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Chapter 1

NEXT STOP DEPENDENCE - BINGE DRINKING ON THE ROAD TO ALCOHOLISM: PRECLINICAL FINDINGS ON ITS NEUROBIOLOGY FROM RAT ANIMAL MODELS

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ABSTRACT

Binge alcohol drinking continues to be a major public health concern worldwide. Thus, continued clinical and preclinical research is needed to understand the neurobiology of this behavior. Substantial progress has been made in defining binge drinking for clinical research. However, the definition of binge-like drinking for preclinical research is still evolving. It has been shown that binge drinkers often manifest many of the same cognitive and emotional deficits seen in individuals that have experienced multiple detoxifications. These findings suggest that neuroadaptations associated with cycles of high blood alcohol concentrations followed by a period of abstinence are common to both binge alcohol drinking and alcohol dependence. This supports a role for binge drinking in the initial stages of alcohol dependence when impulsive drinking and the positive reinforcing properties of alcohol predominate. Moreover, it coincides with clinical evidence that binge alcohol drinking is a developmental phenomenon occurring predominantly in adolescents and young adults. Here we present pre-clinical approaches to examine binge alcohol drinking using selectively bred rats. The selectively bred alcohol-preferring P and the high alcohol drinking HAD1 and HAD2 rat lines display behaviors that in many respects parallel that of humans with alcohol use disorders. This includes differences in binge-like alcohol

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drinking between peri-adolescent rats and their adult counterparts. Findings obtained from research with these rat lines support clinical findings that the mesocorticolimbic dopamine "reward" system is crucial in mediating binge-like drinking and alcohol use disorders in general. Similarly, this research indicates that activity of the glutamate, GABA, dopamine, serotonin, acetylcholine, and multiple peptide systems is crucial in mediating binge drinking, alcohol use disorders and addiction in general. It is clear that substantial progress has been made in understanding the neurobiology of these behaviors. However, the translation of these important findings into the clinical setting will require more research using models that bear some face validity with clinical populations. Towards this end, selectively bred rat lines, such as the P, HAD1 and HAD2 lines will continue to facilitate this endeavor.

1. BACKGROUND ON CLINICAL RESEARCH

1.1. Prevalence and Impact of Alcohol Use Disorders on Society

Over half of adult Americans have a family history of alcoholism or alcohol (ethanol) abuse (Research Society on Alcoholism, 2009), although a smaller percentage of these individuals have this trait in multiple generations. Additionally, nearly half of all individuals meeting life-time diagnostic criteria for alcohol dependence do so by the age of 21, with this percentage increasing to approximately 65% by the age of 25 (Hingson et al., 2006). Previous estimates of the ratio of men to women who abuse alcohol have varied between 2:1 and 3:1 (Brienza and Stein, 2002), with this gender gap narrowing among youth and the elderly [Brienza and Stein, 2002; Nelson et al., 1998; Substance Abuse and Mental Health Services Administration (SAMHSA), 2012; Wilsnack et al., 1991). In the United States alone, the cost of alcoholism is at least $185 billion each year (e.g., Harwood et al., 2000), and the Centers for Disease Control and Prevention (CDC) ranks alcohol drinking as the third leading cause of preventable death (Mokdad et al., 2004). As one example, the mortality of women with substance use disorders is four times that of breast cancer (Blumenthal, 1997). Moreover, research indicates there is a causal relationship between alcohol use and at least 50 different medical conditions (Rehm et al., 2003; also see Reed et al., 1996 for a discussion on the role of genetics regarding this interaction).

Today's youth (Miller et al., 2001; Quine and Stephenson, 1990; Winters, 2001), whether they be men or women (Nelson et al., 1998; Kandel et al., 1997), are initiating alcohol use earlier and experiencing more alcohol-related problems than ever before (Bava and Tapert, 2010; Gore et al., 2011; Miller et al., 2007; Pitkanen et al., 2005). Approximately 80% of high school seniors in the United States have consumed alcohol and half of them initiated drinking before the eighth grade (Johnston et al., 1999). This is significant as early onset of alcohol use is a strong predictor of future alcohol dependence (Anthony and Petronis, 1995; Chou and Pickering, 1992; Grant and Dawson, 1997; Hawkins et al., 1997); although, in some populations, this effect is dependent upon the presence, vs. absence, of a conduct disorder (Rossow and Kuntsche, 2013; see also Capaldi et al., 2013). Moreover, adolescent onset of use is associated with a more rapid, compared with individuals who initiated use as adults, progression to dependence (Clark et al., 1998). In the United States, approximately 30% of high school seniors report binge drinking (Johnston et al., 1991, 1993), with more than 70% of college students reporting binge drinking during high school (Wechsler et al.,

2000). Therefore it is not surprising that, among college students, binge drinking is becoming more prevalent and is also a strong predictor of future alcohol-related problems in North America (Dawson et al., 2004; Johnston et al., 2008; Presley et al., 1994; Wechsler et al., 2000; White et al., 2006) and Europe (Kuntsche et al., 2004). It is estimated that greater than 1 out of 3 male college student engage in binge drinking in the United States and that a significant proportion of these consume at least 2 to 3 times the binge definition threshold (e.g., Wechsler et al., 2000; White et al., 2006). However, in some locales adolescent girls may actually engage in binge drinking more than adolescent boys (c.f., Plant and Plant, 2006). Regarding younger individuals, the seriousness of this problem is underscored by the fact that adolescents between 12 and 20 years of age drink 11 percent of all alcohol consumed in the United States, with more than 90 percent of it consumed in the form of binge drinking (NIAAA, 2012).

Pattern of drinking (e.g., social vs. binge vs. episodic vs. chronic) and total volume consumed are important characteristics for evaluating alcohol abuse and dependence as well as their antecedents and trajectory (Flory et al., 2004; Heather et al., 1993; Lancaster, 1994; Zucker, 1995). This characterization has led to the development of different typologies and/or drinking profiles for alcoholics (Babor et al., 1992; Cloninger, 1987; Conrod et al., 2000; Epstein et al., 1995; Lesch and Walter 1996; Moss et al., 2007; Prelipceanu and Mihailescu, 2005; Windle and Scheidt, 2004; Zucker, 1987). In addition, the pharmacological efficacy of some treatments for alcoholism appears to depend upon where an individual ranks within a particular typology (Cherpitel et al., 2004; Epstein et al., 1995; Dundon et al., 2004; Johnson et al., 2003). Therefore, age-of-onset and pattern of drinking have significant predictive validity for a life-time diagnosis of alcohol abuse or dependence and, in some cases, can predict the effectiveness of treatments targeting these disorders.

1.2. Alcohol Abuse, Dependence and the Addiction Process

In general, alcohol dependence is a chronic, progressive, relapsing disorder that advances in stages from experimentation to dependence (Heilig and Egli, 2006; Jupp and Lawrence, 2010; Koob, 2009; Koob and LeMoal, 2008; Koob and Volkow, 2010; Spanagel, 2009; Volkow and Li, 2005). Alcohol dependence progresses from rewarding, euphoric and positive-reinforcement aspects of alcohol intake, in the early stages, to the dysphoric and negative-reinforcement aspects that drive dependence in its later stages. Alcohol is positively reinforcing by producing a euphoria/high or a perceived positive sense of well-being (e.g., increases in perceived confidence). Alcohol is negatively reinforcing by removing dysphoria (e.g., anxiety) or a negative sense of well-being (e.g., hangover and physiological withdrawal). Once dependence is acquired, alcohol's negative-reinforcement aspects tend to overshadow alcohol's positive-reinforcement aspects. Progression from experimentation to dependence is not linear in nature, with individuals often returning to earlier stages of the disease process before advancing to the final stages of dependence. Similarly, as a chronic disorder, alcoholism is often associated with multiple detoxifications, periods of abstinence and subsequent relapse. Regarding this, many of the emotional (e.g., impaired processing of perceived facial expressions and anxiety), physiological [e.g., altered hypothalamic-pituitary-adrenal (HPA) axis activity] and cognitive deficits (e.g., impaired response inhibition) seen in individuals that have experienced multiple detoxifications (Duka et al., 2002, 2003, 2004;

Sinha et al., 2011; Townshend and Duka, 2003) are also seen in individuals that engage in regular binge drinking or binge drug intake (e.g., Townshend and Duka, 2005), with preclinical studies supporting these findings as well (Zorrilla et al., 2001; see Stephens and Duka, 2008 for a discussion of both). It is noteworthy that a very recent study (Gierski et al., 2013) reported that nonalcoholic family history positive (FHP) for alcohol dependence individuals displayed greater impulsivity and lower executive function relative to nonalcoholic family history negative (FHN) for alcohol dependence controls. This suggests that these two characteristics, associated with binge alcohol drinking, may predate the development of alcohol abuse and dependence in some genetically predisposed individuals. Forensically, it has been hypothesized that the alcohol elimination rate of binge drinkers and alcoholics are approximately the same, with both eliminating alcohol at a higher rate than that of moderate drinkers (Jones, 2010). The latter point suggests metabolic tolerance is seen in both binge drinkers and alcoholics.

The roles of positive-reinforcement and negative-reinforcement also have been characterized in terms of impulsive and compulsive alcohol drinking. Essentially, impulsive drinking leads to binge drinking and intoxication, which in turn leads to compulsive drinking to mitigate physical and behavioral withdrawal from alcohol; and, in the absence of alcohol, there is a preoccupation with, and anticipation of, future alcohol consumption (Koob and Le Moal, 2008). Thus, impulsive drinking and positive reinforcement predominate in the early stages of alcohol dependence, whereas compulsive drinking and negative reinforcement predominate in later stages of alcohol dependence (Koob and Le Moal, 2006, 2008). These cycles are repeated and become more exaggerated over time, such that when these repeated cycles are coupled with the development of tolerance, alcohol intake increases and signs/symptoms of alcohol withdrawal worsen. This conceptualization allows for the hypothesis that the impulsive stage(s) of alcohol abuse is mediated, at least in part, by the ventral striatum [the nucleus accumbens (NAc)] and the compulsive stage(s) of alcohol dependence/addiction is mediated, again at least in part, by the dorsal striatum (the caudate-putamen). Both preclinical (c.f., Everitt et al., 2008; Robison and Nestler, 2011) and clinical (e.g., Rominger et al., 2012; Weerts et al., 2011; also see Andrews et al., 2011; Yau et al., 2012 on findings with family history positive for alcoholism subjects) evidence support alterations in the NAc and caudate-putamen during the development of alcohol dependence/addiction. Regarding binge drinking, this type of drinking is directly associated with alterations in NAc function (e.g., George et al., 2012; Lallemand et al., 2011; Szumlinski et al., 2007).

1.3. Towards a Clinical Definition of Binge Alcohol-Drinking

In an extensive discussion on binge drinking in Britain, Plant and Plant (2006; also see Marczinski et al., 2009 as well as Martinic and Measham, 2008) note that until the last decade-and-a-half binge drinking often was defined as what many clinicians and laypeople would call a "bender." Binge/bender in this context refers to the act of consuming high amounts of alcohol in a sustained manner for at least two days that results in intoxication, gross impairment and possibly unconsciousness (e.g., Cloninger, 1987; Newburn and Shiner, 2001; Schuckit, 1998; Wechsler and Austin, 1998). More recently in seminal reviews (e.g., Courtney and Polich, 2009; Marczinski et al., 2009; Martinic and Measham, 2008) the history

and development of a definition for binge alcohol-drinking have been discussed at length. Some key points are that prior to Wechsler and colleague's (1995) definition of binge-drinking as 4 drinks in a row for women and 5 drinks in a row for men during the past 2 weeks, the definition for binge-drinking was greater than the "4/5 rule" (Wechsler et al., 1994). A similar definition defined binge drinking as greater than 10 drinks consumed during no more than 2 days per week (Kokavec and Crowe, 1999). By modifying the definition to 4/5 drinks at one time with time of inclusion extended to at least 90 days, significantly more respondents were identified as binge-drinkers than would have been identified using the "in the past 2 weeks" rule (Cranford et al., 2006; Vik et al., 2000). An early study that incorporated blood alcohol concentrations/levels (BACs, 0.08 or greater) suggested the 4/5 rule was too low and should be changed to a 5/6 rule (Lange and Voas, 2000). Wechsler and Nelson (2006) discuss and provide a cogent argument (initially in 2001) for the at least 4/5 drinks in a row in the past 2 weeks definition of binge drinking. Subsequent research included the role of periodicity, defined by "heavy episodic" or "frequent" vs. "infrequent bingers", as to how often the individual engaged in binge drinking (Clapp et al., 2003; Knight et al., 2002; Miller et al., 2007; Okoro et al., 2004). These findings as well as the work of Duka and colleagues (Townshend and Duka, 2002, 2005; Weissenborn and Duka, 2003), who developed the "Binge Drinking Score," highlight the importance of pattern of drinking in identifying binge drinking behavior.

Noteworthy is the point made by Townshend and Duka (2002) that the characterization of binge drinking should include a behavioral/physiological component beyond the mere act of drinking (e.g., intoxication/drunkenness). This may stem, in part, from the Prime Minister's Strategy Unit's classification of individuals who "drink to get drunk" as binge drinkers (Prime Minister's Strategy Unit, 2004). Given the variance in how an individual might define drunk, it is clear this definition has its own difficulties (Marczinski et al., 2009). Nevertheless, it does have merit as a conceptual definition of binge drinking because recent definitions of binge drinking involve levels of intake and BACs that result in intoxication for individuals without dependence upon alcohol.

1.4. National Institute on Alcohol Abuse and Alcoholism's Definition of Binge Drinking

In 2004, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) proposed a standardized definition of alcohol binge drinking as "…a pattern of drinking alcohol that brings BAC to 0.08 gram percent or above. For the typical adult, this pattern corresponds to consuming five or more drinks (male) or four or more drinks (female) in about two hours" (page 3: NIAAA, 2004). Moreover, NIAAA sought to place the definition within the context of alcohol-drinking as a continuum with the following caveats (a) "Binge drinking is distinct from 'risky' drinking (reaching a peak BAC between .05 gram percent and .08 gram percent) and a 'bender' (2 or more days of sustained drinking)" and (b) "People with risk factors for the development of alcoholism have increased risk with any level of alcohol consumption even that below a 'risky' level" (page 3: NIAAA, 2004). In general, this definition of binge drinking, or its modification to reflect a similar amount of alcohol in a country's standard unit of measure (c.f., Marczinski et al., 2009; Plant and Plant, 2006 for discussion), has been

accepted by the clinical community. However, the preclinical research community has lagged in developing a standardized definition of binge drinking, a point which we return to later.

1.5. Binge-Drinking As a Developmental Phenomenon

To the best of the authors' knowledge, all recent studies indicate that binge drinking behavior is engaged by adolescents and young adults more often and to a greater magnitude than older (>24 years old) adults (c.f., Courtney and Polich, 2009; Marczinski et al., 2009; Martinic and Measham, 2008; Plant and Plant, 2006). Possible early studies reporting contrary findings may have been influenced by the changing definition of binge drinking over time. The fact that binge alcohol drinking occurs mostly in adolescents and young adults (ages associated with high school and college) is undoubtedly due in part to the observation that, for some behavioral measures, younger subjects are less affected by alcohol than older individuals. Most of the literature evaluating this observation has been done in rodent models (see discussion by Spear, 2010), with some evidence from clinical observations supporting this contention. The most obvious observation is that adolescents tend to drink substantially more alcohol per occasion than their adult counterparts (NIAAA, 2012; SAMHSA, 2012) even though younger adolescents can achieve the same BACs as adults with fewer drinks (Donovan, 2009; NIAAA, 2012; SAMHSA, 2012). Regarding insensitivity to alcohol's effects, Rohsenow and colleagues (2012) examined college seniors, with a 1 to 4 year follow-up, and found that hangover insensitivity was significantly correlated with intoxication insensitivity and future alcohol problems, even after controlling for demographic variables. Another recent study (Gilman et al., 2012) has examined the effects of alcohol in heavy and light social drinkers although not all subjects were in the adolescent to young adult age range (light drinkers average age ~29, heavy drinkers average age ~25). The study examined individual subjective and objective, as measured by fMRI to emotional stimuli, responses while BACs were clamped (via controlled intravenous infusion of 6% alcohol) at 80 mg% (0.08 in clinical terms). These authors reported that not only do heavy, relative to light, drinking individuals have reduced sensitivity to alcohol's subjective effects, but they also display reduced activation of the NAc and Amyg to emotional stimuli, relative to light drinkers.

In addition, there is some evidence suggesting that young heavy drinkers, although not necessarily restricted to binge drinking, experience greater stimulation on the rising limb of the BAC-curve and experience lower sedation on the descending limb of the BAC-curve than young light drinkers (e.g., Holdstock et al., 2000; King et al., 2002). In a follow-up study, King and colleagues (2011) replicated their previous findings that young heavy drinkers (defined as weekly binge drinkers) experience greater stimulation and less sedation following alcohol consumption than young light drinkers. Moreover, these authors reported that greater stimulation and lower sedation predicted escalated binge drinking behavior during quarterly follow-ups, which occurred for 2 years. In turn, escalated binge drinking behavior predicted an increased likelihood of meeting diagnostic criteria for alcohol abuse and dependence (King et al., 2011). These findings parallel research indicating that FHP individuals experience greater stimulation on the ascending limb of the BAC-curve and less sedation on the descending limb of the BAC-curve and a greater propensity to abuse alcohol compared with

family history negative (FHN) for alcoholism controls (e.g., Brunelle et al., 2004, 2007; Newlin and Thomson, 1990, 1999).

A recent study, indicated that, in alcohol-dependent individuals, a polymorphism of the mu-opioid receptor (OPRM1) is also directly associated with the hedonic (those experienced during the rising limb of the BAC curve), but not anhedonic, effects of alcohol (Ray et al., 2013). The difficulty with evaluating whether adolescent and young adult binge drinkers experience greater reward (e.g., stimulation) and less aversion (e.g., sedation) than light drinkers or older drinkers is that it is illegal to provide alcohol to individuals less than 21 years old in the United States. Another problem is the role that expectancies play in describing a subjective response and that younger individuals that engage in binge-like drinking report positive outcome expectancies from drinking to intoxication, such as increased peer affiliation as well as feelings of high, excitation, etc. (c.f., Duka et al., 1998; Marczinski et al., 2009; Martinic and Measham, 2008; Plant and Plant, 2006).

Unfortunately, the rubric of binge drinking includes drinking behaviors that could be considered "extreme" drinking (see also White et al., 2006), although the term "extreme drinking" has been associated with a conceptual definition of binge drinking as well (e.g., Martinic and Measham, 2008).

A noteworthy example of extreme drinking would be the common, and often socially accepted, excessive drinking associated with an individual's 21st birthday, at least in the United States where the legal purchase of alcohol commences at age 21. The population most commonly associated with this type of drinking is the college population, such that approximately 80% of college students engage in this "rite-of-passage" with an estimated average of 13 drinks consumed resulting in BACs approaching or greater than 200 mg% (0.20 in clinical terms) (Neighbors et al., 2006; Rutledge et al., 2008). The present authors believe alcohol-drinking that results in BACs approaching 200 mg% and greater should be considered extreme drinking and clearly falls within the framework of the addiction cycle and escalation of intake.

These levels of intake undoubtedly result in the development of tolerance to alcohol-associated effects, which is a significant diagnostic criterion for alcohol abuse and dependence [*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision* (DSM-IV-TR: American Psychiatric Association (APA), 2000)].

As part of the addictive process, binge alcohol drinking (or binge drug intake) has been defined as an escalation in self-administration (c.f., Covington and Miczek, 2011) seen in the development of alcohol and/or drug abuse as well as dependence. This, to some degree, is supported by the BAC requirement (greater than 0.08 gram percent) found in NIAAA's definition of binge-drinking (NIAAA, 2004). There is preclinical evidence (e.g., Bell et al., 2000, 2001) indicating that alcohol-exposure approximating these BAC levels can induce tolerance to alcohol-induced motor impairment (i.e., ataxia).

As noted in the discussion on the addiction process, escalation of intake is associated with tolerance to effects induced by alcohol which, in turn, leads to abuse and dependence. However, as noted by (Ahmed, 2011), escalation in alcohol drinking, or the intake of substances of abuse, does not necessarily stem from the development of neuronal tolerance in humans. Although, it also should be noted that these other possible explanations for the development of tolerance in humans (Ahmed, 2011), such as social and economic factors, are not easily amenable to examination using animal models.

Table 1. Approximate parallel ages between the rat, associated developmental stage, and the human equivalent

Rat Ages [Post-Natal Days (PNDs)]							
1—7	8—21	21	22—27	28—42	43—60	61—75	76—90
Neonate	Prejuvenile	Weaning	Juvenile	Adolescent	Peri-Adolescent	Early Young Adult	Young Adult
-3 to 0 Months	0—6	6	7—12	13—18	18—21	21—24	25—28
Human Ages (Years)							

Nevertheless, animal models have been used to evaluate the effects of alcohol, as well as drugs of abuse, exposure on a subject's behavior and neurobiology with an emphasis on the adolescent and young adult stages of development (see Table 1 for a comparison of rat and human ages; for reviews of peri-adolescent animal models examining alcohol and drug abuse see Adriani and Laviola, 2004; Andersen, 2003; Chambers et al., 2003; Smith, 2003; Spear, 2000, 2004a, 2004b, 2007, 2010; Spear and Varlinskaya, 2006; Witt, 1994, 2006, 2010; also see Cudd, 2005 for a discussion of early post-natal development as the third trimester equivalent in humans).

2. BACKGROUND ON PRECLINICAL RESEARCH

2.1. Peri-Adolescent Stages of Development in the Rat

When discussing developmental stages it must be kept in mind that there are individual differences regardless of the species examined. Therefore, the concept of "early bloomers" and "late bloomers" should not be restricted to the context of humans alone. In important reviews, Spear (2000, 2007; Spear and Brake, 1983) has indicated that the boundaries of the adolescent window of neurobehavioral development for rats often differ given the parameters (e.g., behavioral vs. neurochemical) examined. Nonetheless, neurochemical and neurobehavioral differences from post weanling through adulthood support a hypothesized adolescent developmental window of postnatal days (PNDs) 28 to 42 (Spear, 2000, 2007; Spear and Brake, 1983). When assessing the effects of pharmacological pretreatment, during adolescence, on adult behaviors in male and female rats, Spear (2000, 2004a, 2007) has suggested that this conservative window (PNDs 28 to 42) could be extended to PND 60. This extended window allows one to examine the earliest adolescent/pubertal changes in the female rat as well as the latest adolescent/pubertal changes in the male rat. As a caveat, the focus of this review will be on rat animal models because an examination of mouse animal models is beyond the scope of this chapter (c.f., Bennett et al., 2006; Crabbe, 2008, 2012; Crabbe et al., 2006, 2010a, 2010b, 2011, 2013; Ehlers et al., 2010; Milner and Buck, 2010).

These windows of development correspond with adolescent (a) changes in glutamatergic *N*-methyl-D-aspartate (NMDA) receptor binding of the prefrontal cortex (Insel et al., 1990); (b) decreased excitatory synaptic transmission in the NAc relative to juveniles (Kasanetz and Manzoni, 2009); (c) changes in central gamma-amino-butyric acid-A (GABA-A) receptor

subunit levels and GABAergic activity (Hedner et al., 1984; Yu et al., 2006); (d) changes in GABAergic interneurons of the medial prefrontal cortex, during early peri-adolescence, and dopaminergic projections, as well as their modification by serotonin, to these interneurons during the peri-adolescent window (Benes et al., 2000); (e) modulation of early adolescent hyperactivity of central dopaminergic, noradrenergic and serotonergic systems by sex hormones (Knoll et al., 2000); (f) changes in accumbal dopaminergic activity (Philpot and Kirstein, 2004, also see Spear and Varlinskaya, 2006); (g) changes in central (primarily within later maturing regions such as the frontal cortex) serotonergic, dopaminergic, and noradrenergic transporter densities, which appear to be related to level of innervation (Moll et al., 2000); (h) changes in central cholinergic systems (Won et al., 2001); (i) greater cerebral metabolic activity relative to adults (Chugani et al., 1987; Spear 2000, 2007; Tyler and van Harreveld, 1942); (j) synaptic pruning/remodeling of subcortical regions, in early peri-adolescence, and cortical regions, in later peri-adolescence (Casey et al., 2000; Dumas, 2004; Schochet et al., 2008; Trommer et al., 1996); (k) timing of the growth spurt (Kennedy, 1967; Spear, 2000); (l) timing of emergence from the protected nest in the wild (Galef, 1981); and (m) maturation of genitalia in female (Döhler and Wuttke, 1975) and male (Clermont and Perry, 1957) rats. Neurogenesis is age-dependent (e.g., He and Crews, 2007), and male as well as female gonadal hormones can facilitate or interfere with certain stages of neurogenesis (c.f., Galea, 2008). Thus, it is important to remember that more gonadal hormones, as seen during peri-adolescence, is not necessarily better with level of gonadal hormones exerting an inverted U-shaped effect on neurogenesis (c.f., Galea, 2008; also see Nixon et al., 2010 for a discussion about neurogenesis and adolescent vulnerability to develop alcohol abuse and dependence). For discussions on possible roles for central glutamatergic and GABAergic activity in the development of adolescent alcohol abuse and the vulnerability to develop alcohol dependence see reviews by Chin and colleagues (2010), Ehlers and Criado (2010), Guerri and Pascual (2010; also Pascual et al., 2009), as well as Nixon and colleagues (2010). For a discussion of the mesocorticolimbic DA system and its alteration by adolescent alcohol exposure see a review by Maldonado-Devincci and colleagues (2010). For a discussion of genetic markers for a predisposition towards adolescent alcohol abuse and dependence see a review by Schwandt and colleagues (2010).

2.2. A Primer on Neurotransmitters and Neuromodulators Mediating Alcohol Abuse and Dependence

Several neurochemical systems are activated by exposure to rewarding stimuli. And, many of these neurotransmitter systems operate within the brain's mesocorticolimbic DA system (described in the next section). Increased activation of these systems promotes behaviors aimed at repeating prior hedonic/positive experiences. This activation of the mesocorticolimbic DA system reinforces behaviors that are necessary for an individual's survival, such as the procurement and ingestion of food and water as well as procreation. Evidence indicates that reinforcement from drug use as well as non-substance behavioral compulsions, such as binge eating and gambling, is processed by the same neurocircuitry that promotes behaviors oriented toward gaining natural rewards. However, these maladaptive behaviors are typified by a loss of control and escalation, reflective of dysregulations of these neural pathways. Repeated experience with alcohol and drugs of abuse leads to compensatory

neuroadaptations, the brain's efforts to maintain homeostasis, that result in dampened reward and increased negative reinforcement processes which motivate addiction-related behaviors (see the previous section on the addictive process). Alcohol, as a small (two carbon chain) molecule, has widespread neurobiological effects. It is due to this diverse action, and the neuroadaptations associated with alcohol abuse and dependence that makes developing pharmacological treatments for these disorders difficult. Acute or repeated binge alcohol drinking alters the activity of a number of neurotransmitter and neuromodulatory systems, such as the glutamate, GABA, dopamine, serotonin, norepinephrine, acetylcholine, as well as peptides including the endogenous opioids, neuropeptide Y (NPY), corticotrophin releasing factor (CRF), and ghrelin.

2.2.1. Glutamate and GABA

The amino acid glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS). It interacts with several receptor subtypes, including NMDA and Group I and II metabotropic glutamate receptors (mGluRs). Substantial evidence suggests that glutamatergic activity mediates natural reward as well as reward from drug and non-drug abuse through direct and indirect interactions with other neurotransmitter/neuromodulatory systems within the mesocorticolimbic DA system and associated brain regions (Carlezon and Wise, 1996, Grace et al., 2007, Kupila et al., 2012, Sun et al., 2008). One hypothesis that has received considerable attention is that sensitized mesocorticolimbic glutamate neurotransmission and the subsequent hypergluatmatergic state that it creates is a major contributor to alcohol abuse and dependence (Gass and Olive, 2008, Vengeliene et al., 2008). Regarding the addictive process, alcohol-associated positive and negative reinforcement are both mediated, in part, through glutamate neurotransmission (Kryger and Wilce, 2010). Pre-clinical evidence supports clinical findings that alcohol acutely inhibits, and chronically sensitizes and upregulates glutamate neurotransmission, in brain regions such as the NAc, mPFC, and CeA (Carlezon and Wise, 1996; Chandler et al., 1993; Ding et al., 2012a; Floyd et al., 2003; Gass and Olive, 2008; Kapasova and Szumlinski, 2008; Nevo and Hamon, 1995; Nie et al., 1993, 1994; Weitlauf and Woodward, 2008). The hyperglutamatergic state associated with alcohol abuse and dependence may be due, in part, to changes in glutamate clearance mechanisms (Ding et al., 2012b; Kapasova and Szumlinski, 2008; Parks et al., 2002; Sari et al., 2011; Smith, 1997; Smith and Zsigo, 1996; Thoma et al., 2011).

Changes in glutamatergic neurotransmission are also associated with binge alcohol drinking. Work with animal models of binge drinking indicate that binge-like exposure resulting in high BACs induces neuroadaptations in the glutamate system, including changes in glutamatergic-associated gene expression (Coleman et al., 2011; McBride et al., 2010) and alterations in downstream signaling cascades (Cozzoli et al., 2009), which result in enhanced glutamate neurotransmission and receptor activation in areas such as the mesocorticolimbic system (Li et al., 2010; Szumlinski et al., 2007). In support of these findings glutamate receptor antagonists such as acamprosate and MPEP reduce binge drinking dose-dependently (Grace et al., 2007; Gupta et al., 2008). Increases in excitatory neurotransmission may be greater during periods of acute ethanol withdrawal, such as those commonly associated with binge drinking, compared to more protracted withdrawal periods (Ward et al., 2009). Thus, it has been suggested that binge alcohol abuse could increase susceptibility to alcohol-induced excitotoxic brain damage, relative to on-going alcohol dependence (Hunt, 1993). Overall, it is likely that glutamatergic adaptations following repeated binge-drinking behavior leads to a

glutamate-GABA functional imbalance (Enna, 1997; Fadda and Rossetti, 1998; Szumlinski et al., 2007), and are responsible, in part, for withdrawal symptomology. This withdrawal symptomology in turn increases the negative reinforcement-associated properties of continued binge drinking. These effects are consistent with a neural signaling-related transition from repeated binge alcohol drinking to dependence. Taken together, it is likely that glutamatergic adaptations contribute to the excitotoxic and oxidative events associated with the hyper-glutamatergic CNS state seen with chronic alcohol intake, as well as withdrawal anxiety. Moreover, these findings provide evidence that glutamate is involved in some of the cognitive and behavioral effects that promote alcohol drinking, as well as the escalation from the initial alcohol experience to binge drinking to dependence. As one neurochemical equilibrant to glutamate, GABA is the primary inhibitory neurotransmitter in the CNS. Several research groups have reported associated differences in GABA gene variants, expression levels, and activation in areas such as the mesocorticolimbic system and the extended amygdala (which includes substructures of the bed nucleus of the stria terminalis, amygdala and nucleus accumbens), with high alcohol-consuming phenotypes and risk for developing alcohol dependence in alcoholics as well as alcohol-preferring rats (Dick and Bierut, 2006; Enoch et al., 2012; Herman et al., 2012; Korpi and Sinkkonen, 2006; McBride et al., 2010; Tabakoff et al., 2009). Thus, differential GABA signaling could reflect one mechanism that predisposes individuals to consume alcohol. In addition, GABA receptor systems are functional modulators of the mesocorticolimbic system (Eiler and June, 2007; Melis et al., 2002; Rahman and McBride, 2002), supporting the role of GABA in DA-associated responses to reward.

Acute alcohol experience potentiates GABA signaling and facilitates its hyperpolarizing actions (Koob, 2004). GABA-A and GABA-B receptors are involved in some of the rewarding, reinforcing, and motivational effects of alcohol consumption and alcohol binge drinking (Eiler and June, 2007; Nowaket al., 1998; Tanchuck et al., 2011; also see Agabio et al., 2012). Although the GABAergic mechanisms affecting binge alcohol drinking are not fully known, there is evidence for its involvement. For instance, binge alcohol drinking alters GABA gene expression in the whole brain of C57BL6/J mice (Coleman et al., 2011), as well as in the NAc and CeA of alcohol-preferring P rats (McBride et al., 2010). Also, selective reductions of the GABA-Aalpha1 subunit in the ventral pallidum and GABA-Aalpha2-regulated toll-like receptor 4 in the CeA were found to reduce DID-MSA (described later) binge alcohol drinking in alcohol-preferring P rats (Liu et al., 2011). In addition, the partial inverse GABA-A receptor agonist Ro15-4513 reduces alcohol binge drinking (using the DID model) when administered systemically or directly into the posterior VTA of C57Bl/6J mice (Melon and Boehm, 2011). It is possible that a GABA system impaired by binge alcohol drinking exacerbates binge drinking-induced excesses in glutamate activity. This may lead to a general state of behavioral and neural disinhibition. By extension, neural disinhibition may lead to deficits in cognition and impulse control. Given these reasoning skills are still maturing during adolescence, binge drinking during this critical stage of development may compromise attainment of this developmental milestone. For example, acute withdrawal from chronic binge-like alcohol drinking interferes with working memory due, in part, to changes in mPFC GABA neurotransmission (George et al., 2012). In addition, chronic binge-like drinking induces long-lasting changes in tonic GABA-A-regulated neurotransmission in the dentate gyrus and CA1 region of the hippocampus (Fleming et al., 2012), areas associated

with learning and memory. In line with the above findings, some current and potential medications for the treatment of alcoholism concomitantly affect glutamate and GABA neurotransmission. For a review of glutamate and GABA-associated ligands tested in five of the selectively bred high alcohol-consuming (AA, HAD1, HAD2, P and sP) international rat lines and CNS disturbances of the glutamatergic and GABAergic systems in these rat lines see Bell et al. (2012b). For reviews on patented treatments for alcohol abuse and dependence that target the glutamatergic and GABAergic systems see Agabio et al. (2012), Barron et al. (2012), and Bell et al. (2012a). Together, these findings implicate a glutamate-GABA imbalance in binge and excessive alcohol drinking (De Witte, 2004). In addition, they suggest a strong role for these amino acids in the loss of control and cognitive deficits associated with escalated alcohol consumption from initial exposure to binge drinking to dependence.

2.2.2. Dopamine

Substantial evidence indicates dopamine (DA) plays a large role in the processing of reward, reinforcement, and motivation to obtain reinforcing stimuli. DA release is increased in several brain regions associated with reward and motivation following the ingestion of alcohol and other drugs of abuse, or when an individual engages in other addictive activities. This increased DA activity serves to promote further use of these addictive stimuli through positive reinforcement processes. However, following prolonged alcohol abuse or addictive behavior, individuals display tolerance to their DA-releasing properties, which promotes further addiction through negative reinforcement processes. In addition, individuals (humans or animals possessing the requisite genotype) with a predisposition to develop alcoholism may display a reduction in basal DA tone that makes alcohol-stimulated DA overflow more reinforcing. In line with this suggestion, alcohol-naïve rats bred for high alcohol consumption exhibit reduced NAc tissue DA levels, compared to outbred rats or their alcohol non-preferring counterparts (Engleman et al., 2006; McBride et al., 1993a; Murphy et al., 1982, 1987; Quintanilla et al., 2007; Smith and Weiss, 1999; Strother et al., 2005; also see Bell et al., 2012b for a review of this effect in five international rat lines selectively bred for this phenotype). A prevailing hypothesis for the role of DA in alcohol dependence is that alcohol is consumed to compensate for this reduced DAergic activity.

Considerable evidence supports the involvement of the mesocorticolimbic DA system in the rewarding and reinforcing effects of alcohol (e.g., Di Chiara and Imperato, 1988; Melendez et al., 2002; Palmer et al., 2003) as well as alcohol preference (McBride and Li, 1998). Pharmacologically relevant alcohol levels increase VTA-DA neuronal firing (Brodie et al., 1990; Gessa et al., 1985). In addition, local or systemic alcohol treatment increases extracellular DA levels in the NAc (Franklin et al., 2009; Imperato and Di Chiara, 1986; Smith and Weiss, 1999; Yoshimoto et al., 1992). Evidence that systemic alcohol exposure increases extracellular mPFC DA levels is mixed (Engleman et al., 2006; Fadda et al., 1990; Hegarty and Vogel, 1993; Tu et al., 2007). Also, alcohol stimulation of VTA-DA neurons has been reported to increase DA levels in the mPFC of female Wistar rats (Ding et al., 2011). Behaviorally, mesocorticolimbic DA neurotransmission has been implicated in alcohol self-administration (Gonzales and Weiss, 1998; Hodge et al., 1996; Melendez et al., 2002; Samson and Chappell, 2003; Weiss et al., 1996). For a review of DAergic-associated ligands tested in five of the selectively bred high alcohol-consuming (AA, HAD1, HAD2, P and sP) international rat lines and CNS disturbances of the DA system in these rat lines see Bell et al.

(2012b). For a review on patented treatments for alcohol abuse and dependence that target the DAergic system see Bell et al. (2012a).

Alcohol also acts to disinhibit mPFC functioning and by extension interferes with some of the executive processes mediated by cortical brain regions (de Oliveira and Nakamura-Palacios, 2003; Kähkönen et al., 2003). This dysregulation could have extensive effects on an individual's situation-specific decision-making capacity, particularly in younger drinkers who exhibit the greatest incidence of binge drinking. Thus, it is not surprising that there is a growing literature indicating a role for DAergic activity in binge alcohol drinking. For example, the DA-D1-like receptor antagonist S33138 has been reported to reduce alcohol binge-like drinking in high alcohol-consuming rodents (Rice et al., 2012; Sabino et al., 2013). Sabino et al. (2013) reported that this suppressant effect was maintained longer in subjects receiving intermittent vs. continuous alcohol drinking access, and could be indicative of a sensitized state in DA-D1 receptors following binge-like alcohol drinking. Taken together, these results suggest that binge or chronic alcohol drinking/exposure interferes with DA regulatory mechanisms within the mesocorticolimbic system, and the CNS recruits adaptive mechanisms to compensate for these dysregulations in basal DA tone.

2.2.3. Serotonin

The neurotransmitter serotonin (5-HT) is associated with addictive behaviors, appetite regulation, behavioral inhibition, mood, and cognitive functions. A dysregulation in the 5-HT system has been implicated as a factor in alcohol addiction. There are seven families of 5-HT receptors (5-HT1–7) and at least 14 distinct 5-HT receptor subtypes (Barnes and Sharp, 1999), which makes the task of understanding which 5-HT receptor subtypes mediate addictive behaviors a complex one. The raphe nucleus, where 5-HT neurons originate, sends 5-HT projections to numerous regions including the VTA, NAc, and PFC and studies have shown that the 5-HT system regulates DA neuronal activity in these subregions of the mesocorticolimbic system (Azmitia and Segal 1978; Herve et al. 1987; Parent et al. 1981; Halliday and Tork, 1989; Van Bockstaele et al. 1994). For example, 5-HT activates VTA-DA neurons (Pessia et al. 1994), induces DA release in VTA slices (Beart and McDonald 1982), enhances DA release in NAc when locally applied to the VTA (Guan and McBride 1989), potentiates the excitatory actions of alcohol on VTA-DA neurons (Brodie et al. 1995), and increases extracellular DA release in the PFC (Iyer and Bradberry, 1996). In addition, there is evidence that activation of the dorsal raphe nucleus can increase extracellular levels of DA in the NAc (Yoshimoto and McBride, 1992).

Alterations in the 5-HT system are believed to mediate some of alcohol's effects in rat lines selectively bred for high alcohol consumption (c.f., Bell et al., 2012b) and alcoholic individuals with a polymorphism of the 5-HT transporter can respond favorable to certain medication combinations (Johnson, 2010). Acute alcohol exposure appears to increase 5-HT activity (McBride et al., 1993b; Smith and Weiss, 1999), whereas chronic exposure to alcohol may result in the development of tolerance to this effect (Smith and Weiss 1999). Clinical and/or pre-clinical studies have reported deficiencies of 5-HT and/or its major metabolite 5-HIAA in the brains of human alcoholics (Schmidt et al., 1997; Pivac et al., 2004) and genetically selected alcohol-preferring rats (Murphy et al., 1987; Zhou et al., 1991; McBride et al., 1993b). Moreover, treatments that reduce 5-HT neurotransmission can elevate self-administration of alcohol (Lyness and Smith 1992; Ciccocioppo et al. 1999). Drug treatments with antidepressants that affect 5-HT CNS activity have been shown to reduce craving and/or

symptomatic behavior associated with alcohol dependence (c.f. Goodman 2008). Therefore, it has been proposed that modulation of the 5-HT system is a viable therapy for alcoholism in a sub-set of patients (Johnson 2004, 2010; Wrase et al., 2006). For a review of 5-HT-associated ligands tested in five of the selectively bred high alcohol-consuming (AA, HAD1, HAD2, P and sP) international rat lines see Bell et al. (2012b). For a review on patented treatments for alcohol abuse and dependence that target the 5-HT system see Bell et al. (2012a). Research on the involvement of 5-HT in binge alcohol drinking has been limited. Pre-clinical studies have shown that binge drinking induced a blunted 5-HT response in the Scheduled High Alcohol Consumption (SHAC) binge drinking model (Szumlinski et al., 2007). Additionally, acute withdrawal from alcohol after binge-like exposure lead to a wide-spread reduction in 5-HT and other neurotransmitters in several brain regions including those associated with the mesocorticolimbic system (Smith et al., 2008). In general, these findings indicate that serotonergic treatments may disrupt binge alcohol drinking and may interfere with the progression to alcohol dependence, in certain individuals, as well.

2.2.4. Acetylcholine (Cholinergic)

The cholinergic (ACh) system has been implicated in addiction. Nicotinic acetylcholine receptors (nAChRs) are widely distributed throughout the brain (Perry et al., 2002). There are 12 subunit-associated nAChRs (with combinations of alpha2 through alpha10 and beta2 through beta4 subunits) with neuronal nAChRs being pentameric in nature (Dani and Harris, 2005). The alpha4-beta2 nAChR combination is the most common in the CNS, it has the highest affinity for nicotine, and rapidly desensitizes (nonfunctional state in which associated ion channels are closed) to the effects of nicotine (Dani and Harris, 2005). The alpha7-associated nAChR has the lowest affinity for nicotine and are present on excitatory glutamatergic terminals within the mesocorticolimbic system (Albuquerque et al., 2009; Gotti and Clementi 2004; Nayak et al., 2000; Wonnacott 1997). Pidoplichko and colleagues (2004) have suggested that nicotine's prolonged effect on DA neurotransmission may be due to alpha7 nAChRs on these presynaptic glutamate terminals, because they do not desensitize to nicotine as rapidly as alpha4 and alpha6 associated receptors.

nAChRs are thought to mediate the reinforcing effects of alcohol as well. nAChRs receptors are present in the VTA and NAc where they are thought to mediate the rewarding/reinforcing effects of alcohol and nicotine (Blomqvist et al., 1996, 1997; Corrigall et al., 1994; Nisell et al., 1994; Soderpalm et al., 2000). Regarding this, alcohol appears to elevate DA levels within the mesocorticolimbic system via indirect activation of nAChRs (Ericson et al., 2003). Interestingly, it has been shown that alcohol can interfere with the desensitization of nAChRs caused by nicotine and this may be one of the contributing factors to the high prevalence of alcohol and nicotine co-abuse (Schlaepfer et al., 2008; Marszalec et al., 1999). As described below, selectively bred P rats are more sensitive to the reinforcing effects of alcohol (Rodd et al., 2004a) and nicotine (Hauser et al., 2013) when self-administered directly into the posterior VTA than outbred control Wistar rats. In addition, recent findings indicate that nicotine exposure can enhance alcohol-seeking and alcohol relapse drinking by P rats (Hauser et al., 2012a), which suggests continued use of nicotine during alcohol abstinence may increase the probability of relapse, at least in individuals genetically predisposed to abuse alcohol. In addition, P rats readily consume alcohol-nicotine solutions in sufficient amounts to achieve binge-like BAC's (> 80 mg%) while achieving nicotine blood levels found in 'heavy smokers' (~56 ng/ml; Hauser et al., 2012b).

Collectively, these findings provide support for the hypothesis that nicotine and alcohol addiction may share common genetic vulnerabilities.

There is some evidence implicating nAChRs in binge alcohol drinking. For instance, Hendrickson et al. (2009) found that nicotine, cytisine (nAChR agonist) and mecamylamine (non-selective nAChR antagonist) reduced binge-like alcohol drinking (Sprow and Thiele, 2012). Similarly, lobeline, a mixed agonist-antagonist of nAChRs, reduced binge alcohol drinking (using the DID model) without altering sucrose intake (Sajja and Rahman, 2011; Sprow and Thiele, 2012). For a review of acetylcholine-associated ligands tested in five of the selectively bred high alcohol-consuming (AA, HAD1, HAD2, P and sP) international rat lines and CNS disturbances of the cholinergic system in these rat lines see Bell et al. (2012b). For reviews on both promising and patented treatments for alcohol abuse and dependence that target the cholinergic system see Rahman and Prendergast (2012) and Rezvani et al. (2012). It is clear that the cholinergic system is involved in alcohol and drug abuse as well as addiction, however, more research needs to be done to develop pharmacological treatments targeting this system.

2.2.5. Opioids

There are several classes of endogenous opioids including enkephalins, endorphins, dynorphins, and endomorphins. These classes of ligands bind with some specificity to the delta, kappa and mu-receptors, respectively. One role of these peptides in the brain is to process information about rewarding stimuli, including alcohol (Oswald and Wand, 2004). These peptides have been shown to influence the development of alcohol abuse and dependence, including binge drinking behaviors. Opioid receptors are found pre-synaptically on DAergic neurons of the mesocorticolimbic system (e.g., within the NAc) where they control the release of DA. Thus, opioid activity like that of the glutamatergic and GABAergic systems modulates DA activity in this "reward" neurocircuit.

Variations in opioid-related gene expression and function may contribute to high levels of alcohol consumption as well (e.g., Marini et al., 2013). For example, high alcohol drinking rats exhibit a greater level of mu-opioid receptor (MOR)-associated and enkephalin mRNA, compared to low alcohol drinking rats (Morganstern et al., 2012). For a review of neurobiological differences in the opioid system between selectively bred high and low alcohol-consuming rats see Bell et al. (2012b). A great deal of existing evidence for the role of opioids in alcohol abuse and dependence comes from pharmacological experiments using the FDA-approved treatment for alcoholism, naltrexone (ReVia) and other non-specific opioid antagonists. Naltrexone blocks alcohol-induced changes in gene transcription in several receptor systems, including the mu-opioid system. Evidence from knock-out mice lacking MORs or dynorphin suggest that MORs and kappa-opioid receptors (KORs) are involved in the rewarding or reinforcing effects of alcohol (Blednov et al., 2006; Hall et al., 2001; Roberts et al., 2000).

In line with a role in alcohol reward and reinforcement, opioid ligands alter alcohol consumption, although the direction of alteration is receptor subtype- and CNS site-specific (Barson et al., 2010; Kemppainen et al., 2012; Margolis et al., 2008). For a review of opioid ligands tested in five of the selectively bred high alcohol-consuming (AA, HAD1, HAD2, P and sP) international rat lines see Bell et al. (2012b). For a review on patented treatments for alcohol abuse and dependence that target the opioid system see Bell et al. (2012a). There is a limited amount of pharmacological evidence that directly implicates opioids in binge drinking

behavior. Naltrexone was found to reduce alcohol intake dose-dependently, using the DID (Kamdar et al., 2007), SHAC (Tanchuck et al., 2011), limited access (Ji et al., 2008), and intermittent alcohol access (Sabino et al., 2012) models of binge drinking. It is impossible from these reports to associate a particular opioid receptor system with binge drinking, as these studies did not utilize receptor-specific agents. However, recent evidence that binge drinking maintains an immature adolescent-like high distribution of mPFC DORs (Nielsen et al., 2012) suggests a role for these receptors in this behavior. In conjunction with reports that DOR blockade reduces alcohol drinking (June et al., 1999), this finding may suggest that overactive DORs are associated with impulsive binge alcohol drinking. The fact that naltrexone reduces (a) the risk of relapse in some alcoholic patients (Farren and O'Malley, 1997; Volpicelli et al., 1992), (b) alcohol cue-induced human brain activity (Dayas et al., 2007; Myrick et al., 2008), (c) alcohol-induced DA efflux in the NAc (Benjamin et al., 1993), and (d) alcohol reinstatement/relapse in rodents (Ciccocioppo et al., 2002; Le et al., 1999) indicates continued research will be conducted on the endogenous opioid system in order to produce more effective compounds to treat alcoholism.

2.2.6. Neuropeptide Y

Neuropeptide Y (NPY) is a 36-amino acid neuromodulator that is expressed throughout the brain in regions such as the cortex, hypothalamus, hippocampus, and Amyg (Allen et al., 1994; Gray and Morley, 1986; Heilig and Widerlov, 1990; Wettstein et al., 1995) and it acts on five receptor subtypes (Y1, Y2, Y4, Y5, and Y6) (Palmiter et al., 1998). It is involved in regulating a number of behaviors such as feeding (Clark et al., 1984), anxiety (Heilig et al., 1993; Heilig and Widerlov, 1995), and alcohol addiction (Pandey, 2003; Pandey et al., 2003). In the alcohol research field, a number of studies have focused on understanding NPY's actions in the Amyg. The Amyg is a focal brain region involved in the negative reinforcing properties of alcohol.

For example, it has been postulated that the P rats' high alcohol intake is due to higher anxiety levels than its low alcohol-consuming NP counterpart (Badia-Elder et al., 2007; Pandey et al., 2005; Suzuki et al., 2004). Support for this hypothesis comes from the observation that, depending upon the behavioral test used, P rats do express innate anxiety (Stewart et al., 1993) and alcohol acts as an anxiolytic for P rats (Gilpin and Roberto, 2012; Stewart et al., 1993; Zhang et al., 2010). Neurobiological support comes from the observation that P rats have lower basal levels of NPY in the central amygdala (CeA) and/or medial amygdala (MeA) compared to NP rats (Ehlers et al., 1998; Hwang et al., 1999, 2004; Pandey et al., 2005). In addition, NPY expression levels in the CeA and/or MeA can be increased in P rats following alcohol exposure (Pandey et al., 2005; Zhang et al., 2010). Also, quantitative trait locus (QTL) analyses have identified NPY as a candidate gene for the high alcohol drinking/preference phenotype in inbred P rats (Spence et al., 2005, 2009, 2013).

Currently, other than the observation that central treatment with NPY reduces the alcohol deprivation effect (ADE) in P rats (Bertholomey et al., 2011; Gilpin et al., 2008), there are no reports of the effects of NPY on binge alcohol drinking by P rats. However, there is some evidence that NPY mediates binge-like drinking using the drinking-in-the-dark (DID) mouse model. Central administration of NPY and a selective Y2 receptor antagonist reduces binge alcohol intake using this model (Sparrow et al., 2012; Sprow and Thiele, 2012). In contrast, activation or inhibition of the Y1 receptor appears to have reciprocal effects, such that a Y1 receptor agonist decreases whereas a YI receptor antagonist increases DID binge-like

drinking (Sparrow et al., 2012; Sprow and Thiele, 2012). In addition, a history of binge-like drinking reduced NPY and Y1R expression levels in the CeA and removal of alcohol following three cycles of binge drinking increased the expression of both Y1 and Y2 receptors (Sparrow et al., 2012; Sprow and Thiele, 2012). Collectively, these findings indicate that NPY signaling is involved in regulating excessive alcohol intake during binge alcohol drinking and, by extension alterations in NPY function contribute to the development of alcohol dependence.

2.2.7. Ghrelin

The neuropeptide ghrelin is a 28-amino acid gut peptide that acts on the growth hormone secretagogue receptor (GHS-R1A). The GHS-R1A is located both peripherally (e.g., gut and stomach) and centrally (e.g., hypothalamic nuclei and the VTA) (Guan et al., 1997; Kageyama et al., 2008; Kojima et al., 1999; Zigman et al., 2006). Given the location of its receptor, it is not surprising that ghrelin promotes the consumption of palatable food, alcohol and drugs. Ghrelin is postulated to mediate reward through actions on VTA-DA neurons. A numbers of studies have shown that systemic and central administrations of ghrelin increases extracellular levels of DA in the NAc (Abizaid et al., 2006; Jerlhag et al., 2006, 2007, 2008, 2010a) and/or induces excitation of VTA neurons (Abizaid et al., 2006). In addition, systemic administration of ghrelin can reorganize VTA neurons, such that these neurons experience greater excitatory input and diminished inhibitory input (Abizaid et al., 2006).

It appears that ghrelin's mediation of rewarding stimuli includes interactions with both glutamatergic (NMDA) (Jerlhag et al., 2011) and nACh (containing alpha3beta2, beta3, and/or alpha6 subunits) (Jerlhag et al., 2006) receptors. A recent study reported that alcohol preferring AA rats have increased gene expression for the GHS-R1A in the VTA, NAc, PFC, hippocampus and the Amyg compared to low alcohol-consuming ANA rats (Landgren et al., 2011). Similar to some clinical studies (Addolorato et al., 2006; Badaoui et al., 2008) chronic alcohol consumption leads to a reduction in ghrelin in AA rats compared with ANA rats (Landgren et al., 2011). In general, central ghrelin signaling stimulates the mesocorticolimbic reward pathway and is necessary for the ingestion of rewarding stimuli including food, alcohol and drugs of abuse, and has been posited as a possible drugable target for addiction (c.f., Jerlhag et al., 2010, 2011; Jerlhag and Engel, 2011; Leggio et al., 2011; Perello and Zigman, 2012; Schellekens et al., 2012).

2.2.8. Other Neurotransmitter and Neuromodulatory Systems

While the neurotransmitter/neuromodulatory systems reviewed above play important roles in addiction to a number of rewarding stimuli, there are a number of other neurotransmitter/neuromodulatory systems that influence neurotransmission in the mesocorticolimbic reward system as well. Some of these other systems include the endocannabinoid system and its receptors in the VTA and NAc; glycine and its binding site on the NMDA receptor as well as its own receptor in the NAc; corticotrophin releasing factor (CRF) as well as orexin and their receptors in the VTA and NAc (particularly for orexin), along with projections from the hypothalamus and activity in the amygdala; the melanocortin system [adrenocorticotrophic hormone (ACTH) and its fragments including alpha-melanocyte stimulating hormone (alpha-MSH)] and its receptors in the VTA and NAc, as well as the hypothalamus; glucocorticoids [an end-product of hypothalamic-pituitary-adrenal (HPA) axis activity] and their receptors in the amygdala; and other sytems [e.g., leptin, orphanin, brain-

derived neurotrphic factor (BDNF) and glial-derived neurotrophic factor (GDNF)]. For recent reviews on the neurobiology of alcohol use disorders see Bartlett and Heilig (2013), Charlet et al. (2013), Deehan et al. (2013), Filbey and DeWitt (2012), Kenna et al. (2012), Koob (2013), Mason and Higley (2013), Noori et al. (2012), Soderpalm and Ericson (2013), as well as Spanagel and Vengeliene (2013).

2.3. A Primer on Neurocircuitry Mediating Alcohol Abuse and Dependence

The mesocorticolimbic dopamine (DA) system has long been known to mediate various aspects of rewarding behavior in vertebrate animals (Koob et al., 1998; Ikemoto, 2007). The mesocorticolimbic DA system has been found to be involved in the orientation to, and procurement of rewards including food, sex, and drugs. Theorists suggest that addictive drugs may "hijack" this system to perpetuate and increase levels of self-administration (e.g., Schultz, 2011). Research with animals and humans has increased our understanding of some of the neurotransmitter systems and receptors involved in mediating the rewarding effects of alcohol and how the mesocorticolimbic DA system system is involved. Although many different brain sites have been found to play a role in addiction (Noori et al., 2012), the mesocorticolimbic DA system can be described as a core neurocircuit mediating most addictions, such that all addictive behaviors alter the mesocorticolimbic DA system. Key sites within the mesocorticolimbic DA system (see Figure 1) include the medial prefrontal cortex (mPFC), amygdala (Amyg), ventral tegmental area (VTA), and nucleus accumbens (NAc); and subnuclei within each of these sites have been shown to mediate various aspects of addictive behavior (Ikemoto, 2007; McBride, 2002; Noori et al., 2012).

2.3.1. Medial Prefrontal Cortex

The mPFC is a critical site for behavioral and cognitive regulation, and undergoes very active neuronal development (synaptic proliferation and subsequent pruning) during peri-adolescence. During this stage of development, it may be particularly vulnerable to the effects of alcohol and other drugs of abuse (Spear, 2000; Chambers et al., 2003; Clark et al., 2008). The mPFC receives glutamate, acetylcholine (Ach), and DA inputs and has glutamatergic projections to mesolimbic brain areas involved in drug and alcohol abuse (Kalivas, 2009; Kalivas et al., 2005; see Figure 1) and the prelimbic and infralimbic subregions of the mPFC are thought to mediate distinct functions of drug acquisition and intake (Peters et al., 2008). Cues associated with consumption of, or access to, natural rewards also elevate DA in the mPFC (Phillips et al., 2008). Data from our laboratory (author EAE) indicate that eight weeks of alcohol free-choice drinking increases the extracellular levels of DA in the mPFC, and microinjections of DA-D2, but not -D1, antagonists into the mPFC reduce scheduled-access alcohol drinking in P rats. In addition, microinjections of a CB1 anatagonist into the mPFC reduce operant responding for alcohol (Hansson et al., 2007). Other findings indicate a role for other neurotransmitter and peptide systems in regulating mPFC efferents and various aspects of reward behavior (e.g., Berglind et al., 2009; Corominas, et al., 2010; Giacchino and Henriksen, 1998; Van den Oever, et al., 2010a, 2010b). Together, these data indicate a role for the mPFC in reward processes and suggest that drugs of abuse (including alcohol) can produce a dysregulation in the glutamatergic outputs from the mPFC, which may impair the ability of an individual to evaluate the risks and rewards of engaging in drug-taking behavior.

2.3.2. Nucleus Accumbens

The nucleus accumbens (NAc) is a key brain structure supporting the self-administration of alcohol and other drugs of abuse (Koob et al., 1998; Engleman et al., 2009). It is a mesocorticolimbic site that receives DA input, mainly from the VTA, but also from the substantia nigra (Noori et al., 2012). It has glutamatergic input from the mPFC and Amyg and has GABAergic efferent projections to the VTA and Amyg as well (see Figure 1). Administration of drugs of abuse and natural rewards elevate DA levels in the NAc and these elevations are associated with the incentive/motivation properties of these compounds (Hernandez et al., 2011; Phillips et al., 2008). Moreover, several drugs of abuse (Katner et al., 2011; McBride et al., 1999) including alcohol (Engleman et al., 2009) are self-administered directly into the NAc. In at least some cases, this behavior is dependent on DA-D1 and -D2 receptor function (McBride et al., 1999). Repeated moderate alcohol exposure via systemic administration (Smith and Weiss, 1999) or voluntary oral intake (Melendez et al., 2002; Thielen et al., 2004), increases extracellular DA levels in the NAc. These effects are thought to be mediated, in part, through a reduction in DA-D2 autoreceptor function in the NAc (Engleman et al., 2000, 2003; Thielen et al., 2004). Glutamate release in the NAc is enhanced during alcohol self-administration, and the increases are directly associated with increased motivation to consume alcohol (Li, et al., 2010). Moreover, these enhanced levels of glutamate may be due to altered glutamate transport/uptake (Melendez et al., 2005; Sari et al., 2011) and continue into protracted abstinence (Melendez et al., 2005). Alcohol self-administration is blocked by microinjections of LY279268, an mGluR2/3 agonist which reduces glutamate release (Besheer et al., 2010). Similarly, microinjections of an mGluR5 antagonist into the NAc also reduced alcohol self-administration (Besheer et al., 2010) as did antagonism of opioid receptors (June et al., 2004). Similar to findings in the mPFC, a CB1 receptor antagonist microinjected into the NAc blocks alcohol drinking in selectively bred high alcohol-consuming AA rats (Malinen and Hyytia, 2008). There is evidence that alcohol drinking or self-administration is mediated by GABA-A receptor activity in the NAc as well (Liu et al., 2011; June et al., 1998).

2.3.3. Ventral Tegmental Area

The VTA contains DA cell bodies which are the main source of DA in the mesocorticolimbic DA system. Activity in these neurons and their projection fields is thought to mediate various aspects of reward and the reinforcing properties of drugs of abuse including alcohol (Koob et al., 1998; McBride et al., 1999). The DA efferents from the VTA innervate many forebrain areas including the mPFC, NAc and Amyg (see Figure 1). The VTA also receives glutamatergic input from the Amyg and mPFC as well as receiving GABAergic input from the NAc (Ikemoto, 2007; see Figure 1). The posterior portion of the VTA in selectively bred high alcohol-consuming P rats supports the self-administration of cocaine (Rodd et al., 2005a) and alcohol (Rodd-Henricks et al., 2000a; Rodd et al., 2005b, 2005c).

This effect is dependent upon the activation of DA neurons and is sensitized after cycles of forced abstinence and re-exposure (Rodd et al., 2005b, 2005c). Alcohol drinking or self-infusion into the VTA has been found to be dependent on the activity of VTA-DA neurons (Nowak et al., 2000; Rodd et al., 2004c; Hauser et al., 2011); serotonergic (5-HT) 5-HT2A (Ding et al., 2009) and 5-HT3 (McBride et al., 2004; Engleman et al., 2008; Rodd et al., 2010) receptors, as well as GABA-A (Nowak et al., 1998; Eiler and June, 2007), mGluR5 (Bäckström et al., 2004), muscarinic ACh (Katner et al., 1997) and nicotinic ACh (Söderpalm

et al., 2009) neurotransmission in the VTA. Opioid (June et al., 2004) and cannabinoid-CB1 receptor antagonism in the VTA of selectively bred P and AA rats, respectively, also blocks alcohol intake (Malinen and Hyytia, 2008). A recent study from our laboratory suggests that chronic alcohol drinking may produce reduced extracellular DA levels in the VTA; which, in turn, may result in lower auto-feedback regulation of DA neurons and thus enhance DA output to mesocorticolimbic DA system projection areas (Engleman et al., 2011).

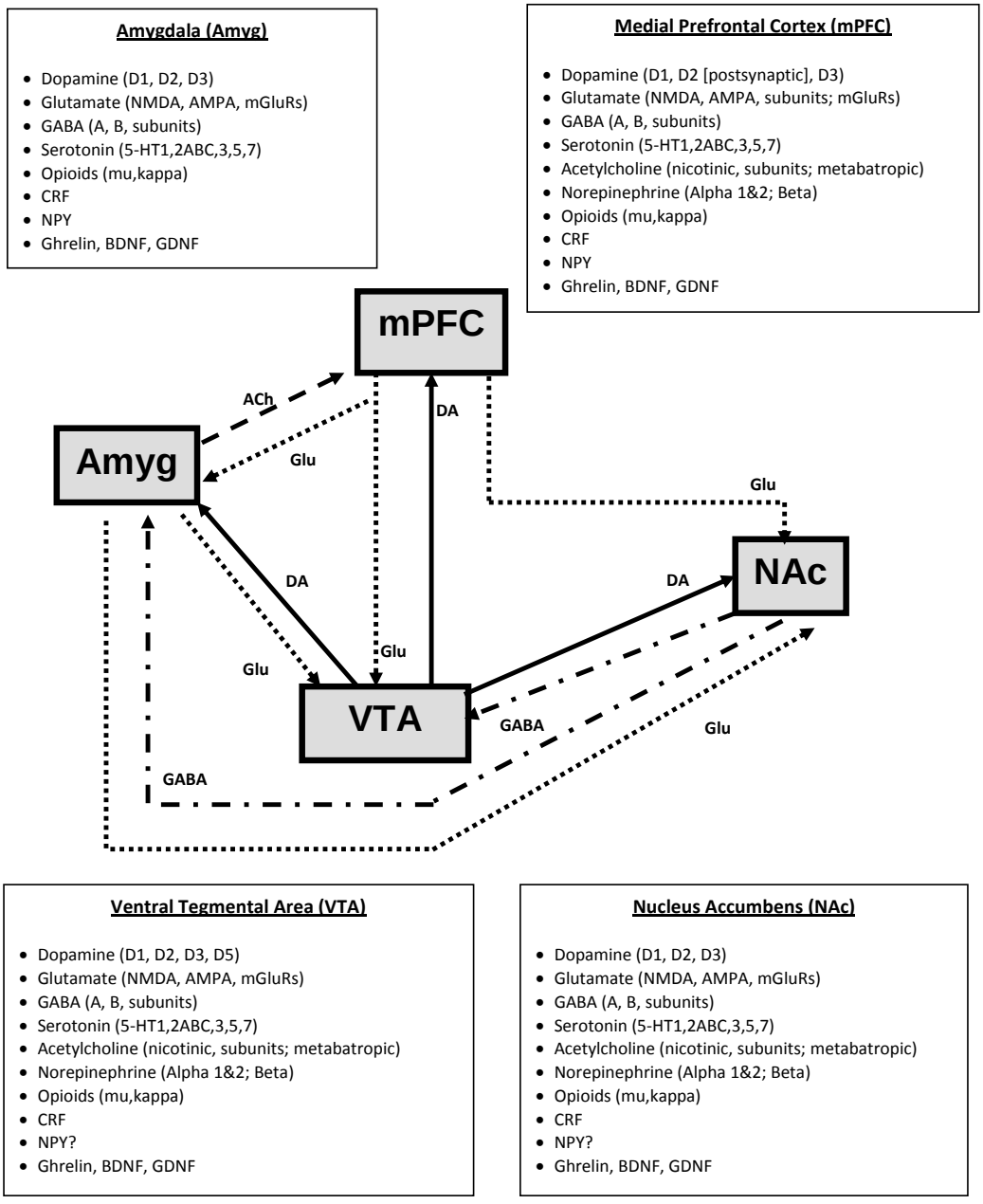


Figure 1. Key Subregions of the Mesocorticolimbic Dopamine System.

2.3.4. Amygdala

The Amyg is a brain structure that serves to integrate information regarding stress and emotional states, as well as modulate the anhedonic/aversive effects associated with drug dependence and withdrawal. Within the Amyg, the basolateral and central nuclei play major roles in addiction (McBride, 2002), in particular these nuclei promote the negative reinforcing properties of drugs during periods of withdrawal (Koob and Volkow, 2010). The Amyg is well connected with other structures in the mesocorticolimbic DA system and receives DA input from the VTA, GABA input from the NAc, and glutamate input from the mPFC (Ikemoto, 2007; Koob and Volkow, 2010; see Figure 1). Many neurotransmitter systems within the Amyg have been shown to play a role in addiction. For instance, glutamatergic receptors, in particular NMDA and AMPA, are thought to play key roles in the development of alcohol dependence (McCool et al., 2010). Similarly, activity of the GABA (Liu et al., 2011; Foster et al., 2004; Koob and Volkow 2010), corticotropin-releasing factor (CRF) (Koob and Volkow, 2010), neuropeptide Y (NPY) (Pandey et al., 2005; Gilpin et al., 2008; Zhang et al., 2010), substance P (SP) (Yang et al., 2009) and opioid (Foster et al., 2004) systems within the Amyg has been implicated in alcohol and drug dependence as well.

2.3.5. Other Brain Structures

Many brain structures outside the core mesocorticolimbic DA system structures also provide input and affect processing of reward-related stimuli. Some of these include: olfactory bulb, insula, caudate-putamen (striatum), septal region, bed nucleus of the stria terminalis, globus pallidus, hypothalamus, habenula, hippocampus, pedunculopontine nucleus, thalamus, subthalamic nucleus, substantia nigra, raphe nuclei, and the locus coeruleus (c.f., McBride, 2002; Noori et al., 2012; Spanagel, 2009).

3. USING SELECTIVELY BRED RATS TO INVESTIGATE THE NEUROBIOLOGY OF BINGE DRINKING

3.1. Usefulness of Selectively Bred Animal Models to Study Alcohol-Associated Effects

Animal models have been successfully used to investigate the treatment of psychiatric disorders and other medical conditions (e.g., Griffin, 2002; McKinney, 2001; Nestler and Hyman, 2010). An animal model has the advantage of allowing the experimenter to control characteristics of the animal's genetic background, environment and prior drug exposure. An animal model also permits the examination of neurobehavioral, neurochemical and neurophysiological correlates with the disorder being modeled. Despite reservations as to whether a valid animal model of alcoholism could be developed (Cicero, 1979), certain criteria for an animal model of alcoholism have been proposed (Cicero, 1979; Lester and Freed, 1973; McBride and Li, 1998). Briefly, these criteria are as follows: 1) the animal should orally self-administer alcohol; 2) the amount of alcohol consumed should result in pharmacologically relevant blood alcohol levels; 3) alcohol should be consumed for its post-ingestive pharmacological effects, and not strictly for its caloric value or taste; 4) alcohol should be positively reinforcing, in other words, the animals must be willing to work for

alcohol; 5) chronic alcohol consumption should lead to the expression of metabolic and/or functional tolerance; 6) chronic consumption of alcohol should lead to dependence, as indicated by withdrawal symptoms after access to alcohol is terminated; and 7) an animal model of alcoholism should display characteristics associated with relapse as well.

Selective breeding is a powerful genetic tool for studying the genetics of many alcohol-associated phenotypes (Crabbe, 2008). Compared to pure association studies such as genome-wide association studies (GWAS) and recombinant inbred lines (RILs), selective breeding from a heterogeneous outbred stock can make low frequency/rare alleles (minor allele frequency <0.05) more common (i.e., these rare alleles are captured within the respective high- or low-expressing line for the trait). Thus, selective breeding will result in phenotypic expression levels in the high and low lines that will greatly exceed the range found in the foundation stock from which they were selectively bred. Additionally, selective breeding for any phenotype, such as alcohol preference, is hypothesis driven and genetically correlated traits of the primary selected phenotype (presumably due to pleiotropic actions of genes: Crabbe et al., 1990) can be identified and studied. The alcohol-preferring P and high alcohol-drinking HAD (replicate 1 and 2) rat lines were selectively bred to prefer a 10% alcohol solution over water and consume greater than 5 g of alcohol/kg body weight/day (Bell et al., 2005, 2006b, 2012b; McBride and Li, 1998; Murphy et al., 2002). A substantial literature (reviewed in Bell et al., 2005, 2006b, 2012b; McBride and Li, 1998; Murphy et al., 2002) indicates that the alcohol-preferring P rat meets all, and the high alcohol-drinking HAD1 and HAD2 replicate rat lines meet most, of the existing adult criteria proposed for a valid animal model of alcoholism (Cicero, 1979; Lester and Freed, 1973; McBride and Li, 1998). Because alcohol binge-drinking is such a serious public health issue and often is directly associated with the development of alcohol abuse and dependence, its inclusion as a criterion for an animal model of alcoholism appears to be paramount.

3.2. Towards a Pre-Clinical Definition of Binge-Like Drinking

For the most part, the NIAAA (2004) definition of binge drinking as determined by the amount consumed, length of time spent drinking per incident, and peak BACs achieved has been widely accepted in the human literature. However, a clear definition of binge-exposure/drinking for animal studies has evolved much more slowly; and, for that matter, remains elusive even now. For example, a quick online literature (2010-2012) search of [binge and (alcohol or ethanol) and rat] revealed 34 studies (see Table 2). From this literature search, only 7 “binge” studies examined free-choice alcohol drinking, where water and food were freely available; 3 studies examined forced-choice alcohol liquid diet, where water and food were not freely available; 20 studies examined intragastric administration of alcohol; 2 studies examined intraperitoneal administration; and 1 report was an in vitro study of a cell line. The alcohol exposure in the vast majority of these studies resulted in peak BACs approximating 300 mg% (0.30 in clinical terms) and greater, which almost quadruples the NIAAA (2004) definitional threshold (80 mg%) for binge drinking. With this in mind and depending upon the research question examined, each of these model systems has certain strengths and weaknesses. Simpler methodology (i.e., experimenter-administered alcohol) is important in evaluating questions on the effects of alcohol binge-exposure as it pertains to molecular biology and neuropathology.

Table 2. Pre-clinical conception of binge, from an Ovid MEDLINE® search (2010-2012) of [binge and (alcohol or ethanol) and rat]

No. Studies	Alcohol Exposure	Description (X% = concentration of alcohol)
1	Free-choice 24 hr/7 days/week	HAD1 and HAD2 rats (15%)
3	Free-Choice 24 hr/3 days/week (M, W, F)	Intermittent access in outbred rats (20%)
1	Free-Choice 24 hr/3 days/week (M, W, F)	Intermittent access in outbred rats (beer)
2	DID-MSA 3 hr/day/5 days/week (M—F)	P rats (15%)
1	Operant (90 min/day)/ 5 days/week (M—F)	P rats (15%)
2	Liquid diet 24 hr/7 days/week	>300 mg%
1	Lieber-DeCarli 24 hr/7 days/week	4 weeks then IG 5g/kg
20	Alcohol Intragastric (IG, ~3x/day for 4 days)	2.75—6 g/kg/infusion
2	Alcohol Intraperitoneal (IP)	3 g/kg/injection
1	Alcohol in vitro (cell culture)	50—200 mM

Effects of binge-like exposure on these parameters may not be apparent following more subtle alcohol treatments, such as free-choice drinking. Because alcohol abuse and addiction are mediated by complex neurobiological, environmental and behavioral interactions; findings from experimenter-administered studies should be confirmed with methods that have greater face-validity, such as free-choice drinking. However, even research conducted with selectively bred high alcohol-consuming rats, which naturally consume significant amounts of alcohol, has its own limitations. For instance, the clinical literature indicates that a majority of adolescents and young adults experiment with alcohol, and many of these individuals also binge drink; but (a) most of these individuals do not become dependent upon alcohol and (b) only a subset of these individuals have a genetic predisposition (i.e., are FHP for alcoholism) to abuse alcohol. Nevertheless, many and possibly a majority of FHP, especially if FHP across multiple generations, individuals do (a) have an early onset of alcohol use; (b) engage in alcohol abuse, including binge and extreme drinking; (c) experience more problems associated with alcohol; and (d) become dependent upon alcohol more often and quicker, compared with FHN individuals that don't have this genetic predisposition. Thus, our laboratory uses these selectively bred animal models to investigate alcohol binge-drinking across peri-adolescence and adulthood.

3.3. Modeling Binge-Like Drinking and Its Consequences Using Alcohol Deprivation Effect Protocols

The first model of binge-like drinking established in our laboratory was based on protocols resulting in an alcohol deprivation effect (ADE). The ADE is a transient increase in alcohol consumption, above basal levels, displayed by animals when given free-choice access to alcohol after a period of forced abstinence (Sinclair and Senter, 1967). Our laboratory's standard protocol for examining the effects of an ADE include an initial 6 week free-choice (alcohol, water and food are all freely available) continuous (24 hours/day, 7days/week) access stage followed by cycles of 2 weeks of deprivation from and 2 weeks of re-exposure to alcohol access.

The ADE model was chosen because, upon re-exposure to alcohol access, BACs exceeding 80 mg% are readily achieved. Regarding the ADE, the P rat line has been the best rat line characterized under both home-cage and operant access conditions thus far (Engleman et al., 2011; Guccione et al., 2012; Hargreaves et al., 2011; McKinzie et al., 1998; Rodd et al., 2003, 2006; Rodd-Henricks et al., 2000d, 2001; Schroeder et al., 2005; Thielen et al., 2004; Toalston et al., 2008; Vengeliene et al., 2003; also see Bell et al., 2012b for review). Behaviorally, the P rat will display an increase in alcohol consumption that escalates in magnitude and duration (across days of re-exposure to alcohol) over repeated deprivation cycles (Figure 2). This pattern of escalation, associated with the ADE, in rats has led to its characterization as a model of relapse-like alcohol drinking/self-administration (Martin-Fardon and Weiss, 2013; Rodd et al., 2004b; Spanagel and Holter, 1999). The high alcohol-drinking rat lines (replicates HAD1 and HAD2) also display a robust ADE when multiple concentrations of ethanol are made available and/or multiple deprivations are experienced (Oster et al., 2006; Rodd et al., 2008; Rodd-Henricks et al., 2000c).

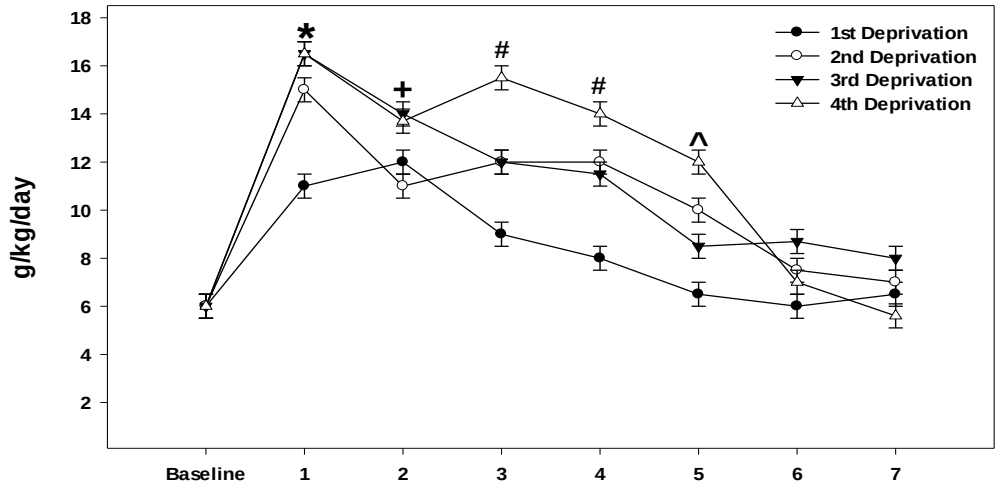


Figure 2. The mean (±SEM) alcohol consumed (g/kg/day) by P rats (n =9 per group) under 24-hr free-choice conditions. The rats had continuous access to multiple concentrations of alcohol (10%, 20%, 30%, vol/vol, available concurrently) for 6 weeks. Food and water were available ad libitum. The original 6-week access period was followed by 4 cycles of deprivation from and re-exposure to alcohol access. The data reflect a 3-day baseline (the 3 days before each deprivation period) and the first 7 days of re-exposure to alcohol access following each deprivation period. *, $p<0.05$, alcohol intake on the 1st day of re-exposure exceeded that of each baseline and 1st day alcohol intakes following the 2nd through 4th deprivation periods exceeded the 1st day alcohol intake following the 1st deprivation period. +, $p < 0.05$, 2nd day alcohol intakes exceeded that of their respective baselines, but did not differ from each other. #, $p< 0.05$, 3rd as well as 4th day alcohol intakes exceeded their respective baselines and 3rd as well as 4th day alcohol intakes following the 4th deprivation period exceeded 4th day alcohol intakes following the 1st through 3rd deprivation periods. ^, $p < 0.05$, 5th day alcohol intakes following the 2nd through 4th deprivation periods exceeded their respective baselines; although alcohol intakes following the 2nd and 3rd deprivation periods did not differ from each other, alcohol intake following the 4th deprivation period significantly exceeded alcohol intakes following the 2nd and 3rd deprivation periods (adapted from Rodd-Henricks et al., 2001).

It is noteworthy that even rat lines selectively bred to avoid alcohol (i.e., the alcohol-nonpreferring NP and low alcohol-drinking replicates LAD1 and LAD2) will display a significant escalation in alcohol intake across a multiple deprivation ADE protocol (Bell et al., 2004). Adaptive changes in DA neurotransmission are thought to be associated with the transition from heavy drinking to alcohol dependence (Koob et al., 1998). Previous work from our laboratory showed that adult P rats receiving 24 hours free-choice access to alcohol for eight weeks, with or without 2-weeks of alcohol deprivation (i.e., forced abstinence/detoxification), resulted in elevated extracellular levels of DA in the NAc (Thielen et al., 2004). This parallels findings of elevated DA levels in the NAc induced by daily scheduled alcohol access sessions (1 hr/day) in adult P rats (Engleman et al., 2000, 2003) or peripheral administration of alcohol in adult rats (Smith and Weiss, 1999; Franklin et al., 2009). These increased extracellular levels of DA in the NAc may be due to dysregulated auto-regulatory feedback from the NAc to the VTA, and/or functional or physiological down-regulation of presynaptic DA-D2 autoreceptors, which normally reduce the release of DA (Engleman et al., 2000, 2003; Thielen et al., 2004). Although these studies indicated that the observed elevations in DA were likely due to changes in release rather than clearance (Engleman et al., 2000, 2003; Thielen et al., 2004), other studies have shown that animal self-administration of alcohol can up-regulate DA transporter (DAT) activity in the NAc (Carroll et al., 2006; Sahr et al., 2004), whereas experimenter-administered alcohol does not appear to alter DAT function in the NAc (Badanich et al., 2007). The latter two studies were conducted in peri-adolescent animals (P and outbred albino rats) and the Carroll et al. (2006) study was conducted in adult animals (HAD1 rats).

In an early study, Engleman and colleagues (2002) examined the effects of alcohol deprivation length on DA efflux in the NAc. P rats had access to multiple concentrations of alcohol (18% and 44% available concurrently with water and food). A water control group received water as its only fluid throughout the study.

The other four groups received free-choice access to alcohol in their home cages according to the schedules illustrated in Table 3. Briefly, the groups were: Nondeprived (ND); one two-week deprivation (1DP2W); one eight-week deprivation 1DP8W; four two-week deprivations (4DP2W). At the end of the respective access periods, extracellular levels of DA were determined by no-net-flux microdialysis. The results (Figure 3) revealed that non-deprived rats displayed reduced extracellular DA levels in the NAc and the deprivation interval of 6 weeks resulted in an even greater reduction in DA levels than that seen after 2 weeks of deprivation. It is noteworthy that in other studies where elevations of DA in the NAc have been reported (Engleman et al., 2000, 2003; Thielen et al., 2004) peak alcohol intakes approximated 1 g/kg/1 hr session to 5g/kg/day and the studies lasted 4-6 weeks, and 8 weeks, respectively.

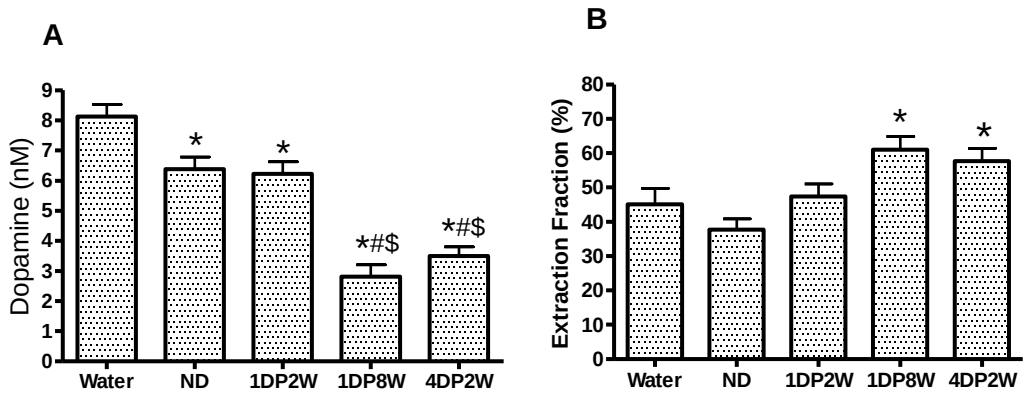
In the study by Engleman and colleagues (2002), the nondeprived group consumed approximately 8 g/kg/day, whereas the group experiencing four 2-week deprivation intervals displayed peak alcohol intakes approaching 15 g/kg/day. Therefore, one possibility for the disparate findings (decreased DA efflux in the NAc reported by Engleman et al., 2002 vs. increased DA efflux in the NAc reported by Engleman et al., 2000, 2003; Thielen et al., 2004) is due to greater levels of alcohol intake, longer periods of alcohol access and possibly greater dependence. Although dependence was not assessed in any of these studies, there is evidence that P rats display signs of alcohol dependence after chronic free-choice alcohol drinking (Kampov-Polevoy et al., 2000; Waller et al., 1982).

Table 3. Alcohol drinking protocol used in Engleman et al. (2002) for assessing adaptive changes in extracellular dopamine in the NAc using quantitative microdialysis.

A Water group received water as its only fluid throughout the study. The other four groups always had water and received free-choice access in the home cage to 18 and 44% (v/v) alcohol according to the schedules illustrated in the timeline above. The groups were: Nondeprived (ND); one two-week deprivation (1DP2W); one eight-week deprivation 1DP8W; four two-week deprivations (4DP2W). At the end of the respective access periods, extracellular levels of dopamine (DA) were determined by no-net-flux microdialysis.

Regarding DAergic receptor changes, one study (Sari et al., 2006) examined the effects of continuous access to alcohol (15% and 30%) for 14 weeks vs. alcohol access for 6 weeks followed by 2 cycles of 2 weeks of deprivation from and 2 weeks of re-exposure to alcohol access (repeated ADE) vs. alcohol naïve adult male inbred P (iP) rats on DA-D1 and -D2 receptor expressions levels in the extended Amyg (NAc and Amyg nuclei). These authors found that D1 receptor expression levels were increased in the anterior NAc core in both the repeatedly deprived and continuous access animals along with increases in the lateral and intercalated Amyg in the repeatedly deprived animals only. D2 receptor expression levels were increased in both the anterior NAc core and shell in both repeatedly deprived and continuous access animals.

These findings indicate that there may be differential effects of alcohol which are dependent upon the presence or absence of deprivation intervals (i.e., repeated detoxifications). In addition, pharmacological evidence indicates that the serotonergic (5-HT) and glutamatergic systems also modulate the ADE. For instance, peripheral administration of antagonists, MDL 72222 and ICS 205-930, of the 5-HT3 receptor interfere with the ADE in P rats (Rodd-Henricks et al., 2000b). Regarding the glutamatergic system, peripheral administration of LY404039, an antagonist of the metabotropic glutamate 2/3 receptor (mGluR2/3) subtype, significantly reduces the operant ADE displayed by P rats (Rodd et al., 2006).



The access to multiple alcohol concentrations produced high average levels of alcohol intake (greater than 8 g/kg/day). Analysis showed that there were no differences in alcohol intake for any groups receiving alcohol access prior to any deprivation. A multiple regression analysis of the DA levels in the no-net-flux experiment (DAin plotted against DAout: DAout subtracted from DAin) provided regression lines for each treatment group. Panel A shows that extracellular DA levels significantly decreased in all of the treatment groups compared with the water only group [Overall DA concentration X group interaction effect: $F(4,404) = 19.60$; $p < 0.0001$]. The 1DP2W group that only received one 2 week period of alcohol deprivation was not significantly different from the ND group ($p = 0.63$). However, rats receiving 8 weeks total of alcohol deprivation, with or without periods of alcohol re-exposure (the 1DP8W and 4DP2W groups), showed further reductions in extracellular DA levels that were significantly lower than rats in the ND group ($p < 0.0001$). Panel B shows that the DA extraction fraction (which is an indication of clearance; i.e., DAT activity) was elevated in the 1DP8W and 4DP2W groups compared with the Water group. * = different from Water ($p < 0.05$); # = different from ND ($p < 0.05$); $ = different from 1DP2W ($p < 0.05$) (Adapted from Engleman et al., 2002).

Figure 3. Effects of excessive alcohol drinking and forced abstinence on extracellular levels of dopamine (DA) in the NAc.

In addition, a potent noncompetitive antagonist of the mGluR5 subtype, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), reduces both alcohol-seeking behavior and the ADE in rats (Backstrom et al., 2004). The glutamatergic N-methyl-D-aspartate (NMDA) receptor has also been implicated with antagonists, including ifenprodil which has selectivity for the NMDA-2B subunit containing receptor (NR2B), disrupting the ADE in albino rats (Vengeliene et al., 2005). Multiple peptide systems have been pharmacologically implicated in the expression of the ADE as well.

The opioid system has been implicated, such that peripheral administrations of both naltrexone, a pan-opioid receptor antagonist, and LY255582, a selective mu-opioid receptor antagonist, disrupt the operant ADE displayed by P rats (Dhaher et al., 2012b). Similarly, there is evidence that the orexin system is involved in the expression of the ADE, since peripheral administration of SB-334867, an orexin-1 receptor antagonist, attenuates this behavior in P rats (Dhaher et al., 2010). In addition, neuropeptide Y (NPY) has been linked to the ADE since central [intracerebroventricular (ICV) and CeA] administration of this peptide interferes with the expression of an ADE by P rats (Bertholomey et al., 2011; Gilpin et al., 2008).

3.4. Modeling Binge-Like Drinking and Its Consequences Using Episodic Alcohol Access

A subsequent animal model of binge-like alcohol intake incorporated shorter periods, than that used for the ADE, of alcohol access and forced abstinence. In this intermittent alcohol access model, rats are given free-choice access to alcohol for an initial 8 days followed by cycles of 4 days of deprivation from and 4 days of re-exposure to alcohol access. One study examining this protocol in male and female, adult, high alcohol-consuming rats (P, HAD1 and HAD2) found an escalation in alcohol intake which peaked after the 3rd deprivation interval (Bell et al., 2008). These authors also reported that an ADE, relative to initial levels of intake, was expressed by both HAD lines but not by the P line of rats. In addition, the control group which had uninterrupted free-choice access to alcohol also escalated their alcohol intake, which matched intakes of rats, of all 3 lines, experiencing episodic access after the 4th deprivation interval.

This "episodic" protocol was modified slightly to examine changes in glutamatergic receptor-subunit-associated protein levels in the extended Amyg (NAc and Amyg nuclei) of adult P rats (Obara et al., 2009). Three groups of P rats were run: group (1) remained alcohol-naïve throughout the experiment, group (2) had uninterrupted free-choice access to alcohol for 6 months, and group (3) had free-choice access to alcohol 4 days/week for 6 months. After the 6 months of alcohol-drinking, half of the animals from each group were sacrificed after 24-hrs and half of the animals were sacrificed after 4 weeks. Overall, the findings (see Table 4, adapted from Obara et al., 2009) indicated that there are differential effects on glutamatergic receptor-associated proteins within the extended Amyg following either continuous or episodic alcohol access as well as following either a 24-hr or 4-week final deprivation period.

Table 4. Summary of the findings examining the effects of either episodic (EA: 4 days/week) or continuous (CA: 7 days/week) alcohol (15% and 30% concurrently with water and food) access on Homer and glutamate receptor-associated protein expression levels in the NAc shell (NACsh) and core (NACc) as well as expression levels in the central nucleus (CeA) of the Amyg of adult P rats following a final short-term (24 hr) withdrawal (SW) or long-term (4 weeks) withdrawal (LW) period

	Homer2a/b		mGluR1		mGluR5		NR2a		NR2b	
	EA	CA	EA	CA	EA	CA	EA	CA	EA	CA
NACsh	nc	nc	nc	nc	nc	nc	+sw, lw	nc	-sw, lw	-sw
NACc	+sw	+sw, lw	+sw	+sw	+sw, lw	+sw	+sw	+sw	+sw	+sw
CeA	+sw, lw	+sw, lw	+sw	+sw	+sw	nc	+sw	+sw	+sw, lw	+sw, lw

+, indicates significant ($p < 0.05$) increase in the level of protein relative to alcohol-naïve animals;
-, indicates a significant ($p < 0.05$) decrease in the level of protein relative to alcohol-naïve animals;
"nc" indicates no change relative to alcohol-naïve animals; "nd" indicates the protein was not detected;
sw, indicates significant ($p < 0.05$) changes detected after the short-term withdrawal (24 hrs) period;
lw, indicates significant ($p < 0.05$) changes detected after the long-term withdrawal (4 weeks) period.

3.5. Modeling Binge-Like Drinking and Its Consequences Using an Alcohol Drinking-in-the-Dark—Multiple-Scheduled-Access Procedure

The most recent model of binge-like drinking used by our laboratory is the drinking-in-the-dark—multiple-scheduled-access (DID-MSA) procedure (e.g., Bell et al., 2006a, 2006b, 2009, 2011; McBride et al., 2010). This procedure parallels the DID procedure used in mice to model alcohol binge drinking (e.g., Boehm et al., 2008; Crabbe et al., 2009; Lyons et al., 2008; Moore and Boehm, 2009; Navarro et al., 2009; Rhodes et al., 2005). Again, the focus of this review is on rat animal models because a discussion on mouse animal models is beyond the scope of this paper. The DID-MSA protocol used by our laboratory involves giving selectively bred (P and HAD) rats multiple scheduled 1-hr access sessions to two concentrations of alcohol (15% and 30%) during the animals' active period (the dark-/nocturnal-cycle/phase). As with all of our procedures, water and food are freely available ad libitum. The initial session is initiated at the beginning of the dark cycle, with each session (between 2 and 4 each day) being separated by 2 to 5 hours. Note that the initiation of the first session in the DID rat model differs from that used in the DID mouse model. Early work on the DID procedure in mice indicated that maximal ethanol intake required initiating the procedure 2 to 4 hours into the dark cycle (Rhodes et al., 2005), whereas, in P rats, maximal intake requires the first session to be initiated at the beginning of the dark cycle (Bell et al., 2006b). DID-MSA access is available 5 days a week, with the animals experiencing a 2 day deprivation interval each weekend.

Regarding validation of the model, our laboratory has shown that this model results in alcohol drinking behavior yielding BACs greater than 80 mg% [the threshold BAC in NIAAA's (2004) definition for binge drinking] and motor impairment as a measure of intoxication (Bell et al., 2006b, 2011). These benchmarks were achieved in both peri-adolescent and adult P rats of both sexes. Moreover, Bell and colleagues (2011) reported that whereas adult P rats, of both sexes, given continuous access consumed more alcohol than those given binge-like access; the reverse was true for peri-adolescent P rats, of both sexes, with binge-like access animals consuming significantly more than their continuous access counterparts each day. The latter finding provides some "face" validity for this developmental alcohol binge-drinking model, such that peri-adolescent rats consumed more alcohol than their adult counterparts both in terms of total consumption per day and consumption per one hr access period. It is noteworthy, that an examination of the 24-hr alcohol drinking behavior of P (Bell et al., 2006c) and HAD (Dhaher et al., 2012a) rats has revealed that both rat lines display repeated 6-min bouts of alcohol intake, across each 24-hr period, that exceed 1.0 g of alcohol/kg body weight/6-min bout. These levels of alcohol intake within this relatively short time span result in BACs approximating 80 mg% or greater. However, under 24-hr access conditions the timing of these bouts of alcohol drinking varies from day-to-day. Therefore, to repeatedly capture these levels of alcohol intake we use the DID-MSA procedure, with 60% of the alcohol drinking occurring within the first 6-min and over 95% of the alcohol drinking occurring within the first 12-min of each 1-hr session (Bell et al., 2006b).

An early study using the DID-MSA procedure examined protein expression changes in the NAc and Amyg after six-and-a-half weeks of DID-MSA (4 sessions/day) binge (rats consumed ~ 5 g of alcohol/kg body weight/day) vs. continuous alcohol (rats consumed ~ 5 g of alcohol/ kg body weight/day) drinking vs. alcohol-naïve adult male inbred P (iP) rats (Bell et al., 2006a). These authors reported three key findings: first, DID-MSA altered expression

levels for 12 of the 14 identified proteins in the NAc, compared with controls; second, continuous access changed expression levels for 22 of the 27 identified proteins in the Amyg, compared with controls; and, third, 86% of the proteins that changed in the NAc showed greater expression levels vs. controls, whereas 58% of the proteins that changed in the Amyg displayed reduced levels of expression vs. controls. These results indicate brain-region specific effects contingent upon the presence or absence of multiple deprivation (i.e., detoxification) intervals. The identified proteins could be grouped into biological categories associated with intracellular chaperones, cytoskeleton/synaptic plasticity, intracellular communication, membrane transport, metabolism, energy production and neurotransmission. Of the neurotransmitter systems mediating alcohol abuse and dependence within the mesocorticolimbic DA system, the protein expression changes observed in this study implicated the neurosteroid/GABAergic system to the greatest degree.

A second study using the DID-MSA procedure examined gene expression changes in the NAc after 8 weeks of DID-MSA (3 sessions/day) binge (rats consumed ~ 6.5 g of alcohol/kg body weight/day) vs. continuous alcohol (rats consumed ~ 9.5 g of alcohol/kg body weight/day) drinking vs. alcohol-naïve adult male P rats (Bell et al., 2009). Unexpectedly, when the whole NAc (see McBride et al., 2010) was examined the only group that displayed significant differences from the controls was the continuous access group (i.e., the gene expression levels in the NAc of the binge-drinking group did not differ significantly from that observed in the control group). Gene Ontology (GO) analyses revealed over representation of significantly changed genes in 20 GO categories of biological function. These GO categories included negative regulation of protein kinase activity, anti-apoptosis, and regulation of G-protein-coupled receptor signaling.

Ingenuity® pathway analyses indicated a network of transcription factors including the *Fos, Jun, Junb* oncogenes, which suggests chronic alcohol drinking increased neuronal activity in the NAc. Several neurotransmitter-associated genes implicated in alcohol abuse and dependence were also altered within the NAc, including activity regulated cytoskeletal-associated protein [ARC which is associated with brain derived neurotrophic factor (BDNF) and neuropeptide Y (NPY) activity]; cholinergic receptor, nicotinic, alpha polypeptide 7 (*Chrna7*), which modulates glutamatergic and DAergic activity within the mesocorticolimbic DA system; corticotrophin releasing hormone (CRF), which is implicated in the negative reinforcing properties of alcohol during withdrawal, craving and relapse; and Homer homolog 1 (*Homer1*), which serves as a glutamatergic receptor-associated scaffolding/membrane-docking protein.

A third study using the DID-MSA procedure examined gene expression changes in the NAc shell and central nucleus of the Amyg after 8 weeks of DID-MSA (3 sessions/day) binge (rats consumed ~ 5 g of alcohol/kg body weight/day) drinking vs. alcohol-naïve adult male P rats (McBride et al., 2010). These authors reported that there were significantly more genes up-regulated than down-regulated by alcohol binge drinking. Ingenuity Pathway Analysis of gene changes in the NAc shell revealed one biological pathway that included cytoskeletal-, calmodulin- and glutamate receptor-associated genes. The findings indicated that binge-like alcohol drinking by P rats produced region-specific changes in gene expression levels, with biological functions associated with transcription, synaptic function and neuronal plasticity implicated. Moreover, similar to the findings in the proteomics study (Bell et al., 2006a), different mechanisms may underlie alterations in these biological functions, because very few genes that displayed significant changes in expression were common to both the NAc shell

and the central nucleus of the Amyg. Combined, these studies indicate that binge-like alcohol drinking by P rats alters neuronal activity within brain structures of the mesocorticolimbic DA system and the associated extended Amyg. These changes involve physiological alterations in the glutamatergic, DAergic and GABAergic neurotransmitter systems corroborating other research implicating these neurotransmitter systems in the development of alcohol abuse and dependence as well as binge drinking. These neurobiological findings as well as the pharmacological treatments discussed above, and elsewhere (e.g., Bell et al., 2012b) parallel other reports in the alcohol abuse and dependence literature using mice and nonhuman primates as well as human subjects. Overall, the results support the conceptualization that binge alcohol drinking (or drug intake) is part of the addiction process and is mediated by similar neurocircuitry as that seen in alcohol (or drug) abuse and dependence.

CONCLUSION

Alcohol abuse, especially binge drinking, and dependence continue to be serious public health concerns. Adolescents and young adults are particularly vulnerable to the cognitive as well as emotional disruptive effects of alcohol and are prone to engage in binge drinking. Binge alcohol drinking appears to be a developmental phenomenon with the majority of this type of drinking occurring during adolescence and young adulthood. Early onset of alcohol use, usually in the form of binge drinking, markedly increases the probability of developing alcohol dependence during one's life-time.

Within the context of addiction, the progression from casual alcohol drinking to dependence is incremental and cyclical in nature. Early in the addiction cycle alcohol drinking is impulsive and binge-like, with the positive reinforcing/hedonic properties of alcohol driving the process. During the later stages of addiction alcohol drinking is compulsive and appears to be driven by the negative reinforcing/anhedonia and anxiety reducing effects of alcohol. The addiction cycle is marked by escalation of intake overtime, which is exacerbated by repeated cycles of abstinence and relapse. However, progress through the addiction cycle is not linear, with many individuals returning to earlier stages of the cycle before progressing to full-blown dependence.

Definitionally, escalation of alcohol or, for that matter, any drug or reinforcer, intake is a primary characteristic of binge drinking or self-administration. The present clinical definition of binge alcohol drinking identifies individuals who consume at least 4 or 5, for women and men respectively, standard alcoholic drinks within 2-hrs, and this drinking results in BACs of 80 mg% (0.08 in clinical terms) or greater as well as the expression of overt intoxication at least once in a set period of time (usually 2 weeks). A preclinical definition of binge alcohol exposure is still evolving. At this point, the primary preclinical characteristic is alcohol exposure that results in BACs greater than 80 mg%. Most preclinical models of binge alcohol exposure result in BACs that approximate 300 mg% or greater. In humans, BACs of 200 mg% or greater are readily achieved during extreme drinking (which is, perhaps unfortunately, often characterized as binge drinking in the clinical literature), such as celebrating ones 21st birthday in the United States. This type of drinking clearly results in the

development of tolerance to alcohol's effects, which is a diagnostic criterion for alcohol abuse and dependence.

Findings from the existing clinical research on the effects of binge alcohol drinking indicate that many of the cognitive and emotional disruptive effects of alcohol seen in binge drinkers are also seen in alcoholics who have experienced multiple detoxifications. Therefore, many of the preclinical (and clinical) findings on the neurobiology of alcohol abuse and dependence appear to be relevant for research on the antecedents and consequences of binge drinking. Neurobiological evidence indicates that alcohol, and drug, abuse is mediated by the mesocorticolimbic DA system, which includes the VTA, NAc, mPFC and Amyg. These key brain regions are highly interconnected and are essential in the acquisition and valuation of rewards, including natural reinforcers such as food and sex. Within these brain regions, a number of neurotransmitter systems including glutamate, GABA, DA, serotonin, acetylcholine, opioids, NPY and ghrelin mediate (a) the acquisition of, (b) the maintenance of, and (c) relapse to alcohol drinking and abuse. Moreover, these neurotransmitter systems and their associated neurocircuitry are altered by both acute and chronic exposure to alcohol.

From the preclinical perspective, animal models have been essential in determining the neurobiological antecedents and consequences of alcohol abuse and dependence. In particular, selectively bred rat lines have been shown to be valid animal model systems for studying this neurobiology. In general, the selectively bred alcohol-preferring P and high alcohol-drinking HAD1 and HAD2 meet all or most, respectively, of the criteria proposed for valid animal models of alcoholism. These lines of rats display binge-like alcohol drinking under (a) free-choice, 24-hr access; (b) ADE/relapse-like access; (c) both home-cage and operant chamber, limited access; and (d) DID-multiple scheduled access conditions; such that these protocols result in BACs that exceed 80 mg% and rats often displaying overt intoxication.

Moreover, binge-like alcohol drinking is displayed by both peri-adolescent and adult as well as male and female rats from these selectively bred lines. Genomic [messenger-ribonucleic acid (mRNA) levels detected by microarray and reverse transcription-polymerase chain reaction (RT-PCR)] and proteomic (protein levels detected by 2-dimensional gel electrophoresis and Western blots) studies using these binge-drinking protocols have provided evidence that the GABAergic (including neurosteroid), glutamatergic, DAergic, serotonergic, and cholinergic neurotransmitter systems within multiple brain regions of the mesocorticolimbic system mediate this type of drinking behavior. In vivo microdialysis studies targeting subregions of the mesocorticolimbic system of P rats that have experienced these binge-drinking protocols has confirmed a role for the glutamatergic, DAergic and serotonergic systems in this behavior. Pharmacological studies using ligands targeting the above neurotransmitter systems as well as neuropeptide systems discussed in this chapter have provided even further evidence that these neurotransmitter and neuropeptide systems mediate, at least in part, binge alcohol-drinking and its effects. In conclusion, these findings support current theories on the role of neurotransmission in the mesocorticolimbic system and the associated extended amygdala as it pertains to binge drinking, alcohol abuse and dependence. While this research has provided possible pharmacological targets for the treatment of alcohol abuse and dependence, further research is needed to develop greater resolution in determining small-molecule/drugable targets. Towards this end, these selectively bred rat lines and associated alcohol drinking protocols will continue to play a crucial role in this research.

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