. Decades of research employing operant paradigms have provided valuable insights regarding the neurobiological mechanisms of alcohol seeking behavior and reinforcement.

2.2.2 Routes of administration

A unique opportunity afforded by the use of animal models is the variety of options for the route by which ethanol is administered. Oral ethanol consumption provides the greatest face validity for human ethanol use, but rodents show an innate taste avoidance for ethanol and thus, researchers typically must incorporate strategies [i.e. food and/or fluid deprivation, adding sweeteners to the drinking solution, several weeks of acquisition of ethanol drinking in the home cage (see Section 2.1) etc.] for initiating the consumption of ethanol doses that provide pharmacological stimulation sufficient for reinforcement (Cunningham et al., 2000; Samson et al., 1988). Other commonly used routes of ethanol self-administration are intracranial microinjections, in which ethanol is

locally infused into the brain, and intravenous infusions whereby ethanol is delivered directly to the bloodstream, bypassing liver metabolism and rapidly reaching the brain.

The route of ethanol administration is typically determined by the research question. For example, oral self-administration is a valid experimental model of human use, but interpretations of ethanol's pharmacological actions may be confounded by individual variation in consumption (i.e. lick rates or quantity consumed), ethanol pharmacokinetics, and sensitivity to ethanol's nonpharmacological effects, such as taste, odor, and caloric value (Cunningham et al., 2000; Le and Kalant, 2017; Windisch et al., 2014). Therefore, researchers interested in examining ethanol's specific pharmacological mechanisms of action during operant self-administration may use intravenous or intracranial route of administration; both permit delivery of precise and standardized doses of ethanol while eliminating the influence of its orosensory effects (Gass and Olive, 2007; McBride et al., 1999; Windisch et al., 2014). While intravenous administration provides systemic delivery of controlled ethanol doses, intracranial microinjections facilitate the localization of specific regions and circuits mediating ethanol's reinforcing effects. Indeed, studies have shown that mice, rats, and non-human primates will maintain intravenous or intracranial self-administration (Grahame and Cunningham, 2002; Le and Kalant, 2017; Rodd et al., 2004; Windisch et al., 2014).

2.2.3 Operant models of compulsive ethanol seeking and relapse

AUD in humans is characterized by its chronic and relapsing nature and the continued use of ethanol despite adverse consequences. These clinical features of AUD have been modeled in animals with a history of operant ethanol self-administration.

Using a reinstatement model, animals show relapse-like behavior by resuming ethanol seeking behavior in the presence of ethanol associated stimuli after extinction (Le and

Shaham, 2002). To extinguish responding in trained animals, contextual cues remain in the operant chambers, but responses no longer provide access to the ethanol solution. Several studies have demonstrated that operant ethanol seeking behavior may be reinstated by discrete or contextual ethanol-associated cues (i.e. taste and smell of ethanol or conditioned olfactory, auditory, visual, or tactile stimuli) and by stress (i.e. intermittent footshock) (Chaudhri et al., 2008; Lê and Shaham, 2002; Lê et al., 1998). While administration of low doses of ethanol have been shown to reinstate seeking behavior, the effects in rodents are modest (Gass and Olive, 2007; Lê and Shaham, 2002; Lê et al., 1998), and there is a valid argument that non-contingent ethanol priming in animals does not parallel human lapses to ethanol use (Epstein et al., 2006).

Limited evidence suggests that after a prolonged period of ethanol self-administration or passive induction of ethanol dependence (O'Dell et al., 2004), rodents display compulsive ethanol seeking and use behaviors that may be accompanied by an escalation of ethanol self-administration. Although this remains a nascent area of research, recent studies have employed operant-based assessments of compulsive ethanol-seeking behaviors. For example, in a progressive ratio assay, rats with 3-4 months of intermittent ethanol access continue to seek ethanol despite taste adulteration with quinine. In contrast, rats with a shorter history of ethanol experience and those consuming sucrose in the operant chamber reduce seeking behavior after quinine is added to the drinking solution (Hopf et al., 2010). Similarly, rats show continued alcohol-seeking despite footshock punishments, though rats may vary in their sensitivity to punishment (Marchant et al., 2018). Collectively, this emerging body of literature indicates that operant-based assays may be effective in examining compulsive alcohol behaviors in animal models.

2.3. Self-administration of ethanol in adolescent animals

2.3.1 Ethanol self-administration in adolescent animal models compared to adults

Most animal models of alcohol use indicate that adolescents consume more ethanol per drinking session than adults, similar to human epidemiological data (Bell et al. 2011; Broadwater et al. 2011; Doremus et al. 2005; García-Burgos et al. 2009; Vetter et al. 2007). However, other studies have shown no differences or less intake in adolescents compared to adults (Doherty and Gonzales, 2015; Labots et al. 2018; Schindler et al. 2014; Schramm-Sapota et al. 2010; Siegmund et al. 2005). A detailed review of adolescent drinking models is outside of the scope of this review, however methodological differences such as stress, housing conditions, age, and ethanol administration route or self-administration model all likely contribute to inconsistent results within the literature. Nonoperant self-administration paradigms are utilized in the majority of adolescent work, in part due to the limited timeframe (approximately 20 days in male rats) to facilitate operant training and overcome initial aversive properties of ethanol. As operant self-administration models have high predictive validity (Carter and Griffiths, 2009), more research utilizing operant models in adolescent rats would extend our knowledge on adolescent drinking behaviors and clinical utility of potential treatments in this population.

2.3.2 Modeling treatment in adolescents

The prevalence of adolescents diagnosed with AUD is rising, however only a small proportion receive treatment in part due to lack of data on the effectiveness of available medications in this age group (Miranda and Treloar, 2016; Swendsen et al., 2012). Due to ethical limitations and multiple factors that can significantly impact treatment outcomes in younger individuals (e.g. childhood trauma, age of drinking onset), bridging preclinical models with clinical findings is particularly critical during adolescence. An example from recent clinical work demonstrated that the nonselective opioid receptor antagonist naltrexone reduced heavy drinking and blunted craving in adolescents (ages

15-19) and young adults (ages 18-25), although larger trials are needed to replicate these results (Miranda et al., 2014; O'Malley et al., 2015). It is well established within the animal literature that naltrexone significantly decreases operant ethanol self-administration in adult rats (Ciccocioppo et al., 2003; Gonzales and Weiss, 1998; Hay et al., 2013; Henderson-Redmond and Czachowski, 2014). However, to our knowledge only one previous study had investigated naltrexone efficacy during adolescent ethanol self-administration, using alcohol-preferring (P) rats and a two-bottle choice paradigm (Sable et al., 2006). Recent findings from our lab expanded these results to show naltrexone significantly reduced sweetened ethanol, but not sucrose, operant self-administration during a progressive ratio schedule in adolescents at similar levels to adult rats (**Figure 1**; from dissertation by Zandy C., 2016). There is some evidence suggesting opioid receptor signaling is present in adolescents like that in adults (Ellgren et al., 2008; Palm and Nylander, 2014). However, endogenous opioids have been found to differ between animal strain, housing, and ethanol exposure. Recently, forced ethanol exposure in adolescence was shown to produce residual changes in endogenous opioid peptides in brain areas associated with anxiety and stress (Granholm et al., 2018). Taken together, these results highlight one example investigating treatment effectiveness across animal and clinical models during adolescence. However, more studies are needed to determine if the proposed mechanism of action of naltrexone for reducing ethanol self-administration differs in adolescent rats compared with adults.

***** Figure 1 here *****

2.3.3 Neurochemical development in adolescents

Adolescence is a period of significant development of the central nervous system including synaptic pruning, structural maturation, and changes in neurotransmitter systems, which are proposed to contribute to some of the behavioral characteristics (e.g. risk taking, reward seeking) evident during this age range (reviewed in Crews et

al., 2016; Fuhrmann et al., 2015; Spear, 2018). Due to its role in processing reinforcing stimuli, the dopaminergic system has been extensively studied in adolescence in order to determine if neurochemical differences impact drinking behaviors during this developmental period. Age-dependent differences in firing rates of dopamine neurons (McCutcheon et al., 2012; Marinelli and McCutcheon, 2014) and basal extracellular dopamine concentrations (Badanich et al., 2006; Philpot et al., 2009) in the mesolimbic system appear to peak in mid to late adolescence, earlier than within the prefrontal cortex (Burke and Miczek, 2014). Binge-like ethanol exposure in adolescence has been shown to produce alterations in dopamine dynamics in adulthood within areas such as nucleus accumbens (Shnitko et al., 2016, Zandy et al., 2015) and prefrontal cortex (Trantham-Davidson et al., 2017).

Additionally, many studies examining the development of neurotransmitter systems across adolescence have focused primarily on male animals, limiting generalizability across sexes particularly with pubertal changes occurring during adolescence. Recently, Kopec et al. (2018) described sex-specific differences in microglia regulation of dopaminergic development in the nucleus accumbens. These results highlight the need for additional research to understand if distinct mechanisms underlying neurochemical development between males and females during adolescence could contribute to alterations in ethanol behaviors. Overall, multiple neurochemical differences found between adolescents and adults are hypothesized to contribute to the suggested model that adolescents may exhibit increased reward sensitivity and attenuated aversion to ethanol (Doremus-Fitzwater and Spear, 2016).

2.4 Limitations of existing animal self-administration paradigms

Central to the ecological validity of animal models of ethanol self-administration is the consumption of sufficient quantities of ethanol to produce reinforcement. Orally ingested

ethanol undergoes first pass metabolism before entering systemic circulation and reaching neurobiological targets. In the absence of blood ethanol concentration (BEC) measurements, it is impossible to know whether any ingested ethanol has entered systemic circulation. Thus, the best evidence for an animal's exposure to ethanol's primary reinforcing properties is a non-zero blood (or brain) ethanol concentration (BEC). Yet, many studies fail to obtain BEC measurements in the animal at any point during its conditioning. Studies in our laboratory (Cofresí et al., 2018, 2019) and others (Tomie et al., 2004, 2006b, 2007; LeCocq et al., 2018; Fiorenza et al., 2018) provide direct evidence for the role of ethanol's primary reinforcing properties in the acquisition of cue-elicited ethanol-related behavior by animals (see Section 3.1.1). Typically, BEC at the end of conditioning sessions in these studies is low (0.020-0.060 g/dL), but can be high (0.060-0.100 g/dL) under certain circumstances (e.g., Tomie et al., 2004, 2006b, 2007). In many two-bottle choice home cage paradigms, often only 50% or fewer of the rats will achieve binge levels of intoxication (BECs of 80 mg% or higher) (Carnicella et al., 2014). While it may not always be feasible to assess brain or blood ethanol concentrations either during or immediately subsequent to self-administration sessions, it is necessary to consider this parameter when interpreting findings, comparing across self-administration protocols, and developing animal models of ethanol self-administration.

Another critical issue for the interpretation of many, if not most, animal models is that the source of reinforcement remains unclear. Like the primary pharmacological agents (e.g., cocaine, heroin, nicotine) abused by humans, ethanol has central and peripheral effects on physiology; however, an important distinction is that ethanol is a source of calories. Thus, ethanol reinforcement may be attributed to its pharmacological and/or nutrient properties. Further complicating the issue, many rodent studies motivate ethanol ingestion by using fluid or food deprivation and/or naturalistic drinking solutions

such as commercially available alcoholic beverages or artificially or naturally sweetened ethanol solutions prepared in the laboratory. Even in non-deprived animals, comparisons between conditioning to ethanol and isocaloric liquids remain necessary to dissociate between the two primary sources of ethanol reinforcement.

Numerous challenges exist in developing animal models of the progression from low to moderate to excessive alcohol intake, and it is infeasible for such models to mimic all of the clinical features of alcohol use and AUD. Nevertheless, existing models of self-administration, including home cage access, operant paradigms, and protocols using adolescent rodents, permit investigation of the mechanisms underlying key aspects of alcohol seeking and consumption and evaluation of the therapeutic efficacy of both pharmacological and non-pharmacological approaches for addressing pathological alcohol use behaviors in human.

3. Alterations in behavioral control following chronic ethanol self-administration

3.1. Pavlovian conditioning to ethanol

3.1.1 Cue-elicited appetitive responses in rodents

Following repeated alcohol self-administration, sensory stimuli associated with alcohol availability and intoxication can become conditioned cues that elicit appetitive, and subsequently, consummatory behaviors. The motivational properties of ethanol-related cues can be studied using Pavlovian conditioning paradigms in both rodents and humans. Rodent models provide an opportunity to dissect the neurobiological and behavioral mechanisms of ethanol cue-elicited reactivity and the extent to which it contributes to AUD development with greater experimental control over the quantity and frequency of ethanol exposure over the lifetime. Animal models of the progression to alcohol dependence have consistently demonstrated the role of Pavlovian alcohol cues in eliciting appetitive behaviors for alcohol, which can manifest as attentional bias,

approach tendency, and seeking behaviors (Srey et al, 2015; Maddux and Chaudhri, 2017; Cofresi et al, 2018). However, the attribution of incentive salience and the extent to which ethanol cues elicit appetitive responses in rodents is highly dependent on the behavioral paradigm and its parameters.

In non-human animals, oral ethanol self-administration paradigms provide the greatest face-validity for human alcohol-related behavior. In an operant context, cue-elicited behavior directed toward specific stimuli in the self-administration chamber, including the magazine (the ethanol container; e.g., fluid cup, sipper tube) or lever (or other similar seeking response mechanism), serve as useful models of human ethanol seeking behaviors (e.g. approaching the beer aisle of a grocery store). Within an operant self-administration session, relatively small manipulations of alcohol delivery and availability can substantially impact approach behavior. In paradigms where fixed amounts of drinking solution are delivered into an omnipresent magazine, several factors interact to influence whether the cue acquires the ability to elicit approach behavior towards the cue itself, the magazine, or both, including the temporal relationship between cue and solution delivery, presence or absence of sweetener, food/fluid deprivation states, and the number of training sessions (Chaudhri et al., 2010; Krank, 2003; Krank et al., 2008; Srey et al., 2015; Villaruel and Chaudhri, 2016). In paradigms where time-limited opportunities to consume the reinforcer are presented via a retractable magazine (sipper) (Tomie et al., 2003; Tomie et al., 2006a; Tomie et al., 2011), the temporal relationship between cue and drinking opportunity may be the most important, if not sole, determinant of whether the cue acquires the ability to elicit approach behavior towards the cue itself, the magazine, or both. If the drinking opportunity starts at cue offset, then approach behavior tends to be directed towards the cue because it does not interfere with subsequent drinking. If the cue and drinking opportunity co-occur, then the cue tends to elicit anticipatory magazine-directed

behavior because it facilitates drinking (Cofresí et al., 2018; 2019). Importantly, across the paradigms mentioned above, little to no cue-related behavior has been observed in studies using an explicitly unpaired cue-ethanol condition, indicating that cue-related behavior in these paradigms typically results from associative learning processes.

The use of Pavlovian conditioning paradigms in rodents has enabled investigation of behavioral and non-pharmacological interventions for AUD. For example, precise manipulation of memories for alcohol-related cues may help reduce reactivity to such stimuli (Hon et al., 2016). Retrieval and expression of consolidated long-term memory can, under certain conditions, destabilize the reactivated memory such that it must be reconsolidated. During the reconsolidation window, the reactivated and destabilized memory is vulnerable to interference (for review, see Lee et al., 2017). The vulnerability of maladaptive emotional memories during the reconsolidation window has been exploited to enhance the efficacy of interventions like cue extinctions in animal models, pre-clinical human laboratory models, and small clinical trials (Das et al., 2015a; for reviews, see Walsh et al., 2018; Fredlow et al., 2016; Lonergan et al., 2013). On the basis of its promise and the potential for rapid translation, our laboratory recently tested, in rodents, whether this memory retrieval-dependent reconsolidation window could be harnessed to increase the efficacy of ethanol cue exposure therapy after conditioning of alcohol cue-elicited alcohol seeking and drinking behaviors (Cofresí et al., 2017). Rats with previous alcohol self-administration experience (15 sessions; mean consumption: 3.5 g/kg/24hours) underwent 12 consecutive days of cue conditioning training followed by cue extinction training for 14 consecutive days. We found that the group treated with standard extinction was highly susceptible to post-treatment return of cue-elicited alcohol seeking and drinking behaviors whereas the group receiving the same treatment during reconsolidation of the alcohol cue memory exhibited little to no return of alcohol

cue-elicited seeking and drinking behaviors (**Figure 2**). These studies suggest that cue exposure therapy might be optimized to help patients with AUD to prevent relapse.

***** Figure 2 here *****

3.1.2 Cue-elicited appetitive response in humans

In humans, sensory cues, such as the sight and smell of a preferred alcoholic beverage, and alcohol-related words and imagery can elicit approach, and consequently, consummatory behaviors. Similar to animals, typical ethanol cue-elicited behaviors in humans include attentional bias towards alcohol stimuli and approach tendency. Additionally, clinical research permits assessment of subjective alcohol craving, typically measured as self-reported urge or desire to drink, temptation to drink, or difficulty in resisting a drink if offered.

Ethanol-related pictures and words, as well as the sight and smell of a person's preferred alcoholic beverage can elicit greater attentional bias (Townshend and Duka, 2001; Field et al., 2005; Vollstadt-Klein et al., 2012; Snelleman et al., 2015; Manchery et al., 2017; Qureshi et al., 2019) and approach tendency (Field et al., 2005; Fleming and Bartholow, 2014; Hollett et al., 2017; Kreusch et al., 2017) in human drinkers than non-alcohol related stimuli. Both manifestations of cue reactivity are associated with drinking phenotypes as heavy drinkers and individuals with AUD tend to show greater reactivity towards alcohol cues as compared to occasional and non-dependent social drinkers (Field et al., 2004; Townshend and Duka, 2001; Barkby et al., 2012; Field and Cox, 2008; Fadardi and Cox, 2006; Qureshi et al., 2019). While this may be attributed to poorer cognitive performance among dependent vs non-dependent drinkers, Fadardi and Cox (2006) demonstrated that the greater attentional bias for alcohol stimuli among the former persists even after controlling for cognitive ability. However, an important caveat

is the fact that the criteria defining heavy vs light drinkers varies across studies, hindering accurate comparisons between studies. Going forward, it will be important for research within this domain to achieve greater consistency in defining clinical drinking phenotypes.

Among human drinkers, subjective alcohol craving can be elicited by the sight, smell and/or taste of alcoholic beverages (Kambouropoulos and Staiger, 2004; Kareken et al., 2010; Kiefer et al., 2015; MacKillop et al., 2015; Kreusch et al., 2017; Yoder et al., 2009; Filbey et al., 2008; Oberlin et al., 2013; Oberlin et al., 2013). While cue-elicited craving has been observed in social, heavy, and AUD drinkers, few studies have directly compared drinking phenotypes to determine whether they differ in their sensitivity to sensory stimuli. One study reported that the sight and smell of alcohol elicited similar craving responses in light and heavy drinkers, but the criteria defining these two groups were unclear (Papachristou et al., 2012). With the inclusion of craving as a symptom of AUD in the most recent edition of the DSM, it is increasingly important that craving is assessed as a function of drinking behavior.

3.1.3 Neurobiological substrates of cue-elicited appetitive responses: Findings from animal and human models

Evidence from preclinical research indicates that the basolateral complex of the amygdala (BLA), nucleus accumbens, prefrontal cortex, and the insular cortex are key neurobiological substrates in the regulation of reward seeking behaviors, including ethanol cue-elicited appetitive responses (Stuber et al., 2011; Klenowski, 2018; Chaudhri et al., 2013; Sciascia et al., 2015; Millan et al., 2015; Setlow et al., 2002). Ethanol-related stimuli have been shown to induce activity in the prefrontal cortex, nucleus accumbens, and BLA (Jupp et al., 2010; Dayas et al., 2007), and ablation of prefrontal cortical inputs into the nucleus accumbens, but not the BLA, attenuates cue-

induced reinstatement of alcohol seeking (Keistler et al, 2017). Similarly, pharmacological inactivation of the BLA or nucleus accumbens, reduces cue-induced alcohol seeking (Chaudhri et al, 2010; Chaudhri et al, 2013; Millan et al., 2015). Within the BLA and the nucleus accumbens, increased glutamatergic activity is associated with alcohol seeking behaviors (Gass et al., 2011; Sinclair et al, 2012). While the BLA provides glutamatergic input to the nucleus accumbens (Stuber et al, 2011), another source of excitatory drive into *both* the nucleus accumbens and the BLA is the insular cortex (Shi and Cassell, 1998; Reynolds and Zahm, 2005) and this circuit has been shown to regulate interoceptive cues produced by alcohol ingestion (Jaramillo et al., 2016). Initial findings also indicate that the insular cortex may be a key component of the ability of exteroceptive alcohol-predictive cues to elicit alcohol seeking behavior in non-dependent rats (Cofresí et al., 2019). The orbitofrontal cortex is another region that is highly interconnected with the BLA and nucleus accumbens, and has long been implicated in processing reward-related cues and adaptive responding (Schoenbaum and Shaham, 2008; Lasseter et al., 2011; Takahashi et al, 2009). While initial evidence supports a role for the orbitofrontal cortex in context-induced alcohol seeking behaviors (Bianchi et al., 2018), the region has been remarkably understudied in animals with regards to alcohol cue reactivity (Moorman et al., 2018). Collectively, this emerging literature implicates several limbic, cortical, and striatal regions, which are highly interconnected, in the expression of Pavlovian conditioning to ethanol cues and appetitive behaviors, with research continuing to examine the precise functional roles of specific circuits and subregions.

Achieving consensus among findings from clinical functional neuroimaging studies has been difficult due to methodological inconsistencies [i.e. use of different cue types (gustatory, visual, olfactory), lack of a control group, and varying definitions of heavy drinking behaviors or AUD severity] and small sample sizes. Nevertheless, there are

notable consistencies with the preclinical literature regarding the activation of frontal, striatal, and insular structures by ethanol-related stimuli in humans (for review, see Schacht et al., 2013). Compared to neutral cues, alcohol cues elicit activation of the ventral striatum, anterior cingulate cortex, orbitofrontal cortex, dorsolateral prefrontal cortex, and insula (Filbey et al., 2008; Bach et al., 2015; Park et al., 2007; Myrick et al., 2013; Oberlin et al., 2016; Bragulat et al., 2008; Claus et al., 2011) to a similar extent among controls, heavy drinkers, and drinkers with AUD (Schacht et al., 2013). Heavier drinking and AUD, however, may be associated with selective enhancement of cue-induced activation of parietal and temporal regions, greater connectivity between the insula and nucleus accumbens (Schacht et al., 2013; Grodin et al., 2018), and greater alcohol cue-induced activation of the dorsal striatum (Filbey et al., 2008; Vollstadt-Klein et al., 2010). Further, initial findings suggest that appetitive responses in humans (i.e. approach tendencies and subjective craving) are positively correlated with activity in the dorsal striatum, insula, ventral striatum, medial frontal cortical regions, and orbitofrontal cortex (Bach et al., 2015; Oberlin et al., 2016; Fryer et al., 2013; Weirs et al., 2014; Grodin et al., 2018).

In sum, across animal and human studies, prefrontal cortical regions, the ventral striatum (specifically the nucleus accumbens), and insula are consistently implicated in alcohol cue reactivity and appetitive responses. More broadly, these substrates, along with the basolateral amygdala, regulate the attribution of incentive salience to cue associated with rewards. Of note, however, clinical support for the basolateral amygdala in alcohol cue-elicited behaviors is generally lacking.

3.2. Emergence of “habitual” ethanol seeking behavior

3.2.1 The construct of “habitual behavior”

Behavior performed to obtain a desired outcome can be characterized as goal-directed or purposeful. After extensive repetition (Dickinson et al., 1995) or under certain schedules of reinforcement (Adams and Dickinson, 1981; Adams, 1982; Dickinson and Balleine, 1994), behavior may become less influenced by the outcome and instead, be controlled by conditioned stimuli, such as the context in which the behavior has most frequently been reinforced. Such behavior is characterized as “habitual” (Dickinson, 1985). Fundamentally, the behavior remains goal-directed and purposeful, but its expression no longer requires deliberation or sustained attention or effort; expression has simply become more automatized.

3.2.2 Ethanol seeking as a “habitual” behavior: studies in animals

In animal models, either reducing the value of the reward or manipulating the contingency between behavior performance and reward permits characterization of behavioral expression. Behaviors that persist despite these manipulations are defined as “habitual” (Dickinson, 1985; for review see Vandaele and Janak, 2018). There are two reward value manipulations common in the alcohol literature, both of which attempt to devalue alcohol in experienced animals: conditioned aversion/avoidance (e.g., Barker et al., 2010) and specific satiety (e.g., Shillinglaw et al., 2014). The conditioned aversion/avoidance paradigm pairs the reward (e.g. alcohol) with the experience of illness by injecting the animal with a noxious agent like lithium chloride. After the pairing(s), the current value of the alcohol reward is decreased as a function of its conditioned association with illness, an aversive event. Next, the animal’s expression of reward seeking behavior is tested in its usual context in a non-reinforcement condition. In the specific satiety paradigm, the current value of the alcohol reward is transiently decreased by simply allowing the animal to consume it before testing, though pre-testing consumption should be limited so that acute alcohol intoxication does not interfere with behavioral performance during testing. There are two behavior-reward

contingency manipulations common in the literature: contingency degradation (e.g., Shillinglaw et al., 2014) and reversal (e.g., Mangieri et al., 2014). In the degradation paradigm, non-contingent rewards are delivered periodically to determine the sensitivity of the animal's on-going reward seeking behavior to the relationship between performance and reward receipt. In the reversal paradigm, reward receipt is made contingent upon omission of the learned reward seeking behavior. Both forms of action-outcome contingency degradations entail multiple test sessions in the usual context.

In animals, it has been documented that ethanol seeking can become a habitual behavior after extensive training, particularly under interval reinforcement schedules (Corbit et al., 2012, 2014; Dickinson et al., 2002; López et al., 2016; Mangieri et al., 2012). In one of the first descriptions of habitual alcohol seeking behavior, Dickinson et al (2002), using a conditioned aversion paradigm, reported that in contrast to food seeking, ethanol seeking was insensitive to outcome devaluation in experienced animals. However, two critical methodological concerns limit interpretation of this findings: 1) the use of a sucrose-fading procedure for initiating alcohol self-administration and 2) the animals consumed relatively low doses of alcohol (O'Tousa and Grahame, 2014). Regarding the former, animals acquired the seeking behavior (and thus established action-outcome contingencies) with a sucrose solution as the reinforcer, and as such, habit formation was occurring before alcohol was introduced. Secondly, it is unclear, though based on the solution content it seems unlikely, whether the animals achieved intoxication and experienced any alcohol reinforcement.

More recent work has focused on models that mitigate these confounds in evaluating the time course of habitual alcohol seeking. For example, rather than using a sucrose-fading procedure, Corbit and colleagues (2012; 2014) used a two-bottle choice home cage paradigm to facilitate acquisition of alcohol consumption in which rats had free

access to an unsweetened 10% ethanol solution and water. After the 4-week acclimation period, instrumental training commenced, during which rats self-administered on average 0.5 g/kg/1-hour session. Using a within-subject design, the authors went on to demonstrate that ethanol seeking was sensitive to devaluation by specific satiety after 2 weeks of instrumental conditioning, but after 8 weeks, the behavior was no longer sensitive to outcome devaluation, suggesting that ethanol seeking had become habitual. This effect was specific to ethanol as a separate group of rats continued to show goal-directed sucrose seeking after both 2 and 8 weeks of instrumental conditioning. A limitation of this work is that blood ethanol concentrations were not measured, and so the relationship of the findings to the central pharmacological effects of ethanol are unclear. Using Wistar rats, Lopez et al (2016) also determined that alcohol seeking behavior shows variable sensitivity to outcome devaluation by lithium chloride as a function of the length of self-administration experience in the instrumental context. However, a caveat of this latter study is the lack of data regarding the ethanol doses consumed by the rats. Nevertheless, these studies suggest that habitual alcohol seeking is an observable phenomenon that emerges after prolonged training. In addition to length of training, studies in animals suggest that other factors can influence the emergence of habitual alcohol behaviors, such as reinforcement schedules (Mangieri et al., 2012; Lopez et al, 2016), the number of action-outcome associations, and stress (For reviews see O'Tousa and Grahame, 2014; Vandaele and Janak, 2018; Corbit and Janak, 2016).

3.2.3 Ethanol seeking as a “habitual” behavior: studies in humans

To our knowledge, habitual ethanol seeking has not been demonstrated yet in human laboratory ethanol self-administration paradigms, and indirect evidence from other relevant human laboratory paradigms is mixed (Gladwin & Wiers, 2012; Sjoerds et al., 2013; but see: Hogarth et al., 2019; Rose et al., 2013; Sebold et al., 2014; de Wit et al.,

2018). Using an outcome devaluation paradigm in humans, one cross-sectional study reported impaired goal directed performance in alcohol-dependent individuals compared to healthy controls (Sjoerds et al, 2013), but the primary study task required that participants memorize an assortment of symbols, and thus it is possible that effects were due to specific impairments in memory (De Houwer et al., 2018). Using a contingency reversal paradigm, Gladwin and Weirs (2012) suggested that heavier social drinkers show greater behavioral automaticity in responding to alcohol cues. However, when considering the data and participant characteristics there are several caveats to this interpretation. Participants were young adult college drinkers with relatively low alcohol use and/or alcohol-related problems (as indicated by a mean AUDIT score of 6.2) and no participant drinking behavior data is presented so the distinction of “heavier drinker” is ambiguous.

Other human laboratory paradigms have demonstrated *goal-directed* alcohol choice in social drinkers (Rose et al, 2018) or have not shown a strong tendency towards habitual behaviors in humans across various alcohol use phenotypes (Sebold et al, 2014; Hogarth et al, 2018). However, this clinical research domain remains nascent and limited by existing methods of defining and assessing habitual alcohol behaviors in humans.

3.2.4 Proposed neurobiology underlying habitual ethanol behaviors

Within the past two decades, using the aforementioned paradigms in animals, significant progress has been made in understanding the neurobiological basis of habitual behavior. Most of this work has focused on food reinforcers, and though the substrates involved in habitual ethanol seeking are likely very similar, little work has explored the mechanisms by which ethanol interacts with habit circuitry (for additional review, see Corbit and Janak, 2016; Barker and Taylor, 2014). A growing consensus,

based on an abundance of preclinical evidence, is that habitual behavior is associated with a shift from ventral to dorsal striatal control over behavior. As mentioned above, the ventral striatum, specifically the nucleus accumbens, plays a significant role in establishing Pavlovian-conditioned responses to alcohol, viz., associations between specific cues or contexts and alcohol. With repeated exposures to ethanol reinforcement, there is gradual recruitment of the dorsal striatum, which can be functionally and anatomically divided into the dorsomedial striatum (caudate in primates) and dorsolateral striatum (putamen in primates) (Everitt and Robbins, 2005; Everitt et al., 2008). In rats trained to lever-press to obtain ethanol, pharmacological inactivation of the dorsomedial striatum prevented the expression of goal-directed alcohol seeking, while inactivation of the dorsolateral striatum had no effect on behavior (Corbit et al., 2012). With prolonged training, alcohol seeking became inflexible, and this was blocked by inactivation of the dorsolateral striatum, indicating that as the nature of ethanol seeking behavior transitioned from goal-directed to habitual, the neuroanatomical control over behavior shifted from the dorsomedial to dorsolateral striatum. These observations are consistent with those observed with natural reinforcers (Yin et al., 2005, 2006) and cocaine (Everitt et al., 2008).

The precise mechanisms by which striatal control over behavior shifts from ventral to dorsal are unclear but are likely regulated by inputs from cortical regions and midbrain dopamine circuits (Barker et al., 2015). Indeed, corticostriatal circuits were shown to be altered by chronic ethanol exposure and this was associated with the expression of habitual behavior (Renteria et al., 2018). Dopamine may be a key mediator in the progression to habitual alcohol seeking and consumption due to the ascending serial interconnectivity of the mesolimbic and nigrostriatal dopamine systems (Haber et al., 2000; Yin et al., 2008; Ikeda et al., 2013). Midbrain dopamine systems are important for the acquisition and performance of goal-directed and habitual behaviors (Faure et al.,

2005; Robinson et al., 2007; Murray et al., 2012; Willuhn et al., 2012) and for ethanol reinforcement, but additional research is necessary to determine the mechanisms by which chronic alcohol facilitates the hierarchical recruitment of midbrain dopamine neurons and how this contributes to the development of habitual alcohol seeking.

4. Neurobiological and neurochemical mechanisms of ethanol self-administration: emphasis on recent findings

As indicated above, many neurotransmitter systems have been studied with regard to potential involvement in the mechanisms of action of ethanol and ethanol self-administration. In this section, we review the neurobiological substrates and the neurochemical systems implicated in ethanol seeking and consumption, with a focus on recent updates and translational relevance.

4.1 Brief overview of the role of dopamine in ethanol self-administration

The common action of numerous drugs of abuse including ethanol to increase the concentration of dopamine in the mesolimbic system has been known since the late 1980s (Imperato and Di Chiara, 1986). The convergence of these findings with the proposed role of mesolimbic dopamine in the neurobiological mechanism of motivated behavior in general provided a strong impetus in the field for detailed studies of ethanol and dopamine (reviewed by Gonzales et al., 2004; Siciliano et al., 2018). The most parsimonious explanation is that in well-trained animals that voluntarily consume ethanol the accumbal dopamine response represents a reward prediction signal as suggested by the work of Schultz et al. (1997).

This proposed role of dopamine in the early stages of the development of the reinforcing effects of ethanol self-administration (Weiss et al., 1993) has stood up with subsequent studies. For example, on the first day that a rat has access to an ethanol solution the

rat will consume a low dose, but on the second day the consumption of ethanol doubles (Carrillo et al., 2008). Likewise, the dopamine response in the nucleus accumbens that occurs upon initial licking of the spout where ethanol is being delivered in well-trained rats is not present on the first day of access to ethanol (Carrillo et al., 2011). Additional studies confirmed that dopamine release in the nucleus accumbens is an important response in rats trained to consume ethanol (Shnitko and Robinson, 2015; Bassareo et al., 2017). However, it is now clear that the dopamine response associated with ethanol consumption does not only occur in the nucleus accumbens, but evidence suggests that it also occurs in the dorsolateral striatum (Shnitko and Robinson, 2015) as well as in the medial prefrontal cortex (Doherty et al., 2016). Overall, the data obtained over several decades of research has converged on the idea that mesolimbic dopamine is an important mediator of ethanol self-administration.

4.1.1 Future directions

Interesting data is emerging from preclinical studies that indicates substantial heterogeneity exists among midbrain dopamine neurons, as projection-specific molecular, functional, and anatomical differences have recently been identified (Lammel et al., 2008; Marinelli & McCutcheon, 2014; Ford et al., 2006). Future work must consider this heterogeneity when examining dopaminergic circuits in reward-related behaviors (Juarez & Han, 2016). With the advent of newer techniques to dissect out microcircuit involvement in reinforced behavior, including alcohol reinforcement (Witten et al., 2011; Bass et al., 2013; Juarez et al., 2017), this general idea is likely to evolve as more details about the control and regulation of the mesolimbic system emerges.

Additionally, while studies in humans suggest that chronic alcohol use dysregulates the dopaminergic system (Volkow et al., 2017), this has largely been unconfirmed in animal models. Compared with controls, human alcoholics show reduced striatal dopamine

signaling – positron emission topography (PET) imaging studies have linked AUD with reductions in striatal D2/D3-receptor and dopamine transporter availability (Volkow et al., 1996, 2007, 2017; but see Hirth et al., 2016 and Hansson et al., 2019). Human alcoholics (versus controls) also show reductions in methylphenidate- and amphetamine-induced dopamine release in the ventral striatum (Volkow et al., 2007; Martinez et al., 2005), despite showing a significant alcohol-induced dopamine response in the right ventral striatum (Yoder et al., 2016). As mentioned above, achieving ethanol dependence in animals via prolonged and chronic self-administration has been unsuccessful and is largely unfeasible. Therefore, preclinical studies typically induce ethanol dependence via chronic intermittent cycles of passive exposure to ethanol vapor. Indeed, animals exposed to such paradigms show altered dopaminergic signaling, but specific observations (i.e. changes in receptor or transporter availability) vary across studies and species (for review Siciliano et al., 2018). Further, passive induction of ethanol dependence lacks ecological validity and may differentially alter dopaminergic signaling relative to chronic long-term alcohol self-administration. Overall, evidence from PET imaging studies in humans suggests a hypodopaminergic state in AUD, but this effect has not been reliably reproduced in valid animal models. As such, the mechanisms by which chronic ethanol self-administration produces long-term changes in dopamine signaling remain unclear (Hansson et al, 2019).

4.2. Opioid peptides and receptors

Although the opioid system in the brain is one of the prominent neuropeptides that are involved in the actions of ethanol, we discuss it in this section separate from a few of the other neuropeptide systems (see below). The endogenous opioid system was one of the first neuropeptides to be implicated in ethanol's mechanisms and is the most studied over the years.

4.2.1 Acute actions of ethanol on the opioid system

The acute reinforcing and behaviorally stimulating properties of ethanol have historically been associated with opioid signaling within the mesolimbic system, particularly at mu opioid receptors (Roberts et al., 2000). Acute ethanol has been shown to increase in vivo endogenous β -endorphin and dynorphin release in both rodent models and humans, while ethanol effects on enkephalin release are mixed and may be brain-region dependent (Dai et al., 2005; Jarjour et al., 2009; Lam et al., 2008; Marinelli et al., 2003; 2005; 2006; Olive et al., 2001; Mitchell et al., 2012). Notably, the preclinical microdialysis work with beta-endorphin needs to be confirmed due to the analytical sensitivity of methods used to analyze peptide concentrations (Li et al., 2009).

4.2.2 Chronic adaptation of opioid signaling

In addition to the acute effects of ethanol on opioid peptides, research has also been carried out to determine whether longer term ethanol exposure also alters these neuropeptides. Chronic ethanol self-administration has been shown to produce reduced sensitivity of the mu opioid receptor (MOR) (Saland et al., 2004; Sim-Selley et al., 2002; Chen and Lawrence, 2000). Interestingly, this was further examined to show chronic intermittent ethanol drinking interferes with MOR endocytosis, promoting tolerance to opioid administration (He and Whistler, 2011). Intragastric administration and voluntary ethanol consumption have been shown to produce elevated dynorphin levels (Chang et al., 2007; Kuzmin et al., 2013; Przewlocka et al., 1997), although ethanol injections over 14 days significantly reduced kappa opioid receptor (KOR) expression (Rosin et al., 1999), highlighting potential differences based on route of administration in rats. Increased dynorphin peptide expression and KOR signaling were reported in the amygdala using a chronic vapor model, suggesting a prominent role in ethanol withdrawal (Kissler et al. 2014). Chronic ethanol exposure has been shown to increase delta opioid receptor (DOR) expression levels in the central amygdala,

hippocampus, and spinal cord (van Rijn et al., 2012; Bie et al., 2009; Saland et al., 2005), however not all studies have shown these results (reviewed in Alongkronrusmee et al., 2018). One potential explanation for the variability in DOR expression in the central nervous system after ethanol exposure is that the DOR is highly dynamic and has been found to respond to environmental influences. Inflammation, stress and ethanol exposure have all been shown to modulate DOR function (Margolis et al., 2008; Margolis et al., 2011; Morinville et al., 2004). Following stress, DOR activation can also increase GABA_AR signaling in the ventral tegmental area of rats, a brain region implicated in regulation of ethanol consumption (Margolis et al., 2011).

4.2.3 Opioid modulation of drinking behaviors

It is well known that nonselective opioid receptor antagonists reduce alcohol consumption and preference in animal models (Cowen et al., 1999; Froehlich et al., 1990; Mitchell et al., 2009; Sabino et al., 2013) and alcohol dependent subjects although the clinical significance is debated (Krystal et al., 2001; O'Brien et al., 1996). Naltrexone significantly reduces alcohol seeking, consumption and cue-induced reinstatement in adult rats (Bouton et al., 2006; Ciccocioppo et al., 2003; Gonzales and Weiss, 1998; Hay et al., 2013; Henderson-Redmond and Czachowski, 2014; Katner et al., 1999). More recently, in rats dependent on alcohol, naltrexone displayed sex differences in the ability to reduce ethanol consumption during abstinence. Naltrexone reduced drinking at all time points for females, but only reduced drinking in males at delayed abstinence (Matzeu et al., 2018). Interestingly, studies have shown that antagonism of the opioid system may produce different results on dopamine levels and impulsivity depending on the proportion of opioid receptor subtypes present within the system (Nutt, 2014).

Delta opioid receptors have also been suggested to contribute to the reinforcing properties of ethanol, and there is some evidence beta-endorphin and enkephalins are both necessary for ethanol-induced reinforcement (Tseng et al., 2013). Mice lacking DORs show increased ethanol consumption (Roberts et al., 2001; van Rijn and Whistler, 2009), however blocking DORs either reduces (Froehlich et al., 1991; Krishnan-Sarin et al., 1995; Hyytia and Kiianmaa, 2001) or has no effect on ethanol consumption (Hyytia, 1993; Ingman et al., 2003). DORs also have an important role in cue and stress-induced reinstatement (Ciccocioppo et al., 2002; Marinelli et al., 2009; Nielsen et al., 2012). Recently, it has been suggested that DOR subtypes (DOR-1 and DOR-2) have opposing effects on ethanol intake, which may further explain the variability in past studies with respect to drinking behaviors using systemic, nonselective DOR compounds (Margolis et al., 2008; Mitchell et al., 2014; van Rijn and Whistler, 2009). There is evidence to suggest that DOR-1 forms a DOR-MOR heteromer, whereas DOR-2 does not, which may also contribute to the effects on ethanol intake by DOR-1 selective compounds (George et al., 2000; van Rijn and Whistler, 2009). These results indicate that distinct mechanisms exist between DOR-1 and DOR-2 activation to produce different effects on ethanol consumption and DOR-2 mediated reward. However, the field warrants further investigation in primate models of ethanol self-administration to determine whether targeting the DOR system has clinical value in AUD.

Most studies show KOR antagonists reduce home cage alcohol drinking (Anderson and Becker, 2017), although these effects may be specific to stressed or ethanol-dependent animals (Karkhanis et al., 2016; Sperling et al., 2010; Anderson et al., 2016; Rose et al., 2016). Similarly, KOR blockade significantly reduces operant ethanol self-administration (Schank et al., 2012; Cashman and Azar, 2014; Rorick-Kehn et al., 2014). The ability of

KOR antagonism to reduce drinking appears to be greater in rats that are ethanol-dependent (Walker et al. 2011; Schank et al. 2012).

Disinhibition of dopamine neurons in the VTA through MOR activation is required for opioid reward (Fields and Margolis, 2015), however there are more complex mechanisms present for alcohol reward. Systemic or local MOR antagonism in the VTA did not prevent the initial rise in ethanol-stimulated dopamine release in the nucleus accumbens but did block release from morphine administration (Valenta et al., 2013). More recently, MORs on GABAergic forebrain neurons in the striatum were shown to be critical for alcohol drinking behavior, suggesting that VTA MORs may not be the primary opioid mechanism involved in alcohol reinforcement (Ben Hamida et al., 2019). Further work is required to determine the complex circuitry and mechanisms involved in ethanol's effects on the opioid system, however there is substantial evidence implicating this system in alcohol drinking behaviors that supports ongoing medication development targeting the opioid system (Nutt, 2014; Ripley et al., 2015).

4.3. Neuroimmune signaling

Over the past decade, the neuroscience research community has undergone a rapid expansion of knowledge of the role of glial cells in brain function. It is now recognized that glial cells send and receive molecular signals through the extracellular space, and these signals form a complex network that interacts with neurons within the central nervous system as well as with peripheral tissues. Many of these molecules were previously known to be involved in the regulation of immune function in the periphery, and the presence of these signals within the brain has led to the idea of a neuroimmune system (Rostene et al., 2007). Investigation of the possible role of the neuroimmune system in various behavioral disorders has suggested that neuroimmune mechanisms

may be involved in major psychiatric disorders (Dowlati et al., 2010; Nelson et al., in press), including AUD (see below for references).

4.3.1 Effects of ethanol on neuroimmune signaling mechanisms

Ethanol has been shown to produce inflammatory responses in brain tissue (Valles et al., 2004; Pascual et al., 2007; He and Crews, 2008; Qin et al., 2008). These findings have led to an intriguing new hypothesis that the inflammatory responses may contribute to damage in key areas of the brain that may then eventually lead to behavioral changes that promote the loss of control over drinking (Crews and Nixon, 2009). Key data that support this hypothesis include the findings that proinflammatory cytokines are produced in the brain after acute and chronic alcohol treatment. For example, monocyte chemoattractant protein 1 (MCP-1), a proinflammatory cytokine, was found to be increased in alcoholic brains compared to controls using tissue from a brain bank (He and Crews, 2008). Specifically, MCP-1 protein concentrations were increased by 2-3 fold in the VT₁, substantia nigra, hippocampus, and amygdala in alcoholic brain tissue homogenates compared to controls. Furthermore, this finding of increased MCP-1 protein in brain has also been replicated in a mouse model of high-dose chronic alcohol exposure (Qin et al., 2008). Treatment of C57BL/6J mice with 5 g/kg ethanol (i.g.) daily for 10 days followed by 24 hours of abstinence produced a 30% increase in gene expression of MCP-1 and over 2-fold enhancement of MCP-1 protein in whole brain. In addition, other proinflammatory cytokines such as TNF α and IL-1 β were also significantly increased in brain after the chronic alcohol treatment compared to controls (Valles et al., 2004; Qin et al., 2008). Moreover, protein content of MCP-1 was persistently increased for 1 week of abstinence following the high-dose 10-day alcohol treatment (Qin et al., 2008). Ethanol consumption for 5 months was also shown to increase inflammatory markers in mouse brain, and these responses were mediated in part through the toll-like receptor 4 signaling system (Alfonso-Loeches et al., 2010;

Alfonso-Loeches et al., 2016). Selected markers of neuroimmune function were also found to be increased in brain tissue after a single dose of 4 g/kg ethanol (Doremus-Fitzwater et al., 2015) and also after ethanol vapor exposure (Baxter-Potter et al., 2017). Although the studies cited above show a consistent ethanol-induced neuroimmune response in brain tissue, these studies did not address whether the extracellular concentration of neuroimmune signals were also elevated. A major breakthrough has recently been published showing that an acute ethanol dose of ethanol (3 g/kg) did not alter extracellular cytokines, but that adolescent exposure blunted the time course of extracellular cytokine response to an acute ethanol dose (3 g/kg) in adulthood (Gano et al., in press). Additional studies using microdialysis to monitor cytokines in the extracellular fluid after ethanol exposure are needed.

Investigations of possible mechanisms for the ethanol-induced neuroinflammatory response have largely focused activation of toll-like receptors (Fernandez-Lizarbe et al., 2013; Coleman and Crews, 2018), which are expressed in microglia, astrocytes, and neurons. In addition, it has been suggested that ethanol-induced alterations in microRNA expression may also play a role in the mechanism of the neuroimmune response stimulated by ethanol (Crews et al., 2017).

4.3.2 Changes in neuroimmune signaling alter ethanol consumption

Although these findings that ethanol exposure stimulates a neuroimmune response are novel and intriguing, there is now also data suggesting that changes in chemokine signaling may alter ethanol self-administration. Blednov et al. (2005) studied ethanol preference with a two-bottle choice model in null mutants for various cytokines including MCP-1 and its receptor. Mutants deficient in the MCP-1 receptor showed decreased ethanol preference and intake, while in mutants deficient in the MCP-1 peptide only females exhibited a decreased preference. These data with knockouts could be

influenced by compensation in other systems due to the lifelong deletion of the selected gene. However, other model systems have corroborated these initial findings that modulation of neuroimmune signaling can alter ethanol self-administration. For example, ethanol naïve P rats, which are a strain of rodents that engage in binge-like alcohol consumption, innately show GABA_AR α 2-mediated activation of neuronal toll-like 4 receptor signaling in the central amygdala, which is not present in their non-preferring (nP) counterparts (Liu et al. 2011; Aurelian & Balan, 2019). Both targeted inhibition of α 2 expression and selective knockdown of toll-like receptor 4 in the central amygdala attenuated binge drinking in the alcohol preferring P rat (Liu et al., 2011; June et al., 2015). However, more recent findings suggest that the toll-like receptor 4 may not be a good target for pharmacotherapy (Harris et al., 2017). Furthermore, intracerebroventricular infusion of MCP-1 enhanced operant responding for ethanol (Valenta and Gonzales, 2016). Collectively, these findings that ethanol can alter neuroimmune signaling and also that interfering with neuroimmune signaling can modulate ethanol drinking behavior (for review see Coleman and Crews, 2018) has provided a rationale for testing pharmacotherapeutic agents that target the neuroimmune system as potential treatments for AUD (Crews et al., 2017; Akbar et al., 2018).

4.4. Adrenergic mechanisms

Norepinephrine containing neurons are widely distributed throughout the central nervous system, innervating many regions involved in alcohol-related behaviors and reward. Noradrenergic neurons originate from seven brainstem nuclei; the most well-characterized of which is the locus coeruleus (LC). The LC (all LC neurons produce norepinephrine) functions as a key wakefulness/arousal-promoting region (España and Berridge, 2006; Schwarz and Luo, 2015; Szabadi, 2013) and, via its projections to the amygdala and cortex, facilitates cognitive and sensory processing, as well as anxiety

and stress responses (Berridge and Waterhouse, 2003; Sara, 2009; Szabadi, 2013). Additionally, the mesolimbic and mesocortical dopamine systems, which mediate ethanol's reinforcing and motivational properties, are innervated by noradrenergic projections from the LC and medullary norepinephrine nuclei (A1 and A2 regions) (Mejias-Aponte, 2016).

Adrenoceptors are G-protein coupled receptors found throughout the central nervous system, as well as in the periphery, functioning as key mediators of sympathetic activity. Adrenoceptors are well-characterized and classified as α_1 (with a, b, and d subtypes), α_2 - (with a, b, and c subtypes), β_1 -, β_2 -, or β_3 -adrenoceptors. Norepinephrine has the highest affinity for α_2 -adrenoceptors, which are coupled to Gi proteins and thus, their activation produces sympatholytic effects. Presynaptic α_{2a} - and α_{2c} -adrenoceptors regulate norepinephrine release via a negative feedback mechanism (Haass-Koffler et al., 2018). Alpha 1-adrenoceptors are the most abundant adrenergic receptor in the brain. Coupled to Gq proteins, activation of α_1 -adrenoceptors generally produces excitation (Piascik and Perez, 2001; Ramos and Arnsten, 2007). Norepinephrine has the lowest affinity for β -adrenoceptors, which are coupled to Gs proteins (Ramos and Arnsten, 2007). Drugs selectively targeting adrenoceptors, particularly α_1 -adrenoceptor antagonists and α_2 -adrenoceptor agonists, have been shown to alter alcohol seeking and consumption in both preclinical and clinical studies (for review, see Haass-Koffler et al., 2018).

4.4.1 Manipulations of the norepinephrine system on ethanol behavior and reward

Drugs that have the net effect of reducing central norepinephrine activity appear to reduce alcohol seeking and consummatory behaviors in rodents (for review see Haass-Koffler et al., 2018). Systemic administration of prazosin (1.0-2.0 mg/kg) or doxazosin (1.25-5.0 mg/kg), both selective α_1 -adrenoceptor antagonists, within 15-45 minutes of

alcohol access reduced ethanol seeking and consumption in alcohol-preferring P rats (Froehlich et al., 2013; O'Neil et al., 2013; Rasmussen et al., 2009; Verplaetse et al., 2012) and non-preferring Wistar rats (Walker et al., 2008), and reduced yohimbine-induced reinstatement of alcohol seeking (Funk et al., 2016; Lê et al., 2011). The α 2-adrenoceptor agonists clonidine and guanfacine produced similar effects. In P rats, clonidine [at doses of 40 and 80 μ g/kg (i.p.), but not at 10 and 20 μ g/kg] administered 30 minutes prior to testing robustly reduced ethanol consumption relative to rats treated with vehicle. The 40 μ g/kg dose also reduced saccharin intake by half, but did not affect water intake, suggesting a non-specific effect of clonidine on alcohol and natural reward consumption (Rasmussen et al., 2014). Guanfacine (tested doses: 0.3, 0.5, and 0.6 mg/kg, i.p.) reduced responding for alcohol in a progressive ratio paradigm and reduced both cue- and yohimbine-induced reinstatement of alcohol seeking (Lê et al., 2011; Riga et al., 2014; Fredriksson et al., 2015). At doses of 0.3 and 0.6 mg/kg (i.p.), guanfacine had a greater effect than naltrexone on reducing acute ethanol consumption selectively in high-drinking Wistar rats (Fredriksson et al., 2015). Although these studies implicate adrenoceptors in the motivational properties of alcohol, most relied on systemic drug administration (the aforementioned drugs cross the blood brain barrier), which enhances face validity but undermines the ability to parse out peripheral vs central drug effects on alcohol seeking and consummatory behaviors, and thus limits interpretation of the influence of central norepinephrine signaling in ethanol reinforcement. Nevertheless, systemic blockade of α 1-adrenoceptors or systemic activation of α 2-adrenoceptors reduces alcohol self-administration and reinstatement of alcohol seeking behaviors, suggesting that pharmacological dampening the activity of central and peripheral noradrenergic systems can mitigate alcohol consumption, particularly in alcohol-preferring rodents.

Impairment of norepinephrine synthesis via targeted manipulations of dopamine β -hydroxylase, the enzyme that catalyzes the synthesis of norepinephrine from dopamine, provide direct evidence that central noradrenergic systems may mediate ethanol's reinforcing properties. Dopamine β -hydroxylase knockout mice and mice with selective depletion of norepinephrine in the prefrontal cortex show reduced preference for ethanol (Ventura et al., 2006; Weinshenker et al., 2000). Similarly, systemic administration of nepicastat, a dopamine β -hydroxylase inhibitor, reduced home cage ethanol consumption, ethanol seeking in the operant chamber, and blocked a compensatory increase in alcohol consumption following deprivation in alcohol-preferring sP rats. However, these effects reached significance only at the highest tested doses (50 and 100 mg/kg, i.p.) (Colombo et al., 2014). Dopamine β -hydroxylase knockout mice also showed greater sensitivity to the sedative and hypothermic effects of ethanol, which are generally inferred to be aversive, and this was reversed by acute replacement of central norepinephrine (Weinshenker et al., 2000). Based on these findings, an emerging hypothesis is that central norepinephrine is involved in regulating the stimulating and/or sedating effects of alcohol.

Norepinephrine modulates mesolimbic dopamine activity, and this may be one mechanism by which it influences the motivational properties of alcohol. Noradrenergic afferents from the LC to the VTA have been shown to regulate dopamine neuron firing and extracellular dopamine concentrations in the nucleus accumbens, caudate, and prefrontal cortex (Mejias-Aponte, 2016), likely via activation of α 1-adrenoceptors (Rommelfanger et al, 2009). Recent studies by Shelkar and colleagues (2017) explored the role of this LC-VTA circuit in ethanol reward and reinforcement via targeted pharmacological manipulations in Wistar rats trained to self-administer 200 mg% ethanol directly into the posterior VTA (pVTA). Silencing of LC neurons via lidocaine (4%, 1 μ l/rat) or muscimol (100 ng/rat) reduced responding for intra-pVTA alcohol, while

intra-pVTA infusion of norepinephrine (40 ng/rat) restored ethanol self-administration. To explore whether this noradrenergic modulation of ethanol reinforcement was due to an α 1-adrenoceptor-mediated mechanism, Shelker et al. infused various doses of selective α 1-adrenoceptor agents into the pVTA. Intra-pVTA administration of 10 and 20 ng prazosin decreased intracranial ethanol self-administration, consistent with its previously described effects on oral alcohol consumption, while the α 1-adrenoceptor agonist phenylephrine (5 and 10 ng) produced an opposite effect (Shelkar et al., 2017). This work provides evidence for involvement of α 1-adrenoceptors in the pVTA in the reinforcing properties of alcohol. As α 1-adrenoceptors are present on both dopaminergic and non-dopaminergic VTA neurons (Medias-Aponte, 2016; Pradel et al., 2018), future research is required to determine the precise mechanisms by which LC-norepinephrine neuronal innervation of the VTA regulates ethanol-self administration.

4.4.2 Pharmacological effects of alcohol on central norepinephrine signaling

Remarkably little work has attempted to quantify the pharmacological effects of alcohol on norepinephrine neuronal activity and to monitor central norepinephrine activity during ethanol self-administration. In the only study to examine extracellular norepinephrine during operant ethanol self-administration, sweetened ethanol consumption did not evoke a norepinephrine response in the medial prefrontal cortex of experienced, non-dependent rats. In fact, the temporal pattern of norepinephrine activity was similar among separate groups of rodents self-administering ethanol, sucrose, or nothing (Figure 3; Vena et al., 2017). Without additional research, this observation leads to more questions than answers regarding central noradrenergic responses to alcohol during operant self-administration.

Initial evidence from microdialysis studies with experimenter-administered ethanol in rodents suggests that ethanol's actions are dose-dependent. Intraperitoneal injection of

a very low dose of alcohol (0.2 g/kg) increased extracellular norepinephrine in the prefrontal cortex (Rossetti et al., 1992). Similarly, intravenous infusion of an intoxicating dose of ethanol (1.0 g/kg) stimulated a transient, but significant norepinephrine response in the medial prefrontal cortex (Vena et al., 2017). Higher doses (2-2.5 g/kg, intraperitoneal) of alcohol acutely decreased norepinephrine concentrations, particularly in the cortex (Murphy et al., 1983; Rossetti et al., 1992). Across all studies, saline infusions had no effect on extracellular norepinephrine concentrations (Vena et al, 2017; Rossetti et al., 1992), suggesting an alcohol-specific effect. Collectively, these studies indicate that central norepinephrine systems are acutely modulated by systemic ethanol, but the dose-response relationship remains unclear as the extant literature lacks a complete evaluation of ethanol's acute and chronic pharmacological actions on norepinephrine neurons.

***** Figure 3 here *****

4.4.3 Targeting adrenergic mechanisms in AUD

Recent renewed interest in noradrenergic involvement in alcohol-related behaviors has yielded compelling evidence that noradrenergic mechanisms contribute to alcohol self-administration, likely via mediation of the reinforcing and motivational properties of alcohol. While numerous questions remain, particularly regarding the relative contribution of the central vs peripheral systems, the precise substrates targeted by alcohol, and the consequences of persistent intoxication and withdrawal, these early findings have contributed to emerging hypotheses that have translational significance. For example, if indeed reducing noradrenergic activity enhances sensitivity to the sedative effects of alcohol, currently FDA-approved drugs such as prazosin, doxazosin, clonidine, and guanfacine, may be beneficial for some high-risk drinkers as experiencing greater alcohol stimulation and less alcohol sedation is associated with excessive alcohol consumption (King et al, 2014).

Chronic alcohol consumption and repeated cycles of intoxication and withdrawal induces adaptations in central noradrenergic signaling, which likely to contribute to the progression to AUD. Although these precise adaptations remain largely unexplored in preclinical models, early clinical studies demonstrated enhanced norepinephrine activity during alcohol withdrawal (Linnoila et al., 1987). More recently, adrenergic agents have shown some efficacy as pharmacotherapies for AUD (Fox et al., 2012; Kenna et al., 2016; Simpson et al., 2009), particularly in reducing alcohol craving (Haass-Koffler et al., 2018) and sympathetic overdrive during alcohol withdrawal (Muzyk et al., 2011). In a larger clinical trial with 92 AUD patients (though only 20 were included in the intent-to-treat analyses), Simpson and colleagues reported that prazosin, relative to placebo, reduced the probability of heavy drinking days and the number of drinks per week, but do not affect the number of drinking days per week (Simpson et al. 2018). Although these early studies seem promising, effect sizes have generally been small to moderate so large-scale randomized clinical trials are needed.

4.5. Amino acid involvement

4.5.1 Glutamate

In order to examine extracellular glutamate concentrations during ethanol self-administration, most studies have utilized microdialysis methods. Importantly, the basal glutamate levels measured in these samples often do not fulfill the criteria for neuronal release and likely reflect measurements from an astrocytic glutamate pool (van der Zeyden et al. 2008). Acute ethanol administration is known to produce differential effects on extracellular glutamate concentrations in a biphasic manner. Most studies show lower doses of ethanol increase, while higher doses decrease glutamate levels in the mesolimbic system (Ding et al., 2012; Moghaddam and Bolinao, 1994; Piepponen et al., 2002; Quertemont et al., 2002; Selim and Bradberry, 1996). In separate groups of

rats receiving different doses of ethanol (0.5, 1.0, and 2.0 g/kg, i.p.), repeated injections over 7 days increased basal extracellular glutamate concentration and reduced clearance in the VTA regardless of ethanol dose (Ding et al., 2012), consistent with similar reports in the nucleus accumbens (Kapasova and Szumlinski, 2008; Melendez et al., 2005). Voluntary continuous home cage ethanol drinking in alcohol preferring rats also resulted in increased basal extracellular glutamate and reduced clearance (Das et al., 2015b; Ding et al., 2013). These studies and others highlight alterations in glutamate transport as a potential mechanism of increased extracellular glutamate concentration following chronic ethanol exposure (Spencer and Kalivas, 2017; Rao et al., 2015). Indeed, reduced expression of glutamate transporter 1 has been shown following continuous ethanol access (Das et al., 2015b; Sari et al., 2013), however others have observed no changes in protein levels or function after forced or intermittent exposure (Ding et al., 2013; Griffin et al., 2015; Melendez et al., 2005; Stennett et al., 2017). While there appear to be clear differences in the regulation of glutamate depending on ethanol drinking model, future studies are needed to further outline neurochemical mechanisms by measuring extracellular glutamate concentrations during operant ethanol self-administration.

4.5.2 GABA

While there is significant work implicating inhibitory neurotransmission in maladaptive behaviors (Ostroumov and Dani, 2018), considerably less is known about ethanol's effects on in vivo extracellular GABA concentrations. Potentiation of GABAergic signaling by acute ethanol has been extensively reported in electrophysiology studies (Roberto et al. 2004; Theile et al., 2008; Weiner and Valenzuela 2006; Zuo et al., 2017) although subregional differences have also been described (Guan et al., 2012). Microdialysis experiments have largely found little change following acute ethanol exposure (Fliegel et al., 2013). Initial work found that acute ethanol injections did not

alter dialysate GABA concentration in the nucleus accumbens or VTA of naïve rats or those chronically treated with alcohol or morphine (Dahchour et al., 1994; Dahchour et al., 1996; Kemppainen et al., 2010; Ojanen et al., 2007; Yan et al., 2005). Differences in clearance mechanisms and analytical separation conditions may have contributed to variable results (Rea et al., 2005). More recently, acute ethanol injection (2 g/kg, i.p.) was shown to produce an increase in GABA levels in the nucleus accumbens in the first 60 minutes post-injection in both ethanol-naïve mice and mice exposed to intermittent ethanol injections, the latter of which showed reduced basal GABA levels relative to the former (Pavon et al., in press).

Our lab recently reported inhibiting GABA uptake in the VTA significantly reduced in vivo extraction fraction of the probe, underestimating and/or masking potential changes in dialysate concentration (Zandy and Gonzales, 2018). Local morphine delivered through the microdialysis probe has been shown to significantly reduce dialysate GABA concentration in the VTA (Klitenick et al., 1992; Sotomayor et al., 2005). Interestingly, no changes in GABA concentration were measured after systemic morphine administration (Ojanen et al., 2007) but when GABA transporters were blocked a decrease in GABA concentration during intravenous morphine was recorded (Vihavainen et al., 2009). Together, these results suggest that inhibiting uptake prior to ethanol administration may be one strategy to expand the current evidence on neurochemical effects of ethanol on in vivo GABAergic signaling particularly during operant ethanol self-administration.

4.6. Neuropeptide signaling and receptors

4.6.1 Corticotropin-releasing factor

Corticotropin-releasing factor (CRF) is a 41-amino acid neuropeptide that is critically involved in modulating stress responses via stimulation of the hypothalamic-pituitary-

adrenal axis. An extensive amount of preclinical work directly implicates extrahypothalamic CRF in various features of alcohol dependence, including excessive alcohol consumption (Valdez et al., 2002), withdrawal-related anxiety and negative affect (Baldwin et al., 1991; Zorrilla et al., 2001; Valdez et al., 2002), and stress-induced reinstatement (Zorrilla et al., 2014; Le et al., 2000). Much of this work focused on the CRF1-receptor as antagonists for this CRF receptor subtype blunted binge-like ethanol consumption in nondependent animals (Lowery-Gionta et al., 2012; Cippitelli et al., 2012), withdrawal-induced increases in ethanol seeking behavior in dependent rats (Valdez et al., 2002; Funk et al., 2007), and stress-induced escalation of alcohol consumption and reinstatement (Marinelli et al., 2007; Le et al., 2000).

Encouraged by these findings in preclinical models, recent translational studies evaluated the efficacy of two different CRF1-receptor antagonists in human alcohol dependence. In both relatively small, randomized clinical studies, the CRF1-receptor antagonist showed no efficacy relative to placebo in reducing subjective craving for alcohol, negative affect, or anxiety, and did not affect neural responses to alcohol-related stimuli (Schwandt et al., 2016; Kwako et al., 2015). These clinical studies are among several in which CRF1-receptor antagonists demonstrated a lack of clinical efficacy in treating psychopathology (Spierling & Zorrilla, 2017). Despite the promising preclinical literature, pharmacological interventions targeting the CRF1-receptor do not appear to be viable treatments for AUD.

4.6.2 Neuropeptide Y

The neuropeptide Y (NPY) system is widely expressed throughout the central nervous system and peripherally. NPY is co-secreted with classic neurotransmitters (i.e., GABA, glutamate, norepinephrine) and interacts with four Gi/o protein-coupled receptors. NPY is involved in regulating a variety of biological functions, with its actions in the

hypothalamus regulating feeding behavior, while in the nucleus accumbens and amygdala, it elicits reward behaviors and produces anxiolytic effects, respectively.

Evidence from rodent models suggests an inverse relationship between NPY expression and ethanol intake that is contingent upon genetic background and/or ethanol drinking history (Thiele et al., 1998, 2000; Robinson & Thiele, 2017). In rats, basal NPY levels in the hippocampus, amygdala, and frontal cortex are lower in alcohol-preferring strains compared to non-preferring strains (Robinson & Thiele, 2017; Ehlers et al., 1998; Caberlotto et al., 2001). In an ethanol-preferring strain of mice (C57BL/6J), overexpression of NPY results in decreased ethanol consumption, while NPY knockout mice show increased ethanol consumption, increased sensitivity to ethanol-induced locomotion, and reduced sensitivity to the sedative effects of ethanol (Thiele et al., 2000; Thiele et al., 1998). In the same strain of mice, another study demonstrated reduced NPY immunoreactivity in the central amygdala of mice with 1, 3, and 6 weeks of ethanol binge-drinking experience (vs water-drinking controls), with the greatest reductions observed in mice with 3 and 6 weeks of ethanol binge experience (Sparrow et al., 2012).

Pharmacological manipulations of the NPY system may produce differential effects on ethanol seeking and consummatory behaviors depending on genetic background, ethanol drinking history, and the regional target of the manipulation. In non-dependent rodents, central administration of NPY reduces ethanol seeking and self-administration selectively in ethanol-preferring strains, while increasing self-administration or having no effect in non-preferring strains (Badia-elder et al., 2001; Henderson & Czachowski, 2012; Slawecki et al., 2000; Sparrow et al., 2012; Borkar et al., 2016). Interestingly, Y2-receptor antagonism suppresses ethanol intake in both alcohol-preferring and non-preferring rodent strains (Sparrow et al., 2012; Thorsell et al., 2002), with dependent

animals demonstrating a sensitized response to the antagonist (Rimondini et al., 2005). Across high and low drinking rodent strains, local infusion of NPY into the hypothalamus consistently increases ethanol self-administration in ethanol-experienced animals (Gilpin et al., 2004; Kelley et al., 2001). However, this effect of NPY on ethanol intake is likely region-specific as NPY exerts its orexigenic actions via hypothalamic nuclei.

In sum, evidence from recent investigations of NPY's role in alcohol self-administration generally support an inverse relationship between central NPY activity and ethanol self-administration, suggesting that reduced basal NPY expression and activity is a risk factor for increased alcohol consumption. However, as this literature remains preliminary, this interpretation is likely oversimplified and incomplete. For future research, it will be important to evaluate how targeted manipulations of the NPY system affect behavior across a variety of self-administration paradigms and to characterize the adaptations in NPY signaling induced by chronic alcohol consumption.

Although preclinical work has long supported a role of the central NPY system in alcohol responses and related behaviors, translational support is generally lacking. Genetic studies have found polymorphisms in the genes coding for NPY and the Y2-receptor to be strongly associated with alcohol withdrawal severity and alcohol dependence, respectively (Koehnke et al., 2002; Wetherill et al., 2008). Additionally, NPY levels were reduced in postmortem human brain tissue from alcoholics relative to controls (Mayfield et al., 2002), yet whether this was a cause or consequence of alcohol dependence remains unclear. Nevertheless, this observation is intriguing as a recent study in humans demonstrated an inverse relationship between NPY levels (high vs low) and accumbal responses to salient stimuli (Warthen et al., 2019). Extensive research is required to determine whether the NPY system is a viable target for pharmacotherapies for AUD.

4.6.3 Oxytocin

Oxytocin is a peptide hormone synthesized in the paraventricular and supraoptic nuclei of the hypothalamus that mediates sexual, maternal, and pro-social behaviors in mammals, and may have a role in stress and anxiety responses (Bethlehem et al., 2013). Recently, preclinical findings indicate that oxytocin reduces ethanol appetitive and consummatory behaviors across various self-administration paradigms. In mice, relative to vehicle pre-treatment, oxytocin at all tested doses (1, 3, and 10 mg/kg, i.p.) reduced binge-like ethanol intake (an effect that was blocked by an oxytocin receptor antagonist), and during an operant self-administration session, oxytocin (0.1, 0.3, and 1 mg/kg, i.p.) reduced ethanol seeking and consumption (King et al., 2017). This latter finding was specific to ethanol as oxytocin reduced sucrose self-administration only at the highest tested dose (1 mg/kg). Systemic (i.p.) administration of oxytocin (vs vehicle) acutely reduced alcohol consumption in a two-bottle choice paradigm in mice (King et al., 2017) and prairie voles (Stevenson et al., 2017). While vehicle-treated mice consumed ~7 g/kg ethanol in a four-hour period, mice pretreated with 0.3 mg/kg oxytocin consumed ~4 g/kg in the same period and those treated with 1 and 3 mg/kg oxytocin consumed ~3 g/kg. Similarly, oxytocin (1, 3, and 10 mg/kg i.p.) reduced alcohol consumption in male and female prairie voles (Stevenson et al., 2017). Of note, while dose-dependent effects of i.p. oxytocin were observed in mice in the two-bottle choice paradigm, they were not apparent among prairie voles or among mice in the aforementioned binge-drinking and operant paradigms.

An important caveat of these studies, however, is that the extent of brain penetration of systemically administered oxytocin remains unclear. To circumvent this concern, other studies have used intracerebroventricular (i.c.v.) injection of oxytocin. In rats with a prolonged history of intermittent ethanol access, the hormone (1 μ g/ μ l i.c.v.) acutely

reduced ethanol, but not water consumption (Peters et al., 2017; Bowen & Neumann, 2017). Compared to vehicle, oxytocin (10 nM i.c.v.) selectively reduced reinstatement of alcohol-seeking behavior in alcohol-dependent rats (Hansson et al., 2018).

Initial evidence suggests that oxytocin attenuates the motivational and reinforcing properties of ethanol, possibly via its interactions with the mesolimbic dopamine system (Bahi, 2015; Peters et al., 2017). The oxytocin analog carbetocin reduced the acquisition and accelerated the extinction of conditioned place preference for ethanol in mice (Bahi, 2015). Similarly, systemic oxytocin reduced the progressive ratio breakpoint ratio for ethanol self-administration (King et al., 2017). Conditioned place preference and progressive ratio models both assay the motivational properties of alcohol, which are attributable, at least in part, to activation of the mesolimbic dopamine system, which is also targeted by oxytocin (Melis, 2007). Systemic administration of oxytocin prior to ethanol consumption blocks the ethanol-induced accumbal dopamine response in rats acutely and chronically exposed to ethanol (Peters et al., 2017). Preliminary findings from animal models indicate that oxytocin acutely reduces ethanol preference, seeking, and consumption via attenuation of the reinforcing properties of ethanol, which may be attributable to oxytocin's effects on mesolimbic dopamine signaling (Lee and Weerts, 2016).

Few studies have explored the clinical efficacy of oxytocin in reducing ethanol reward and consumption, though initial studies suggest that exogenous oxytocin may have therapeutic benefit specifically in heavy and/or problematic alcohol users. In two small studies, intranasal oxytocin reduced the severity of withdrawal symptoms in AUD patients undergoing acute detoxification and reduced alcohol consumption in heavy drinkers (Pedersen et al., 2013, 2017). In moderate social drinkers, however, a single exposure to intranasal oxytocin did not modulate the subjective reinforcing, behavioral,

or psychomotor effects of acute alcohol intoxication (Vena et al., 2018). Translational research on the influence of oxytocin on alcohol responses and self-administration is hampered by the lack of empirical data on the pharmacokinetic profile of exogenous oxytocin in humans, including brain penetrability of intranasally-administered oxytocin (Lee et al., 2016).

4.6.4 Vasopressin

Alcohol is known to acutely activate the hypothalamic-pituitary-adrenal axis, and while emphasis has generally been on CRF-mediated mechanisms, vasopressin (AVP) also plays an important role (for review see Harper et al., 2018). In rats, acute administration of a high dose of ethanol (2-3 g/kg, i.p.) increases plasma AVP levels and AVP mRNA expression in the paraventricular nucleus of the hypothalamus (Rivier and Lee, 1996; Colbern et al., 1985; Ogilvie et al., 1997). In contrast, dependence induced by chronic ethanol consumption reduces AVP mRNA levels in several hypothalamic nuclei and in the BNST of mice (Gulya et al., 1991; Ishizawa et al., 1990) and the total number of AVP immunoreactive neurons in the paraventricular nucleus of rats (Silva et al., 2002), suggesting that chronic ethanol exposure interferes with AVP synthesis.

Within the brain, AVP binds to two G protein-coupled receptor subtypes - V1a and V1b – the latter of which is directly implicated in alcohol consumption (Zhou and Kreek, 2018). V1b receptors are most densely expressed in the olfactory bulb, hippocampus, amygdala, and hypothalamus where they contribute to the regulation of stress and anxiety responses (Corbani et al., 2018; Zhou & Kreek, 2018). Systemic intraperitoneal administration of the V1b receptor antagonist SSR149415 reduced ethanol consumption and preference in male Sardinian alcohol-preferring rats and male and female C57Bl/6J mice, without decreasing total fluid intake in a 2-bottle choice paradigm (Zhou et al.,

2011, 2018). Similarly, SSR149415 dose-dependently reduced lever press responding in ethanol-dependent rats, but not in non-dependent animals (Edwards et al., 2012).

Based on these promising preclinical findings, a Phase 2 randomized clinical trial recently evaluated the efficacy of another V1b antagonist, ABT-436, for alcohol dependence (Ryan et al., 2017). Although the primary outcome, percentage of heavy drinking days, was similar between the ABT-436 and placebo groups (31.3 and 37.6, respectively), participants receiving the V1b antagonist reported a greater percentage of days abstinent than those receiving placebo (51.2 vs 41.3, respectively). Collectively, these preliminary findings from both clinical and preclinical studies implicate the AVP system, particularly the V1b receptors in alcohol dependence, though additional studies are necessary to determine the viability of V1b antagonists as a pharmacotherapy for AUD.

5. Conclusions and future directions

The present review summarizes the behavioral, neurobiological, and neurochemical mechanisms involved in ethanol self-administration, with an emphasis on recent advances. Decades of animal self-administration models show that prolonged and chronic ethanol consumption, especially in large quantities, can induce neuroadaptations that yield functional consequences, specifically increased ethanol cue reactivity, greater automaticity of ethanol seeking behaviors, and the emergence of compulsive alcohol use behaviors. Similar behavioral phenotypes are observed in human alcohol drinkers, with the exception of habitual alcohol seeking, which has been difficult to capture in clinical research with existing measures and tasks. A goal of future research will be to determine if this indeed occurs in the clinical progression to alcohol use disorder.

With regards to neurobiology and neurochemistry, extensive basic research has focused on the mechanisms of action of ethanol on specific brain targets, though there are gaps, particularly in determining the translatability of preclinical findings, in the literature as noted above. This review has highlighted some of the newer targets that have gained attention by the field (neuroimmune systems, noradrenergic systems; reconsolidation of memories), but research has also continued on some of the originally proposed mechanisms (opioid systems, glutamate, GABA). A major challenge is the continued development of these new findings into potential therapeutic strategies for patients who seek help in reducing ethanol self-administration. With the development of novel techniques to map out microcircuits in the brain, and the functions of these newly identified circuits, the hope is that these new more detailed maps of brain structure and function will also help pave the way to new therapeutic strategies for treatment of AUD in the near future.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Figure legends

Figure 1. Preliminary data demonstrating that naltrexone inhibits consumption of sweetened ethanol (upper) but not sucrose (lower) intake during a progressive ratio test. (Upper panel) Naltrexone significantly reduced sweetened ethanol (10% sucrose + 10% ethanol in water) consumption in the progressive ratio test in adolescents and adults (** indicates $p < 0.01$, main effect of naltrexone). (Lower panel) Naltrexone did not alter sucrose (10% in water) consumption during the progressive ratio test in control rats. Naltrexone or vehicle was given subcutaneously 30 min before the session. Details of the operant training and testing are in Dornoty and Gonzales (2015). For both panels data presented as mean \pm sem, and group n is shown within the bars.

Figure 2. Ethanol cue extinction during cue memory retrieval-induced memory reconsolidation attenuates the ability of ethanol odor to reinstate the cue-elicited seeking-drinking response sequence. Ambient ethanol odor was re-introduced into the cue conditioning chambers after extensive cue extinction training. The degree to which responses to extinguished cues are reinstated by ambient ethanol odor is inversely related to the efficacy of cue extinction. The x-axis shows different trial phases beginning before light cue onset and extending from light cue onset through sipper access. During conditioning, the light remained illuminated during sipper access. Light and sipper presentation co-terminated. The first 3 points along the x-axis are plotted on the left y-axis and the last 2 points along the x-axis are plotted on the right y-axis. The left y-axis shows the frequency of sipper site approach states (movement toward and gnawing, nosing, or pawing the hole in the wall through which the sipper is later inserted) whereas the right y-axis shows the frequency of sipper contact states (licking the dry sipper tube while it was inserted). Both approach and contact state frequencies

are expressed as a percentage of total behavioral state observations done by treatment-blinded expert raters from digital video recordings following the method of (Lee et al., 2005). Subjects were individually-housed, adult male Long-Evans rats. Mean \pm sem of approach and contact state frequencies represented using black circles for the group of rats receiving our model of standard treatment and white circles for the group of rats receiving the same treatment after initial reactivation of the targeted cue memory via a single isolated cue presentation. Treatment groups were matched on: total extinction (light+dry sipper) trials, total conditioning (light+sweetened ethanol via sipper) trials, context exposure, experimenter handling, response levels at the end of conditioning, response levels at the end extinction, ethanol doses ingested across conditioning, and ethanol doses ingested in the homecage before conditioning. Asterisks indicate $p < 0.05$ for the indicated comparison via t-test. Data are adapted from (Cofresí et al., 2017).

Figure 3. Dialysate norepinephrine (normalized to baseline) in the medial prefrontal cortex of Long Evans rats during operant self-administration session. Three different groups of animals self-administered either 10% ethanol + 10% sucrose (10S10E), 10% sucrose (10S), or nothing (handle; animals exposed to same experimental conditions but did not receive reinforcer access in operant chambers) for six operant sessions. Microdialysis was conducted during the 7th operant session. Basal samples were collected while animals remained in their home cages. The animals were physically transferred (indicated by the arrow) to the operant chambers, initiating the onset of the 30-minute wait period. Upon completion of the response requirement, animals received 30 minutes of access to a sweetened ethanol solution (10S10E), a sucrose solution (10S), or no reinforcer (Handle). Data points represent mean \pm SEM; some error bars removed for clarity. Asterisk (*) indicates significance from baseline. Unpublished data from the Gonzales lab (Vena et al., 2017).

Figure 1

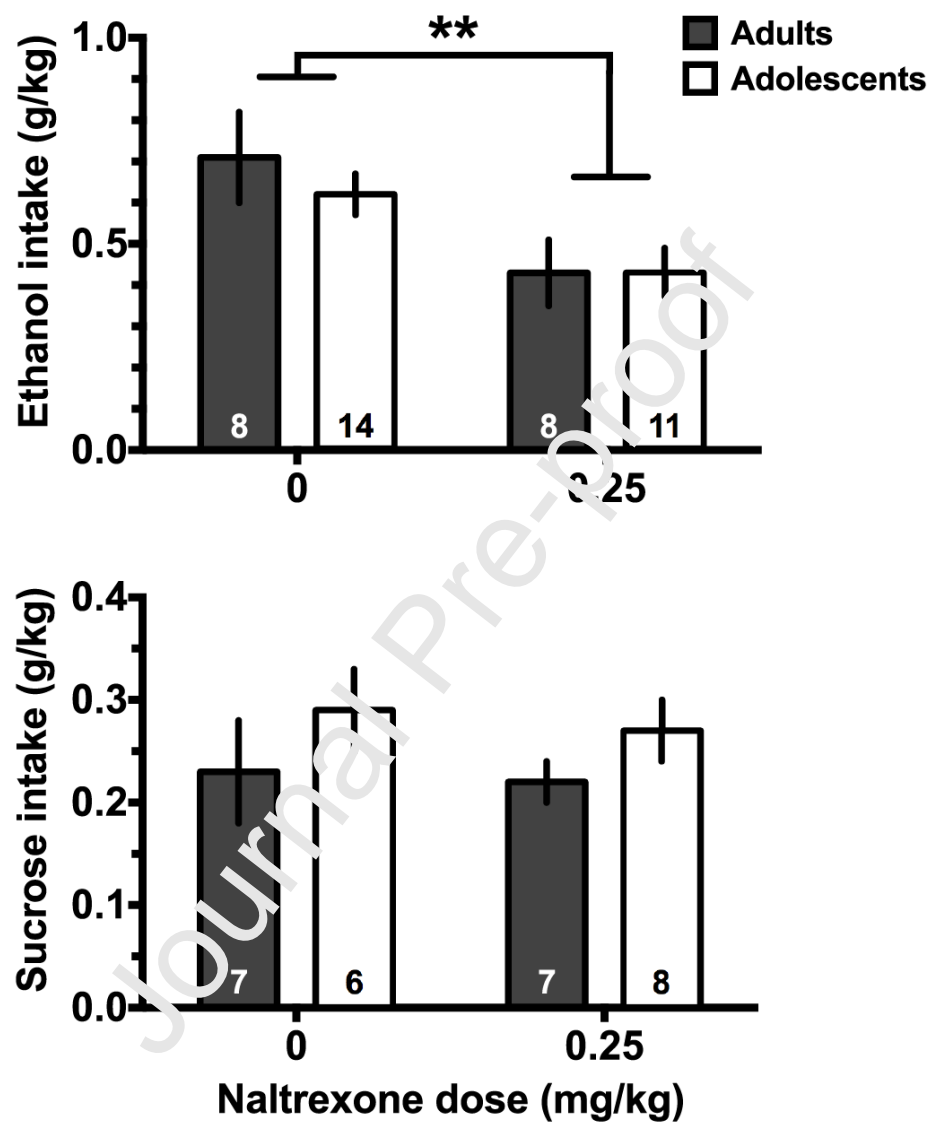


Figure 2

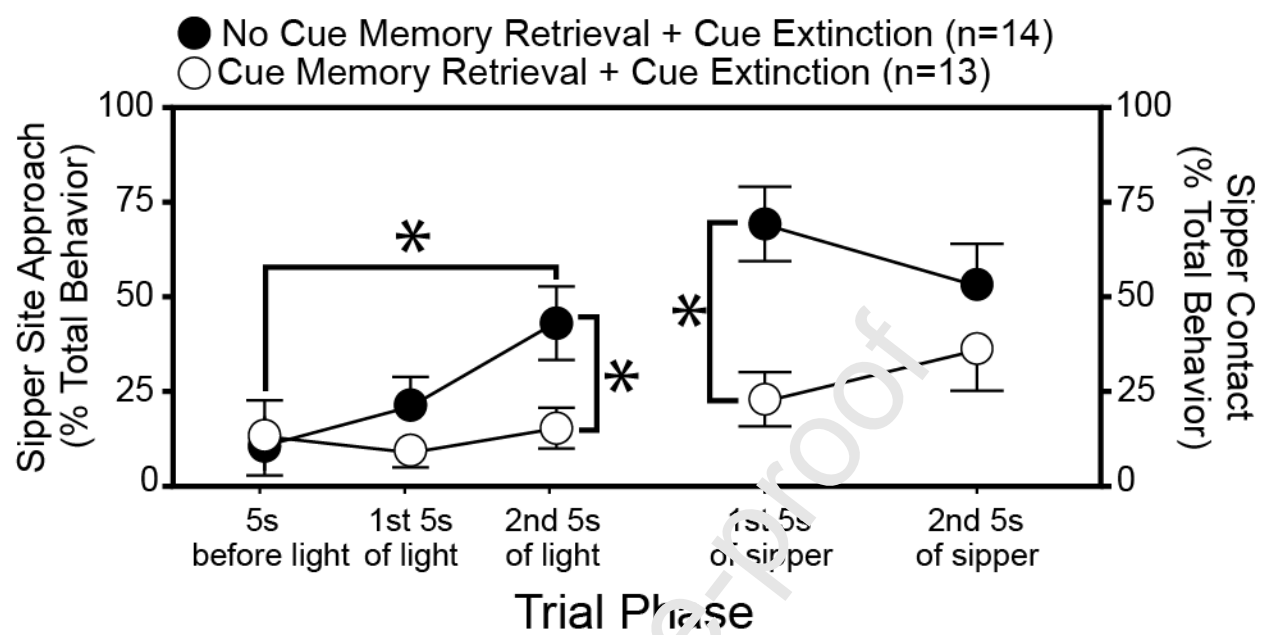


Figure 3

