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Animal Models of Alcohol Use Disorder and the Brain: From Casual Drinking to Dependence

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Alcohol use disorder (AUD) is a chronically relapsing disorder, characterized by a shift from casual to compulsive intake of alcohol that is driven by changes in multiple regions throughout the brain. Animal models, long recognized for their utility in elucidating the biological underpinnings of human diseases, have enabled key advances in our understanding of the risk, development, and treatment of AUD. Here, we provide an overview of animal models used in the study of AUD, including both voluntary consumption and forced exposure models that reflect the range from casual drinking to alcohol dependence. We also review recent updates in the neurobiology across stages of AUD using these models, which have elucidated the profound changes in cellular physiology and molecular markers in key brain regions that are involved in regulation of reward seeking and emotions. Currently available pharmacotherapies as well as emerging treatments informed by the animal literature are also detailed.

What is the significance of this article for the general public?
Alcohol use disorder is one of the costliest public health issues in the United States. This article reviews the preclinical animal models of alcohol exposure that have critically furthered our understanding on the neurobiology of AUD and identified potential pharmacotherapies for the disorder.

Keywords: addiction, alcohol, animal model, drinking in the dark, brain

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has defined alcohol use disorder (AUD) as "a chronic relapsing brain disease, characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using (para. 1)," and estimates that 16 million people in the United States alone meet the criteria for an AUD (NIAAA, 2018a). The most recent version of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–5*; American Psychiatric Association, 2013) describes diagnostic cri-

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teria for having an AUD as meeting a minimum of two out of 11 behavioral criteria, ranging from the intention to drink ("Wanted a drink so badly you couldn't think of anything else") to physical tolerance ("Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?") during a 12-month period. The disorder can be further classified as mild, moderate, or severe, depending on the number of criteria met. Historically, AUD was categorized to include two distinct disorders, with alcohol *abuse* characterized as "harmful use," leading to physical or mental harm in the absence of alcohol dependence, and alcohol *dependence*, focusing on psychological and physiological symptoms, including craving, tolerance, and withdrawal (NIAAA, 1995). Social, low-risk drinking, as defined by the NIAAA (2018b), includes fewer than three drinks per day or seven drinks per week for women, and four drinks per day or 14 per week for men, though the precise biological nature of maintaining appropriate alcohol consumption is not known. Although many theories on addiction have emerged, the addiction field's consensus is that the transition from casual to compulsive intake is thought to involve dysregulation of the reward system and stress systems (Berridge & Robinson, 2016; Dong, Taylor, Wolf, & Shaham, 2017; Koob & Le Moal, 1997; Koob & Volkow, 2016; Volkow, Wise, & Baler, 2017), also commonly characterized as a reward deficit and stress surfeit disorder (Koob, 2013). However, the field currently lacks biological disease markers of the *DSM–5* (American Psychiatric Association, 2013) clinical definition for AUD, highlighting the need for further understanding of the physiological causes and predictors of AUD—a question for which animal research plays an important and irreplaceable role. Animal models have provided a remarkable opportunity to understand the neurophysiological and biochemical perturbations existing before, during, and after various stages of alcohol exposure at an amazing depth unavailable in humans. Importantly, discoveries made with animal models form the foundation of exploration into novel drug therapies. The current treatment options recommended by the NIAAA include behavioral treatments, support groups, and medications (NIAAA, 2014). Several drugs, discussed in this review, have been developed for the treatment of AUD, targeting symptoms during alcohol withdrawal and detoxification as well as during periods of risk of relapse (Akbar, Egli, Cho, Song, & Noronha, 2018). The development and discovery of these compounds (outlined by the U.S. Food and Drug Administration, 2018, as Step 1 in the drug development process) often begins with testing in animal models.

Animal models of alcohol addiction must meet pharmacological characteristics of addiction, such as tolerance and physical dependence (Mello, 1976). Researchers have noted throughout the years that no single animal model will capture all attributes of addiction and that each model will present its own strengths and weaknesses in reflecting the human condition (e.g., Becker & Lopez, 2004; Griffin, Lopez, & Becker, 2009; Rhodes, Best, Belknap, Finn, & Crabbe, 2005; Salimov & Salimova, 1993; Thiele, Crabbe, & Boehm, 2014; but see Becker & Ron, 2014). For example, animal models have struggled to capture the nature of "craving" or "thinking about" alcohol, similar to the "desire" to drink. However, each model can effectively model *some* aspects of addiction and can be used in combination with others. Here, we review some of the most common models of alcohol exposure and their face validity as models of human consumption as well as some of the neurobiological techniques and information discovered using animal models. Although models using nonhuman primates have provided important advances to our understanding of AUD (e.g., Baker, Farro, Gonzales, Helms, & Grant, 2014; Schwandt et al., 2010; Vivian et al., 2001), the current review will focus on rodent literature.

Voluntary Exposure Models

Multiple rodent models of alcohol exposure exist that allow for the voluntary consumption of alcohol based on the traditional premise that drugs of abuse act as positive reinforcers (Lynch, Nicholson, Dance, Morgan, & Foley, 2010). A common theme of these models is that animals are single-housed (allowing for precise measurement of individual alcohol consumption, though some exceptions exist, as noted in the Forced Exposure Models section.), are maintained on a reverse light cycle (i.e., lights off in the morning, allowing their active phase

to coincide with the standard workday), and are provided ethanol (usually diluted in water) during a predetermined schedule. Some models include the addition of sweeteners such as saccharin and sucrose to make the ethanol more palatable (Ji, Gilpin, Richardson, Rivier, & Koob, 2008). The benefits of these models are that they allow natural consumption of alcohol across various lengths of time with little or no training. They are inexpensive and accessible to run. The models also allow individual variability in drinking to be captured. However, it should be noted that one of the major necessities of these models, single housing (a form of social isolation), can influence drinking levels (Chappell, Carter, McCool, & Weiner, 2013) and requires larger vivarium space to house animals.

Drinking in the Dark

The NIAAA (2018b) defines binge drinking as a pattern of drinking producing blood alcohol concentrations (BACs) above 0.08*g*/dL, usually in a pattern of four (for women) or five (for men) drinks over the course of 2 hr, which is considered a key risk factor for the later development of AUD (Gowin, Sloan, Stangl, Vatsalya, & Ramchandani, 2017). "Drinking in the dark" (DID), first developed by Rhodes et al. (2005), is specifically designed to elicit high levels of ethanol consumption in rodents that mirror those levels observed in human binge drinkers. Following single housing and adaptation to the light cycle, mice or rats are provided ethanol in water (typically 20% ethanol volume/volume) 3 hr into the dark cycle for an access period of 2 hr (i.e., on a schedule of lights off at 7:00 a.m., ethanol access is 10:00 a.m. to 12:00 p.m.). This is repeated for 3 days. On the fourth day, the animals receive a 4-hr access period, during which they routinely consume intoxicating levels of ethanol that correspond with human binge drinking (above 0.08*g*/dl). The 4-day protocol can then be repeated any number of times following 3 days of abstinence. Animals are provided no other incentive or motivation to drink, and they have free access to food (Thiele et al., 2014). However, as water is not provided during the short period of ethanol access, some authors have considered DID to be rather a forced consumption model (Blednov, Mayfield, Belknap, & Harris, 2012; Holleran & Winder, 2017), which could result in distinct behavioral and neurobiological profiles (Gilpin, Karanikas, & Richardson, 2012).

This pattern (20% ethanol for 2 hr on Days 1–3, 4 hr on Day 4, and a break from Days 5–7) has been used routinely and successfully by a number of laboratories (Kamens et al., 2017; Lowery-Gionta et al., 2012; Pleil, Rinker, et al., 2015; Rhodes et al., 2005, 2007; Sparta et al., 2008). One of the most important aspects of this model is the similarities to human binge drinking—the rapid consumption of clinically intoxicating levels of alcohol. In addition, repeated cycles of DID (upward of six cycles) results in the emergence of behavioral phenotypes of early stage ethanol dependence (including increased voluntary ethanol intake) but not of later stages (i.e., anxiety-like behaviors and ataxia; Cox et al., 2013). Therefore, DID is a useful procedure for modeling the predependence (i.e., drinking before compulsive use) stages of ethanol consumption (Thiele & Navarro, 2014). The high throughput design makes it efficient to test a large number of animals (Thiele & Navarro, 2014) and includes cohorts of different genetic backgrounds or other manipulations (Vanderlinden, Saba, Bennett, Hoffman, & Tabakoff, 2015). Establishing the DID protocol in an animal laboratory does not require expensive equipment (simply, a scale, fluid bottles with stoppers, and ethanol—though access to a mechanism to assess (BACs) is recommended). Ethanol consumption can be measured as grams of ethanol per kilogram body weight, after accounting for ethanol relative density (Kamens, Silva, Peck, & Miller, 2018).

Two-Bottle Intermittent Access

The intermittent access (IA) model has also been used successfully to model alcohol consumption. The IA model allows similar high-level, binge-like alcohol consumption as DID but often requires longer schedules of access, along with the concurrent availability of water. First characterized by Wise (1973), mice or rats are typically provided 20% ethanol for 24 hr on alternate days, with water freely available throughout the exposure (Carnicella, Ron, & Barak, 2014). About one third of the total ethanol consumed during the 24-hr access period is consumed during the first 30 min, which

matches the patterns seen in the DID model and similarly meets NIAAA criterion for binge drinking (Carnicella, Amamoto, & Ron, 2009). IA can be repeated over long periods of time, leading to an escalation of alcohol intake (Hwa et al., 2011; Hwa, Holly, DeBold, & Miczek, 2016). Others have noted that IA may be used to induce dependence-associated symptoms, including escalation in voluntary alcohol intake (Hwa et al., 2011; Kimbrough, Kim, Cole, Brennan, & George, 2017), with hyperalgesia and other signs of physical dependence (Fu et al., 2015). Interestingly, prolonged exposure (4 weeks and longer) to this model does not result in cognitive impairments or anxiety-like behaviors following protracted cessation of alcohol access (George et al., 2012). Smutek et al. (2014) recently combined IA with radio frequency identification to allow the group housing of mice, overcoming one of the complications of these models (social isolation) and further reflecting the conditions under which human drinking occurs. Because subjects have access to water or alcohol solution, intake measures can include alcohol volume or weight normalized to body weight as well as preference ratios, in which the volumes of alcohol consumed relative to water consumed are compared. Thiele et al. (2014) recently published detailed protocols for both DID and IA, including the materials needed.

Another related model is the restricted access model, in which animals are provided daily access to both ethanol (concentrations ranging from 10% to 20% vol/vol) and water for 30 min to 2 hr (e.g., Gill, France, & Amit, 1986; Martinetti et al., 2006). Similar to the IA model, the restricted access model allows for episodes of highly intoxicating, binge-like bouts of alcohol consumption, with BAC levels exceeding 0.08 g/dl (Becker & Ron, 2014; Ji et al., 2008; Murphy et al., 1986); alcohol consumption levels in these two models are highly correlated (Boyle, Smith, Spivak, & Amit, 1994). Alcohol consumption in the restricted model can vary by genetic backgrounds (Blednov et al., 2012; Martinetti et al., 2006; Murphy et al., 1986). Additionally, a study by Ji et al. (2008) suggests that ethanol consumption in this model can be prevented by pharmacological treatments by the mu-opioid receptor antagonist naltrexone, the selective serotonin-reuptake inhibitor duloxetine, or the corticotropin-releasing factor Type I receptor antagonist MPZP, thus highlighting the potential of this model for future studies on treatment of binge-like drinking.

Continuous Two-Bottle Choice

Although IA engenders high levels of alcohol intake that escalate over time and result in dependence-like symptoms (Fu et al., 2015; Kimbrough et al., 2017), two-bottle choice alcohol consumption elicits levels and patterns of intake that parallel those of moderate or "social" drinkers. Like IA, the two-bottle choice model allows free 24-hr access to alcohol solution and water. However, access to both solutions is available for voluntary consumption over consecutive days. This pattern of access typically elicits low to moderate levels of alcohol intake that can vary substantially by the subject's genetic background (Mayfield, Arends, Harris, & Blednov, 2016; Yoneyama, Crabbe, Ford, Murillo, & Finn, 2008). With two-bottle choice models, the concentration of the alcohol solution can range from barely detectable (<5%) to relatively high (20%) levels. Varying the concentration of the alcohol solution over time can provide information on the sensitivity of subjects to many factors, including alcohol's reinforcing properties and palatability. Because levels of alcohol intake using two-bottle choice are at neither end of the consumption limit, the upper of which often occurs in the DID and IA paradigms, this model is ideal for understanding moderate, social patterns of alcohol intake and for investigating the effects of experimental manipulations that may either increase or decrease alcohol drinking. For example, two-bottle choice was paired with DID to assess the impact of a history of binge drinking on later free-choice alcohol consumption (Cox et al., 2013). One drawback is that peak BACs are difficult to determine on a group level, as the time of greatest alcohol intake varies greatly among individual subjects.

Operant Alcohol Consumption

Operant alcohol consumption has also proven incredibly useful in understanding the nature of AUD (Blegen et al., 2018; Lopez & Becker, 2014; Rassnick, Pulvirenti, & Koob, 1992; Weiss, Lorang, Bloom, & Koob, 1993). Ethanol can be self-administered in an operant paradigm orally (Carnicella, Yowell, & Ron, 2011), intra-

venously (Grahame & Cunningham, 1997; Windisch, Kosobud, & Czachowski, 2014), or as an intragastric gavage (i.e., serving as a positive reinforcer for an experimenter-defined behavior; Czachowski, Prutzman, & DeLory, 2006). In these models, mice or rats are trained to lever press or nose poke for a fixed amount of ethanol (i.e., under a specific schedule of reinforcement, such as a fixed ratio schedule, whereby a specific number of pokes/presses lets to delivery of a predefined fixed amount of alcohol). As reviewed in Lopez and Becker (2014), this model has been particularly useful in animals with a history of alcohol dependence (such as those made dependent via alcohol vapor inhalation, discussed below; e.g., Roberts, Heyser, Cole, Griffin, & Koob, 2000), and has the unique ability to separate appetitive and consummatory behaviors (that is, alcohol seeking vs. alcohol drinking; Samson, Slawecki, Sharpe, & Chappell, 1998).

Additionally, operant conditioning paradigms have been used to model relapse in alcohol seeking after a period of abstinence. Here, the delivery of alcoholic rewards is paired with a sensory stimulus (visual or auditory) or with an addictive drug (e.g., alcohol or cocaine). Following extinction training in which drug-seeking response (i.e., lever pressing or nose poke) is no longer accompanied by reward and cue delivery, animals undergo reinstatement testing in which a cue-induced drug-seeking response is assessed. Additionally, reinstatement could also be initiated by the presence of a stressor, such as intermittent footshock or social defeat (Mantsch, Baker, Funk, Lê, & Shaham, 2016). These models of drug-, cue-, or stress-induced reinstatement of drug-seeking behaviors have been successful in recapitulating aspects of craving and relapse in human alcoholics, with distinct neurocircuitry and neurochemical profiles (Koob & Volkow, 2010; Mantsch et al., 2016).

Forced Exposure Models

Models that involve forced exposure of ethanol are often used for their controlled, limited variability in BACs and their ability to induce ethanol dependence. These models often minimize individual variability via experimenter-controlled doses of ethanol. Administration routes other than oral consumption include intragastric gavage (Khatri et al., 2018) and intravenous infusion (Mello, 1976), each with their own strengths and pitfalls, as outlined below. Models such as oral gavage, whereby the mouse or rat is restrained by the experimenter and ethanol is administered directly into the stomach via a needle with a ball bearing placed down the esophagus, has been noted as particularly stressful (Plackett & Kovacs, 2008). Though oral gavage has been used as a mechanism of alcohol-binge consumption resulting in alcohol-withdrawal symptoms (i.e., the Majchrowicz binge alcohol protocol; Faingold, 2008), others have found that chronic intragastric gavage coupled with an ADH inhibitor does not increase voluntary drinking (Griffin, Lopez, et al., 2009). Intraperitoneal injections into the animal's body cavity allow rapid administration of ethanol in saline, which can be useful for the assessment of the effects of acute doses of ethanol. Acute injections of ethanol have been used to address alcohol-induced effects on peripheral tissue and bone (Iwaniec & Turner, 2013), as well as inflammatory responses (Chen et al., 2013) and alcohol sensitivity, through assays such as the loss of righting reflex (Ponomarev & Crabbe, 2002), in which stress effects are not as large of a concern.

The previously described forced models (i.e., injection, gavage) usually focus on acute, short-term administration of alcohol. These models are particularly useful in their ability to capture predependence exposure to alcohol (e.g., Faingold (2008)). However, they are less effective in capturing long-term, high-intake, dependence-inducing alcohol exposure (Griffin, Lopez, et al., 2009). Animals can also self-administer ethanol for long periods of time in a model that is still forced consumption: In liquid diet models, the animal's daily caloric and nutritional allotment is mixed in a liquid concoction containing alcohol, thereby requiring the animal to drink the alcohol-containing liquid for its daily nutrition (McBride & Li, 1998; Moy, Knapp, Criswell, & Breese, 1997; Obernier, White, Swartzwelder, & Crews, 2002). This model also relies on caloric drive, rather than the alcohol itself, to increase ethanol consumption.

Chronic Intermittent Vapor Ethanol

The chronic intermittent vapor ethanol model (commonly referred to as the "CIE" model)

involves the exposure of rodents to ethanol vapors over a period of days or weeks. This model is noted for its ability to capture the transition to drug addiction via long-term excessive administration while still allowing for tightly controlled levels of ethanol administration and BACs. In addition, this model has been well characterized and elicits postdependent behavioral (e.g., anxiety-related behaviors and further increases in ethanol consumption; Griffin, Lopez, et al., 2009; Jury, Diberto, Kash, & Holmes, 2017; Radke et al., 2017) and neurobiological (DePoy et al., 2013, 2015; Gilpin, Richardson, Cole, & Koob, 2008; Griffin, 2014; Griffin, Lopez, Yanke, Middaugh, & Becker, 2009) alterations observed in human AUD patients. In the CIE model, mice or rats remain group housed and are placed into clear plastic chambers in which vaporized ethanol can be pumped in. Vaporized ethanol (yoked controls receive air) is usually administered for 14 to 16 hr a day, with a subsequent 8 to 10 hr of alcohol withdrawal, over the course of multiple days. The length of vapor ethanol exposure, intended to model the time course and development of alcohol addiction, generally ranges from 4 to 8 weeks (Gilpin & Koob, 2010; Pleil, Lowery-Gionta, et al., 2015). In addition to the vaporized alcohol, for mice, most labs administer injections of an alcohol dehydrogenase inhibitor (such as pyrazole) prior to the placement of animals in the chambers to account for their high rates of alcohol metabolism. Administration of alcohol dehydrogenase inhibitors allow mice to maintain elevated BACs throughout the 14- to 16-hr exposure (Radke et al., 2017); because of their slower rates of alcohol metabolism, rats do not require this step. In contrast to the models allowing choice consumption of alcohol, the CIE model provides forced consumption. Though the aspect of choice is eliminated, it affords the ability to tightly control the access period (including onset, offset, and total length of exposure) and BACs. Additionally, this model is typically paired with voluntary and/or choice alcohol intake models like operant self-administration and two-bottle choice limited access to introduce assessment of relative levels of voluntary intake between alcohol "dependent" and "nondependent" animals (e.g., Anderson, Lopez, & Becker, 2016; Kimbrough et al., 2017; Kreifeldt, Le, Treistman, Koob, & Contet, 2013; Lopez & Becker, 2005; Lopez, Miles, Williams, & Becker, 2017). As noted in Kimbrough et al. (2017), the combination of the IA paradigm of chronic binge drinking and the CIE model allows for the assessment of the transition to excessive drinking seen in humans. Withdrawal-related behaviors can be seen for days following the cessation of vapor ethanol exposure (Schulteis, Markou, Cole, & Koob, 1995), and animals show key anxiety- (Becker, 2000; Kash, Baucum, Conrad, Colbran, & Winder, 2009; Pleil, Rinker, et al., 2015) and depression-related (Slawecki, Thorsell, & Ehlers, 2004) phenotypes in withdrawal and even weeks later, during abstinence. In addition, animals that were exposed to the CIE model showed a rapid escalation in alcohol consumption (O'Dell, Roberts, Smith, & Koob, 2004; Rimondini, Arlinde, Sommer, & Heilig, 2002).

Decades of results show that alternating periods of alcohol vapor exposure and withdrawal over the course of weeks increases alcohol intake and induces symptoms of AUD seen in humans, including increased anxiety, compulsive patterns of alcohol intake, and somatic withdrawal symptoms. These types of experiments have been instrumental in characterizing the neuropathophysiology of alcohol dependence and have thus come to be considered among the best models with which to identify new treatments for AUD. Indeed, as noted by Koob (2013), the alcohol vapor approach shows face validity as a model of alcohol addiction (Heilig & Koob, 2007). However, this model is much more expensive than choice drinking paradigms due to the necessity of a commercially available vaporized ethanol machine (though construction in-house is possible). In addition, as reviewed in Holleran and Winder (2017), only a small percentage of patients suffering from AUD and at risk for alcohol-withdrawal-induced symptoms actually experience severe symptoms (Maldonado et al., 2015). Therefore, this model may be best used as a proxy for intense withdrawal symptoms associated with more chronic and severe AUD like alcohol dependence.

In Utero Exposure

Of the most important advantages of animal models of AUD is the ability to assess in utero exposure to ethanol, allowing for research into the development of fetal alcohol spectrum dis-

order (FASD). Initially characterized in 1973 (Jones & Smith, 1973; Jones, Smith, Ulleland, & Streissguth, 1973), recent work has conservatively estimated that 1% to 5% of U.S. first grade children meet the diagnostic criterion for FASD (May et al., 2018), making it a major and costly public health epidemic, the effects of which cannot be experimentally modeled in humans. Mattson et al. (2010) have attempted to build neuropsychological profiles of individuals diagnosed with FASD versus control individuals, with an 85% overall classification accuracy. However, much work is needed to understand the relationship between time course (when alcohol exposure occurs during the pregnancy), alcohol levels (amount consumed by the mother), and other factors on the development of FASD, which is more easily and more quickly modeled in rodents. The gestational period in rats and mice is incredibly short compared with humans (approximately 18–23 days in total, with the third trimester equivalent occurring during Postnatal Days 1–10), making them ideal candidates for the assessment of prenatal alcohol exposure (for extensive review, see Patten, Fontaine, & Christie, 2014). Researchers have adapted the vapor ethanol chambers in the CIE model to expose both pregnant damns and postnatal pups (equivalent to the human third trimester), allowing for assessment of alcohol exposure across any part of fetal development (Morton, Diaz, Topper, & Valenzuela, 2014). These studies have demonstrated profound and lasting changes in neuronal properties in FASD models at a level of detail not afforded in human studies (for examples, see Baculis, Diaz, & Valenzuela, 2015; Diaz, Jotty, Locke, Jones, & Valenzuela, 2014; Diaz, Mooney, & Varlinskaya, 2016; Rouzer, Cole, Johnson, Varlinskaya, & Diaz, 2017). For example, seminal work by Sulik, Johnston, and Webb (1981) demonstrated that two small doses of alcohol during pregnancy led to craniofacial malformations, and alterations in the developing brain, in embryos within 24 hr of exposure. Other work has shown eye malformations (Cook, Nowotny, & Sulik, 1987) and neural white matter (Cao et al., 2014) following prenatal alcohol exposure. For a detailed protocol in constructing vapor chambers for pre- and postnatal vapor ethanol exposure, as well as suggested ethanol settings, see Morton et al. (2014).

Although there are many experimental benefits to using forced exposure models, some caveats and limitations also exist. For instance, the natural variability in consumption is lost in a forced exposure model. There may also be differences in activation and recruitment of stress-related neurocircuitry, though this remains to be comprehensively investigated. In addition, this is a considerably different administration experience compared with humans drinking alcohol.

Neurobiological Tools and Targets

Animal models of AUD provide the opportunity for the in-depth assessment of brain states involved in addiction. Many of the brain regions identified as crucial to the development and transition to addiction, as well as the key molecular players, were identified using animal models (Koob & Volkow, 2010). Many molecular targets with different sites of action have been identified at the level of both the ligands (neurotransmitters) and their receptors, at the synapse both presynaptically and postsynaptically, and through neuromodulation by neuropeptides and neurohormones (Abrahao, Salinas, & Lovinger, 2017). Though an in-depth overview of all brain regions and known mechanisms is outside the scope of this review, we provide an introduction to key targets in the development and treatment of AUD.

Genetic Models

Multiple tools are available to animal researchers that are as-of-yet unavailable in human research, in addition to the vast array of animal behavioral models (Becker, 2000). Inbred mouse and rat strains, in which littermates are virtually genetically identical, have provided an abundance of information into underlying brain states. Common inbred mouse strains, including 129, C57B/6, and DBA/2, display different basal behavioral phenotypes and thus lend themselves to understanding the molecular profile of susceptibility to various drugs of abuse (Crawley et al., 1997). In addition, selective breeding allowing for the removal or insertion of precise genes has provided a vast array of information into the mechanism of individual genetic alterations (reviewed in Barkley-Levenson & Crabbe, 2012), and identifying

genetic variants that lead to susceptibility to AUD underlies precision medicine (Rinker & Mulholland, 2017). For example, the BXD recombinant inbred strains of mice, which show a range of alcohol consumption (Gill, Liu, & Deitrich, 1996), have recently been used to demonstrate novel gene candidates in brain regions such as the nucleus accumbens and prefrontal cortex (PFC; Rinker et al., 2017).

In addition, both mice and rats have been bred to have specific behavioral traits as opposed to via specific gene introduction or deletion (such as high or low alcohol consumption; Rockman & Glavin, 1984), resulting in unique complex genetic profiles. This strategy, in contrast to single-gene knock-in or knock-out approaches, allows for the selection of *behavioral* phenotypes, resulting in the ability to investigate the complex genetic interactions that mediate that phenotype. The alcohol preferring P rats and nonpreferring NP rats (Lumeng, Hawkins, & Li, 1977), as well as the Sardinian alcohol preferring rats (Colombo, Lobina, Carai, & Gessa, 2006), have been used to identify factors such as sensitivity to other drugs of abuse (Hauser et al., 2014; Lê et al., 2006). In addition, "high drinking in the dark" (HDID) mice have been developed, with high heritability of high BACs (Barkley-Levenson & Crabbe, 2014). Various short-term high- and low-alcohol-preference mice have also been developed, termed HALP/LAP1-3 (Belknap, Richards, O'Toole, Helms, & Phillips, 1997; Green & Grahame, 2008). A full list of selectively genetically bred mice and rats for drinking studies was recently published (Crabbe, Phillips, & Belknap, 2010).

Behavioral Manipulations

Behavioral pharmacology has been the foundation of drug research for decades, allowing for the assessment of both systemic administration of drugs, brain-region specific (via intracranial administration) effects of drugs, and formed the infrastructure of anatomical characterizations of brain regions in drug abuse. As reviewed by Branch (2006), behavioral pharmacology provides the opportunity to use drugs of abuse, such as alcohol, as a stimulus, to produce changes, and to investigate the physiological and behavioral changes produced by those drugs (Branch, 2006; Thompson & Schuster, 1968). For example, microinjection of ethanol directly into the posterior ventral tegmental area (VTA) supports self-administration of ethanol (Ding, Rodd, Engleman, & McBride, 2009; Hauser et al., 2011), and the injection of a dopamine Type II receptor agonist quinpirole (Hauser et al., 2011), a serotonin-3 (5HT-3) receptor antagonist ICS 205–930 (Hauser et al., 2014; Rodd et al., 2010), or nicotine (Hauser et al., 2014) into this area can interfere with it. In addition, behavioral pharmacology is the cornerstone of medication development efforts, in which the therapeutic potential of candidate medications for treatment of addiction are evaluated using preclinical models.

In addition, emerging technologies such as chemogenetic interventions with designer receptors exclusively activated by designer drugs (DREADDs; Roth, 2016; Vardy et al., 2015) and optogenetic interventions with channelrhodopsin and other opsins (Zhang et al., 2010) have allowed for the investigation of specific subclassifications of neurons and neuronal pathways in a variety of behaviors and disorders. Both of these techniques involve stereotaxically injecting virus containing the gene for the receptor of interest (DREADD or opsins), though mouse lines expressing each of these in specific neuronal subsets have recently been developed. DREADDs offer the opportunity to activate intracellular signaling cascades and shift the probability of action potential firing with a systemically (usually intraperitoneally) administered ligand, clozapine-N-oxide, whereas optogenetics involves the insertion of a light-activated cation channel into the cell membrane, allowing for light activation or silencing of the neuron. With optogenetics, no drug is administered, but a fiberoptic cable coupled to a laser is implanted into the brain region of interest. The ability to manipulate (inhibit or activate) specific populations of neurons in specific brain regions and examine effects on behavioral outcomes, including those related to addiction, have already informed our understanding of AUD (Bass et al., 2013; Jaramillo et al., 2018; Millan, Kim, & Janak, 2017). Both of these technologies have been reviewed extensively elsewhere—for DREADDs, see Lee, Giguere, and Roth (2014), and Urban and Roth (2015), and for optogenetics, see Deisseroth and Hegemann (2017), Häusser (2014), and Kim, Adhikari, and Deisseroth (2017).

Electrophysiology

Much of the rodent alcohol literature has focused on electrophysiological measurements. Neurons are known to produce bioelectricity (Hodgkin & Huxley, 1952), and the advent of micropipettes (Graham & Gerard, 1946) has allowed researchers to understand how neuronal communication is changed at the level of the individual neuron, a tool unavailable in humans that allows for precise identification of relevant neuronal subpopulations and systems. In the patch clamp technique, membrane properties, ion channel activity, and neuronal firing can be studied, allowing for the assessment of electrochemical properties of the cell membrane and how other neurotransmitters and factors interact with the membrane (Hamill, Marty, Neher, Sakmann, & Sigworth, 1981). This approach has been used to understand both the acute effects of ethanol on neural activity when applied directly to brain slice preparations and the effects of protracted in vivo ethanol exposure on adaptations in neural activity (Carta, Ariwodola, Weiner, & Valenzuela, 2003; Crowder, Ariwodola, & Weiner, 2002; Herman, Contet, & Roberto, 2016; Lowery-Gionta, Marcinkiewcz, & Kash, 2015; Rinker et al., 2017). For a review and introductory guide to the patch clamp technique, see Molleman (2003), and for a video tutorial and protocol, see Segev, Garcia-Oscos, and Kourrich (2016).

Neurotransmitters, Peptides, and Modulators

Decades of research into the pharmacological actions of alcohol have provided substantial evidence for the widespread interaction between alcohol and classic neurotransmitters, including γ-amminobutyric acid (GABAergic), glutamatergic, dopaminergic, and serotonergic system. These topics have been extensively reviewed in Koob (2004), Koob and Volkow (2010), Marcinkiewcz, Lowery-Gionta, and Kash (2016), and Noble (1996). The current review will focus on recent evidence on peptidergic modulators and their potentials as therapeutic targets for AUD.

Animal models have allowed rapid assessment of potential pharmacological therapies such as those targeting the opioid receptors and dopamine receptors (Sabino, Kwak, Rice, & Cottone, 2013). Neuropeptide Y (NPY) 1-receptor targeting drugs have emerged as a promising therapeutic target (Sparta et al., 2004), as changes are seen in multiple brain regions following multiple alcohol exposure paradigms, lengths, and withdrawal conditions. Thiele, Marsh, Ste Marie, Bernstein, and Palmiter (1998) demonstrated that alcohol-preferring rats had reduced NPY expression in multiple brain regions, and that NPY-deficient mice have increased alcohol consumption and other ethanol-related behavioral alterations (Thiele et al., 1998). Ehlers et al. (1998) demonstrated that although hypothalamic NPY was not affected following 7 weeks of the CIE model, it was upregulated following 1 month of withdrawal. Corticotropin-released factor (CRF) and its receptors (Type I and Type II) are encouraging targets (Lowery & Thiele, 2010; Schreiber & Gilpin, 2018). Alcohol activates CRF-expressing neurons in the hypothalamus (part of activation of the HPA axis; Rivier & Lee, 1996); as reviewed extensively in Schreiber and Gilpin (2018), CRF's interactions with alcohol vary by age, alcohol exposure, and brain region. For example, binge ethanol drinking does not require CRF signaling via the HPA axis activity (Lowery et al., 2010) but does require CRF signaling in the central nucleus of the amygdala (Lowery-Gionta et al., 2012). Interestingly, NPY and CRF have also been shown to interact with each other to influence alcohol drinking. Pleil, Rinker, et al. (2015) demonstrated that NPY suppressed binge drinking (DID) via an inhibition of CRF-expressing neurons specifically within the bed nucleus of the stria terminalis, highlighting the roles not only of NPY and CRF but also of interactions of these peptides within a precise brain region in the control of alcohol consumption. Importantly, Pleil, Rinker, et al. demonstrated that this mechanism is conserved to nonhuman primates, further highlighting the utility of such rodent models, as the effects were preserved across lower and higher order species. This work has been the foundation of the exploration of NPY-targeting drugs, in particular, for AUD (Thorsell & Mathé, 2017). Though outside the scope of this review, confirmation of mechanisms between rodent and nonhuman primate work in the alcohol field has been an important focus and a foundation of exploring new treatment options—see work by Kathy Grant. NPY and CRF

actions in other brain regions have also been identified as important, highlighting that they may have a general, more global role in alcohol addiction (Lowery-Gionta et al., 2012; Sparrow et al., 2012; Valdez, Zorrilla, Roberts, & Koob, 2003; G. Wu et al., 2011). Thus, CRF-releasing neurons, as well as CRF receptors, are particularly promising target for AUD (Koob, 2003; Pleil, Rinker, et al., 2015).

Dynorphin and the kappa opioid receptor system, long known for their role in stress and anxiety (Al-Hasani et al., 2015; Crowley et al., 2016), are also heavily involved in withdrawal (particularly withdrawal-associated anxiety) and may be an effective treatment target (Crowley & Kash, 2015). The kappa opioid receptor system is thought to mediate "antireward" systems in the brain, and activation of this $G_{i/o}$ coupled receptor system often leads to dysphoria and aversion (Crowley & Kash, 2015). Much work has focused on the role of the dynorphin/kappa opioid receptor system in alcohol withdrawal, particularly in mediating stress responses seen during withdrawal (Anderson & Becker, 2017; Karkhanis, Holleran, & Jones, 2017; Lê, Funk, Coen, Tamadon, & Shaham, 2018; Van't Veer, Smith, Cohen, Carlezon, & Bechtholt, 2016), and its importance has recently been identified in the human literature as well (Bazov et al., 2018).

Neurocircuitry of AUD

Multiple brain regions have been identified as undergoing profound changes during the course of alcohol exposure and subsequent addiction. As there are many excellent and comprehensive reviews on this burgeoning topic, here, we briefly describe the highlights of this work (Abrahao et al., 2017; U.S. Department of Health & Human Services, 2016; Koob, 2014; Marcinkiewcz et al., 2016; Roberto & Varodayan, 2017). According to the Surgeon General's report on addiction, the cycle of addiction is described as including (a) the binge/intoxication stage, (b) the negative affect/withdrawal stage, and (c) the preoccupation/anticipation stage (craving for alcohol; Koob & Volkow, 2010). Each of these stages has key brain regions and neurotransmitters involved in the transition to the following stage. This pattern is followed by almost all drugs of abuse (Koob, 2013). During the binge/intoxication phase, initial exposure to drugs of abuse, including alcohol, engages the mesolimbic dopamine system (Leone, Pocock, & Wise, 1991; Morikawa & Morrisett, 2010; Olds & Milner, 1954; Shnitko, Kennerly, Spear, & Robinson, 2014; Q. Wu, Reith, Kuhar, Carroll, & Garris, 2001), both within the VTA and in its target regions. Continual exposure to the drug leads to dysregulation of dopamine and reward-related circuitry.

Though activation of VTA dopamine neurons is certainly a hallmark of substances of abuse (Di Chiara & Imperato, 1988), other brain regions show dopamine-independent activation during alcohol binge and intoxication, such as the central nucleus of the amygdala (Möller, Wiklund, Sommer, Thorsell, & Heilig, 1997) and the ventral pallidum (June et al., 2003; Melendez, Rodd, McBride, & Murphy, 2004). As drug use persists, brain stress systems are engaged during the negative affect and withdrawal stage. This stage involves brain regions that coordinate stress and emotional responses, such as the bed nucleus of the stria terminalis (Kash, 2012; Kash et al., 2015), and the central nucleus of the amygdala, which have been researched at a level of detail otherwise not afforded in human studies. Finally, preoccupation/anticipation/craving is thought to be heavily dependent on the striatum. It is important to note the difficulty in experimentally assessing the human sensation of "craving" a drug of abuse (Tiffany, Carter, & Singleton, 2000). Additionally, the PFC, often thought of as an executive control center exerting "top-down" control of behavior, is heavily influenced by alcohol (Abernathy, Chandler, & Woodward, 2010). Pleil, Lowery-Gionta, et al. (2015) showed that although the CIE model exposure did not alter measurements of synaptic drive in the prelimbic cortex, it did cause presynaptic disinhibition and postsynaptic increase in excitatory transmission in the infralimbic portion of the PFC. Other studies have shown that the preoccupation/anticipation/craving stage involves additional brain regions such as the hypothalamus (Hammarberg et al., 2009; Wayner, 2002), and the dorsal raphe nucleus has emerged as an important site of alcohol-induced changes (Lowery-Gionta et al., 2015).

Current and Future Treatments

There are currently three Food and Drug Administration-approved pharmaceutical interventions as a first line treatment for AUD (NIAAA, 2018c). Naltrexone, a drug that is also used to lessen consumption of opiates and narcotics such as heroin, can help reduce the desire to consume alcohol and maintain abstinence (Laaksonen, Koski-Jännes, Salaspuro, Ahtinen, & Alho, 2008; Rösner, Hackl-Herrwerth, Leucht, Vecchi, et al., 2010). Naltrexone can be injected once per month or administered daily by mouth. However, commonly reported side effects (5%–10% of patients) include nausea, headache, and depression. Acamprosate, a drug with an unknown mechanism of action, reduces the urge to drink in heavy drinkers (Jonas et al., 2014; Laaksonen et al., 2008; Rösner, Hackl-Herrwerth, Leucht, Lehert, et al., 2010). Acamprosate must be administered orally three times per day. Disulfiram lessens the desire to drink by causing unwanted side effects when an individual does consume alcohol, such as nausea, vomiting, and flushed skin (Laaksonen et al., 2008). However, these side effects make treatment compliance difficult (Skinner, Lahmek, Pham, & Aubin, 2014). Despite the limited pharmaceutical treatment options, some off-label treatments have proven promising for AUD. Topiramate, an antiepileptic drug, has been investigated for its potential to treat a variety of psychiatric disorders, including AUD, particularly in veterans and AUD with comorbid posttraumatic stress syndrome (Batki et al., 2014; Del Re, Gordon, Lembke, & Harris, 2013; Ralevski, Olivera-Figueroa, & Petrakis, 2014). Prazosin, typically used to treat high blood pressure, is currently in a Phase 2 clinical trial for alcohol addiction (Pocock & Dietel, 2013). Several other therapeutic targets, including the anti-inflammatory, phosphodiesterase 4 subtype inhibitor Idubilast and Apremiblast, and $\alpha 2$ adrenergic receptor agonist Guanfacine, are currently in clinical trials for treatment of alcohol craving and relapse. Though the lack of a comprehensive treatment with limited side effects for AUD is daunting, emerging targets such as the CRF, NPY, and dynorphin systems are promising. It is nevertheless noteworthy that, despite a majority of preclinical studies supporting the efficacy of CRF antagonists for treatment of affective disorders and addiction, clinical trials have unfortunately failed to demonstrate their antidrinking and anitcraving effects in alcohol dependent individuals (see Spierling & Zorrilla, 2017, for a discussion of the current status of clinical trials using CRF antagonists). The discouraging clinical results therefore have warranted further investigation into the physiological functions of CRF systems in emotion and stress response as well as the physicochemical properties and pharmacokinetics of CRF antagonists for optimal results in human patients.

Conclusion

Animal models have provided vast contributions to both our understanding of AUD and potential treatment options. Various models are available for the assessment of alcohol's effects at different stages of the development of addiction. Generally, choice consumption animal models (drinking in the dark, IA, and two-bottle choice) are inexpensive, high throughput, predependent alcohol consumption models. Forced exposure (such as chronic intermittent vapor ethanol), in contrast, provides a dependent, long-term exposure model, capable of assessing alcohol's effects in utero, though at a much higher purchasing cost. In addition, other forced exposure models (intragastric and intraperitoneal administration) are recommended for acute exposure experiments. Animal models have also provided a key opportunity to understand how individual brain regions and transmitter systems are altered during binge/intoxication, negative-affect/withdrawal, and preoccupation/anticipation/craving stages of alcohol addiction. In particular, animal studies have been able to identify peptidergic populations such as NPY, CRF, and dynorphin, and identify regions of the amygdala, extended amygdala, and PFC as undergoing important changes during this transition through the stages of addiction. In addition, tools such as genetic manipulations, electrophysiology, and brain-site specific behavioral pharmacology, coupled with the rapid gestational period and life span of mice and rodents, make it easy to conduct high-throughput in-depth analysis of the role of specific genes, neuronal populations, and pathways in the development of alcohol addiction. These techniques, coupled with the available behavioral models, will be vital in achieving the goals of the National Institutes of Health's Precision Medicine Initiative in building molecular and phenotypic profiles of individuals and diseases, including AUD (Lloyd, Robinson, & MacRae, 2016).

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