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A Genetic Animal Model of Alcoholism for Screening Medications to Treat Addiction

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Abstract

The purpose of this review is to present up-to-date pharmacological, genetic and behavioral findings from the alcohol-preferring P rat and summarize similar past work. Behaviorally, the focus will be on how the P rat meets criteria put forth for a valid animal model of alcoholism with a highlight on its use as an animal model of polysubstance abuse, including alcohol, nicotine and psychostimulants. Pharmacologically and genetically, the focus will be on the neurotransmitter and neuropeptide systems that have received the most attention: cholinergic, dopaminergic, GABAergic, glutamatergic, serotonergic, noradrenergic, corticotrophin releasing hormone, opioid, and neuropeptide Y. Herein we sought to place the P rat's behavioral and neurochemical phenotypes, and to some extent its genotype, in the context of the clinical literature. After reviewing the findings thus far, this paper discusses future directions for expanding the use of this genetic animal model of alcoholism to identify molecular targets for treating drug addiction in general.

Keywords

Animal models; alcohol; drug addiction; dependence; pharmacogenetics; pharmacogenomics; CNS neurotransmitters; proteomics; selective breeding; genomics; family history; predisposition

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1. Alcohol Abuse and Dependence

Over half of adult Americans have a family member with an alcohol abuse or dependence disorder [alcohol use disorder (AUD)], although only a subset of these individuals have this across multiple generations [Research Society on Alcoholism (RSA), 2009, 2015]. Moreover, approximately 1 in 4 Americans have had an AUD during their lifetime (RSA, 2009, 2015). The repercussions of AUDs cost the US economy nearly a quarter of a trillion dollars per year (RSA, 2015). Much of this is in health care costs, with AUDs being the third leading cause of preventable death according to the Centers for Disease Control and Prevention (CDC, Mokdad, Marks, Stroup, Gerberding, 2004; also see Johnson, 2010) and a causal relationship has been established between AUDs and at least 50 different medical conditions (Reed, Page, Viken, Christian, 1996; Rehm, 2011; Rehm et al., 2003).

Alcohol dependence is a chronic, progressive, relapsing disorder that advances in stages from experimentation to dependence (Heilig & Egli, 2006;Jupp & Lawrence, 2010; Koob, 2009; Koob & LeMoal, 2008; Koob & Volkow, 2010; Spanagel, 2009; Volkow & Li, 2005). During the experimentation stage, the individual experiences the rewarding, euphoric and positive-reinforcing effects of alcohol consumption. These positive reinforcing effects are often associated with acute increases in motor and autonomic (e.g., heart rate) activity as well as pro-social behavior and are generally perceived, by the individual, as euphoric (i.e., pleasant). This learning process results in positive reinforcement; which increases the probability, frequency and magnitude of subsequent drinking behavior. However, with continued usage the individual experiences an increase in the magnitude, duration and/or frequency of dysphoria (as opposed to euphoria), such as anxiety, during periods without access to alcohol. These dysphoric effects can be physiological in nature (e.g., hangover, hyperthermia, tachycardia, etc.) or associated with behavioral sequelae, such as getting arrested for driving while intoxicated. Moreover, given this increase in dysphoria, the individual often seeks to relieve this state by returning to drinking alcohol, often to excess. Therefore, during the early stages of the disease positive reinforcement generally predominates, whereas during the later stages of the disease negative reinforcement predominates (Koob, Arends, & Le Moal, 2014; Koob, Buck et al., 2014).

Fundamentally, reinforcement results in an increase in behavior and its associated cognitive processes. Thus, increases in approach behavior are associated with positive reinforcement during initial stages of the disease, whereas increases in retreat or avoidance behavior (e.g., consuming alcohol upon waking to counter hangover effects) are associated with negative reinforcement during later stages of the disease. The roles of positive-reinforcement vs negative-reinforcement can also be characterized in terms of impulsive vs compulsive alcohol drinking (Koob, Arends, & Le Moal, 2014; Koob, Buck, et al., 2014; Koob & Le Moal, 2006; Koob & Le Moal, 2008). Within this construct, impulsive drinking leads to, and is associated with, binge drinking and intoxication (e.g., Gray & MacKillop, 2014; Hamilton, Felton, Risco, Lejuez, MacPherson, 2014; but see Irimia et al., 2013). However after chronic usage, impulsive drinking, during which an individual will putatively have some volitional control, will be replaced by compulsive drinking to mitigate physical and behavioral withdrawal from alcohol. This, in turn, leads to a preoccupation with, and an anticipation of, future alcohol consumption during alcohol withdrawal (Koob & Le Moal,

2008). Therefore, impulsive drinking and positive reinforcement predominate in the early stages of alcohol dependence, whereas compulsive drinking and negative reinforcement predominate in later stages of addiction (Koob, Arends, & Le Moal, 2014; Koob, Buck, et al., 2014; Koob & Le Moal, 2006; Koob & Le Moal, 2008). However, despite this general trend of cycles of active drinking and relapse, with a concomitant increase in alcohol, or drugs of abuse, intake and the development of tolerance to the effects of alcohol, or drugs of abuse; the progression of the disease is not necessarily linear, such that the frequency and/or duration a person experiences these cycles differs across individuals (e.g., Barker & Taylor, 2014; Mackenzie, El-Gabalaway, Chou, & Sareen, 2014; Sartor, Kranzler, & Gelernter, 2014; van Rizen & Dishion, 2014). Moreover, not all individuals who abuse alcohol, or drugs of abuse, need formal treatment to reduce or stop their excessive intake. For instance, many individuals who abused alcohol during their adolescence and emerging adulthood do not develop alcohol dependence.

Nevertheless, many individuals who abused alcohol during adolescence and emerging adulthood do develop alcohol dependence either during this developmental stage or later in life. Because of this, there is a strong emphasis to study the acute and long-term effects of alcohol and/or drug abuse during the peri-adolescent developmental window (i.e., juvenile to emerging adulthood) (e.g., Bell, Franklin, Hauser, & Engleman, 2013; Gulley and Juraska, 2013; Spear, 2010, 2014; Witt, 1994, 2006, 2010). According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2012), 11% of all alcohol consumed in the U.S. is done so by 12 to 20 year olds and 90% of this drinking is in the form of binges. Additionaly, about a third of high school seniors report binge drinking during high school and ~75% of college students report binge drinking (Johnston, O'Malley, & Bachman, 1999). For ~30% of male college students (Wechsler, Lee, Kuo, & Lee, 2000; White, Kraus, & Swartzwelder, 2006), this behavior continues into college and the magnitude of these binges often exceeds, by to 2- to 3-fold, threshold consumption levels [5 drinks in one sitting resulting in blood alcohol concentrations (BACs) of 80 mg% or higher] put forth in NIAAA's definition of binge drinking (NIAAA National Advisory Council, 2004). Thus, binge drinking during peri-adolescence has become a serious public health concern, with research indicating it is a strong predictor of future alcohol-related problems in North America (Dawson, Grant, Stinson, & Chou, 2004; Johnston, O'Malley, Bachman, & Schulenberg, 2008; Kuntsche, Rehm, & Gmel, 2004; Presley, Meilman, & Lyerla, 1994; Wechsler et al., 2000; White et al., 2006).

Other predictors of AUDs as well as their epidemiological antecedents and trajectory are the pattern of drinking (e.g., social vs binge vs continuous) and amount consumed (Flory, Lynam, Milich, Leukefield, & Clayton, 2004; Heather, Tebbutt, Mattick, & Zamir, 1993; Lancaster, 1994; Shield, Rehm, Gmel, Rehm, & Allamani, 2013; Zucker, 1995). Characterization of these predictors and their antecedents has led to the development of different typologies and/or drinking profiles as well as subcategories of severity associated with a diagnosis of an AUD in the Diagnostic and Statistical Manual of Mental Disorders, 4th and 5th Editions (DSM-4, DSM-TR-4 and DSM-5, American Psychiatric Association, 1994, 2000, 2013; Babor et al., 1992; Cloninger, 1987; Conrod, Pihl, Stewart, & Dongier, 2000; Epstein, Kahler, McCrady, Lewis, & Lewis, 1995; Lesch & Walter 1996; Moss, Chen, & Yi, 2007; Prelipceanu & Mihailescu, 2005; Preuss, Watzke, & Wurst, 2014; Windle &

Scheidt, 2004; Zucker, 1987). It has also been shown that an individual's ranking within a particular typology predict's the efficacy of certain pharmacotherapies (Cherpitel, Moskalewicz, & Swiatkiewicz, 2004; Dundon, Lynch, Pettinati, & Lipkin, 2004; Epstein et al., 1995; Forray & Sofuoglu, 2014; Hulse, 2012; Johnson, 2005, 2010; Johnson, Ait-Daoud, Ma, & Wang, 2003; Keating, 2013). Therefore, age-of-onset and pattern of drinking, recognizing that these are often correlated, have significant predictive validity for a life-time diagnosis of alcohol abuse or dependence and, in some cases, the effectiveness of pharmacotherapies to treat alcohol dependence. In this chapter, alcohol and ethanol are used interchangeably; such that in the clinical setting the term alcohol is preferentially used over ethanol, whereas the term ethanol (scientific name for the two-carbon chain alcohol) is preferentially used over alcohol in the preclinical setting.

2. Neurobehavioral Correlates with Alcohol Abuse and Dependence

Clinical and basic research indicate that 1) lower responsivity to ethanol's effects is directly associated with alcohol abuse and dependence (e.g., Crabbe, Bell & Ehlers, 2010; Draski & Deitrich, 1996; Heit et al., 2013; Morean & Corbin, 2010; Morozova, Mackay & Anholt, 2014; Schuckit & Gold, 1988; Silveri, 2012, 2015; Spear, 2010, 2014); 2) the ability to display greater levels and quicker development of tolerance (a reduction in ethanol's effects after prior treatment with ethanol) to ethanol's effects is also associated with alcohol abuse and dependence (e.g., Lê & Mayer, 1996); 3) additionally, the expression of anxiety-like behavior under basal and/or withdrawal conditions is associated with a propensity to abuse alcohol (e.g., Heilig, Egli, Crabbe, & Becker, 2010; Heilig, Thorsell, et al., 2010; Kirby, Zeeb, & Winstanley, 2011; Pautassi, Camarini, Quadros, Miczek, & Israel, 2010; Thorsell, 2010); and 4) moreover, the expression of low- to moderate-dose ethanol-induced stimulation [which is modeled in rodents by increased motor activity/approach behavior (Chappell & Weiner, 2008; Faria et al., 2008; Wise & Bozarth, 1987), aggression (Chiavegatto, Quadros, Ambar, & Miczek, 2010), and social facilitation (Varlinskaya & Spear, 2009, 2010)] is associated with excessive alcohol consumption. This behavioral phenotype may have pharmacological validity as well, such that the histaminergic (c.f., Panula & Nuutinen, 2011 and references therein) and ghrelin (c.f., Jerlhag, Landgren, Egecioglu, Dickson, & Engel, 2011b and references therein) systems have been implicated in ethanol-induced motor activation, ethanol-induced conditioned place preference, alcohol-preference and high alcohol consumption behavior. However, there remain concerns with the translatability of ethanol-induced stimulation in rodents vs humans (e.g., Crabbe et al., 2010). For instance, other than low- to moderate-dose effects on (a) self-report (Morzorati, Ramchandani, Flury, Li, & O'Connor, 2002; Viken, Rose, Morzorati, Christian, & 2003), (b) heart rate (Finn & Justus, 1997; Peterson et al., 1996), and (c) brain activity (Lukas, Mendelson, Benedikt, & Jones, 1986; Sorbel, Morzorati, O'Connor, Li, & Christian, 1996; Trim et al., 2010), the stimulating effects of ethanol are less apparent in humans compared with rodents.

3. Neurochemical Correlates with Alcohol Abuse and Dependence

Clinical and basic research indicate that alcohol abuse and dependence are mediated in part by a number of neurobiological systems (c.f., Koob, Arends, & Le Moal, 2014; Koob, Buck,

et al., 2014; Noronha, Cui, Harris, & Crabbe, 2014; Pierce & Kenny, 2013; Robbins, Everitt, & Nutt, 2010; Self & Staley, 2010; Sommer & Spanagel, 2013; Spanagel, 2009): acetylcholine (ACh: Chatterjee & Bartlett, 2010; Davis & de Fiebre, 2006; Rahman, Engleman, & Bell, 2015, 2016; Soderpalm, Ericson, Olausson, Blomqvist, & Engel, 2000), adenosine (Filip, Zaniewska, Frankowska, Wydra, & Fuxe, 2012; Nam, Bruner, & Choi, 2013), dopamine (DA: Bhaskar & Kumar, 2014; Engel & Jerlhag, 2014; Heinz, 2002; Nutt, Lingfor-Hughes, Erritzoe, & Stokes, 2015; Soderpalm & Ericson, 2013), endocannabinoid (Moreira, Jupp, Belin, & Dalley, 2015), gamma-aminobutyric-acid (GABA: Agabio & Colombo, 2014; Kumar et al., 2009; Liang & Olsen, 2014; Maccioni & Colombo, 2009), glutamate (Barron et al., 2012; Bell et al., 2016; Davis & Wu, 2001; Gass & Olive, 2008; Rao, Bell, Engleman, & Sari, 2015), purinergic (Franklin et al., 2014), serotonin (5-HT: Engleman, Rodd, Bell, & Murphy, 2008; Hauser et al., 2014; Lovinger, 1999), melanocortin (Olney, Navarro, & Thiele, 2014), opiate (Charbogne, Kieffer, Befort, 2014; Drews & Zimmer, 1997), orexin (Baimel et al., 2015), oxytocin (Buisman-Pijlman et al., 2014), neuropeptide-Y (NPY: Heilig & Thorsell, 2002), corticotropin releasing factor (CRF: Burke & Miczek, 2014; Koob, 2010), substance P (George et al., 2008), nociceptin/orphanin FQ (NOP, N/OFQ: Economidou et al., 2008; Witkin et al., 2014); ghrelin (Jerlhag, Egecioglu, Dickson, & Engel, 2011; Jerlhag et al., 2009; Jerlhag, Landgren, et al., 2011); neurotrophic factors such as BDNF (Logrip, Janak, & Ron, 2009), and hypothalamic-pituitary-adrenal (HPA) activity including corticosteroids, etc. (Gianoulakis, Guillaume, De Waele, & Angelogianni, 1995; Keith, Roberts, Wisen, & Crabbe, 1995; Kiefer, Jahn, Otte, Nakovics, & Wiedemann, 2006; Rasmussen, Boldt, Wilkinson, & Mitton, 2002; Richardson, Lee, O'Dell, Koob, & Rivier, 2008) systems within the brain. More recently there has been a significant increase in research on the neuroimmune system, which can modulate these neurochemical/neuropeptide systems and is an important contributor to the development of addiction (Crews, Qin, Sheedy, Ventreno, & Zou, 2013; Cui, Shurtleff, & Harris, 2014; Kane et al., 2014; Robinson et al., 2014; Ward, Lallemand, & de Witte, 2014). This is one area where basic and clinical research have informed each other, such that innate differences or ethanol-induced changes in neurotransmitter, neuropeptide and neuroimmune systems of subjects genetically predisposed for excessive ethanol consumption strongly suggests these systems play a significant role in the development of alcoholism, at least in predisposed individuals (c.f., Bell et al., 2012; Robinson et al., 2014). By extension, demonstration of these innate neurotransmitter and/or neuropeptide differences in an animal model of alcoholism underscore its utility in screening the efficacy of compounds to treat alcohol dependence.

5. The Genetics of Alcoholism

Family History Positive (FHP) for alcoholism individuals are persons who have relatives that meet diagnostic criteria for AUDs. The strongest expression of correlative phenotypes (discussed later) is observed in FHP individuals with this characteristic across multiple generations, starting with the immediate family. These findings provide strong support for genetics as a mediator in the development of alcoholism (c.f., Schuckit, 2014). Epidemiologically, twin studies have yielded data indicating a strong genetic component to the development and expression of alcohol dependence. Heath (1995) provides an excellent

overview of the early Australian (e.g., Eysenck & Eysenck, 1975; Martin et al., 1985), Finnish (e.g., Kaprio, Rose, Romanov, & Koskenvuo, 1991; Partanen, Bruun, & Markkanen, 1966), London Twin Family Survey (e.g., Clifford, Hopper, Fulker, & Murray, 1984), Swedish (e.g., Cederlof, Friberg, & Lundman, 1977), US National Academy of Science/ National Research Council twin registry (e.g., Hrubec & Neel, 1978; Jablon, Neel, Gershowitz, & Atkinson, 1967), the US Vietnam Era Twin Survey (e.g., Goldberg, Eisen, True, & Henderson, 1990) and his own work with the US Virginia 30,000 Survey. What is most striking about his review of these twin registries and AUDs is that, while the US data tends to suggest that the development of AUDs in men is genetically influenced to a greater extent than that observed in women, multiple European studies suggest that the development of AUDs by women is genetically influenced to the same degree or more so than men (Heath, 1995). For further reading on the genetics of AUDs, see Hesselbrock (1995b) for an overview of early adoption studies, see Hesselbrock (1995a) for an overview of early work looking at Alcoholic Subtypes, see Cadoret (1995) for an overview of early studies on genetic correlates with other psychiatric disorders and see Schuckit (2014) for a recent review on the history of research investigating the genetics of alcohol and drug dependence.

6. Criteria for an Animal Model of Alcoholism

Different animal models have had different levels of success in research to develop treatments for both medical and psychiatric disorders (Gobrogge, 2014; Golbidi, Frisbee, & Laher, 2015; Griffin, 2002; McCairn & Isoda, 2013; McGonigle & Ruggeri, 2014; McKinney, 2001; McLarnon, 2014; Reser, 2014; Nestler & Hyman, 2010; Whiteside, Pomonis, & Kennedy, 2013). An animal model allows an experimenter to control the subject's genetic background, environmental factors and prior drug experience. In addition, it allows for the examination of neurobehavioral, neurochemical and neurophysiological correlates associated with the behavioral, physiological and neurological states being modeled, in the present case alcohol abuse and dependence. These correlates can, in turn, facilitate the development of pharmacological and/or behavioral treatments for these disorders. There have been reservations as to whether a valid animal model of alcoholism could be developed (Cicero, 1979). These concerns stemmed from the fact that, in general, heterogeneous stock rats consume only modest levels of ethanol, such that blood alcohol concentrations (BACs) achieved are modest (c.f., Bell, Rodd, Engleman, Toalston, & McBride, 2014 for a comparison of 22 different rat lines and strains). Nevertheless, certain criteria for an animal model of alcoholism have been put forth (Cicero, 1979; Lester & Freed, 1973). Briefly, these criteria are 1) the animal should readily consume ethanol under free-choice access conditions; 2) the amount of ethanol consumed should result in pharmacologically relevant BACs; 3) ethanol should be consumed for its pharmacological effects; 4) ethanol should be reinforcing, usually demonstrated through operant procedures; 5) chronic ethanol consumption should lead to the expression of metabolic and functional/ neuronal tolerance to alcohol's effects; and 6) chronic consumption should lead to dependence, as indicated by withdrawal signs after access to ethanol is terminated. Other proposed criteria for a valid animal model of alcoholism include displaying characteristics associated with relapse-like drinking, generally demonstrated by an alcohol deprivation effect (ADE: McBride & Li, 1998); as well as excessive ethanol drinking during

adolescence, such that it exceeds adult intake levels and binge-like access results in BACs > 80 mg% as well as motor impairment (Bell et al., 2011, 2013, 2014; McBride, Rodd, Bell, Lumeng, & Li, 2014).

7. A Rat Genetic Animal Model of Alcoholism

The well-documented familial incidence of alcoholism, including multiple international twin studies, indicates a strong (40–70%) genetic component (discussed above) mediates a predisposition for and the development of alcohol use disorders (AUDs) (e.g., Cloninger, 1987; Cotton, 1979; Hesselbrock, 1995a, 1995b; Schuckit, 1986). Given heterogeneous stock rats display a wide-range of ethanol-consumption levels (Richter & Campbell, 1940) and very early work on selective breeding for alcohol consumption, Williams and associates (Williams, Berry, & Beerstecher, 1949) as well as Mardones and colleagues (Mardones, Segovia, & Hederra, 1953; Mardones & Segovia-Riquelme, 1983) proposed a genetic link to ethanol intake in rodents. From their work (e.g., Mardonoes et al., 1953; Mardones & Segovia-Riquelme, 1983) and that of four other international sites, bidirectional selective breeding has resulted in at least six high alcohol-consuming vs. their respective low alcohol-consuming rat lines (c.f., Bell et al., 2012).

Bi-directional selective breeding is a powerful genetic tool for studying alcohol-associated phenotypes (e.g., 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 by segregating these genetic polymorphisms into the opposite extremes of the overall population. This bidirectional selection is accomplished through systematic mating of animals with similar traits (alcohol-preferring on the one hand vs. alcohol-avoiding on the other) over successive generations. Thus, the high and low lines will exhibit extreme phenotypes exceeding the range found in the original parent population. Additionally, selective breeding for any phenotypes (such as alcohol preference) is hypothesis driven and genetically correlated traits of the primary selected phenotype (presumably due to pleiotropic actions of genes: Crabbe, Phillips, Kosobud, & Belknap, 1990) can be identified for further study. A major advantage of this selection process is that the ethanol-drinking phenotype is observed without the stress of environmental manipulations.

8. The P Rat as a Genetic Animal Model of Alcoholism

The alcohol-preferring, P, and alcohol-nonpreferring, NP, rat lines were developed by bi-directional mass selection from a closed-colony of Wistar rats at the Walter Reed Army Hospital and subsequently transferred to the Indiana University School of Medicine, Indianapolis, Indiana, USA (Lumeng, Hawkins, & Li, 1977). Two metrics were used for the selection of an alcohol preference. First, the animals had to prefer an unadulterated 10% ethanol solution over water by a ratio of at least 2:1. Second, the animals had to consume at least 5 g of ethanol/kg body weight/day. The first criterion was used to prevent selecting for an artifact of body weight when using the second criterion (selection for lower body weight will appear to be equivalent to a selection for high ethanol consumption only). To place this

5 g/kg/day selection criterion in a clinical perspective, using 0.793 as the specific gravity of ethanol, 90-proof whiskey as the preferred alcoholic beverage of choice for a 70 kg male, and the fact that rats metabolize ethanol close to 1.4 times the rate of humans, 5 g/kg/day of ethanol intake by a rat would be approximately a fifth of 90-proof whiskey being consumed each day.

Regarding criteria for an animal model of alcoholism, under free-choice conditions (water and food available) P rats readily consume greater than 5 g/kg/day of ethanol, whereas NP rats consume less than 1 g/kg/day (Li, Lumeng, McBride, & Murphy, 1987). P rats readily attain pharmacologically relevant blood alcohol concentrations (BACs, 80 to 250 mg%: this would approximate 0.08 to 0.25 in forensic terms, the latter under operant binge-like conditions) (Bell et al., 2013, 2014, 2011; Bell, Rodd, Lumeng, Murphy, & McBride, 2006; Bell, Rodd, Sable, et al., 2006; Bell, Rodd, Schultz, et al., 2008; McBride, Kimpel, McClintick, Ding, Hauser, et al., 2013; McBride, Kimpel, et al., 2014; McBride, Rodd, et al., 2014; Murphy et al., 2002). Ethanol-drinking in the home-cage also results in intoxication including motor impairment, as measured with an oscillating bar apparatus (Bell, McKinzie, Murphy, & McBride, 2000; Bell et al., 2001). Moreover, P rats will display tolerance to this effect after chronic binge drinking (Bell et al., 2011). P rats operantly self-administer ethanol intragastrically for its post-ingestive effects (Murphy et al., 1988; Waller, McBride, Gatto, Lumeng, & Li, 1984). P rats will operantly self-administer ethanol using a dipper model, indicating these rats will work for access to ethanol (Files, Samson, Denning, & Marvin, 1998; Murphy, Gatto, McBride, Lumeng, & Li, 1989; Rodd et al., 2003; Rodd-Henricks et al., 2002a, 2002b; Samson, Files, Denning, & Marvin, 1998; Toalston et al., 2008) or sipper tube model (Beckwith & Czachowski, 2014; Bertholomey, Verplaetse, & Czachowski, 2013; Czachowski & Samson, 2002; Samson & Czachowski, 2003; Verplaetse, Rasmussen, Froehlich, & Czachowski, 2012; Verplaetse & Czachowski, 2015) indicating these rats will work for access to ethanol.

Whereas ethanol-naïve P and NP rats display similar levels of ethanol clearance (Li & Lumeng, 1977; Lumeng, Waller, McBride, & Li, 1982), after chronic ethanol-drinking (6–8 weeks) P rats display metabolic as well as functional tolerance to the motor impairing and aversive effects of ethanol (Gatto et al., 1987; Lumeng & Li, 1986; Stewart, McBride, Lumeng, Li, & Murphy, 1991). Moreover, similarly treated P rats also display dependence-associated signs when ethanol access is terminated (Kampov-Polevoy, Matthews, Gause, Morrow, & Overstreet, 2000; Waller, McBride, Lumeng, & Li, 1982). In addition, P rats display relapse-like drinking by exhibiting a robust alcohol deprivation effect (ADE: Rodd et al., 2003; Rodd-Henricks et al., 2001; Rodd-Henricks, McKinzie, Shaikh, et al., 2000). The ADE is a transient increase in ethanol intake after a period of ethanol withdrawal (c.f., Rodd, Bell, McKinzie, et al., 2004; Rodd, Bell, Sable, Murphy, & McBride, 2004; Vengeliene, Bilbao, & Spanagel, 2014). Regarding initial sensitivity, compared with NP rats, P rats are less sensitive to the ataxic (Bell et al., 2001) and hypothermic (Stewart, Kurtz, Zweifel, Li, & Froehlich, 1992) effects of ethanol; and P rats develop tolerance quicker to the ataxic (Bell et al., 2001) and hypnotic (Kurtz, Stewart, Zweifel, Li, & Froehlich, 1996) effects of ethanol as well. During ethanol withdrawal, P, but not NP, rats display greater acoustic startle reactivity compared with basal conditions (Chester, Blose, & Froehlich, 2004). P rats display greater low dose ethanol-induced locomotor activity, compared with NP rats (Rodd,

Bell, McKinzie, et al., 2004; Waller, Murphy, McBride, Lumeng, & Li, 1986), and display locomotor activation during ethanol drinking or self-administration (Bell, Rodd, Toalston, et al., 2008; Bell et al., 2002; Melendez et al., 2002). The latter provides additional support to the view that P rats find ethanol rewarding. Thus, the P line of rats satisfies criteria proposed by multiple authors for a valid animal model of alcoholism. The key behavioral features of this genetic rat animal model of alcoholism are outlined below:

Key features of the P genetic rat animal model of alcoholism

1. >7 g ethanol/kg body weight/day is orally consumed under home-cage, free-choice, 24 hr conditions (Bell et al., 2011, 2013, 2014; Bell, Rodd, Schultz, et al., 2008; Li et al., 1987)
2. >1 g/kg ethanol is orally consumed during the first 15-min of home-cage, limited access conditions (Bell et al., 2014; Bell, Rodd, Lumeng, et al., 2006; Murphy et al., 1986; Russell, McBride, Lumeng, Li, & Murphy, 1996)
3. Pharmacologically relevant blood alcohol concentrations (BACs: 80 to 250 mg%), which parallel those observed in alcoholics, are achieved during ethanol drinking and self-administration (Bell et al., 2011, 2014; Bell, Rodd, Lumeng, et al., 2006; Bell, Rodd, Sable, et al., 2006; Bell, Rodd, Schultz, et al., 2008; Murphy et al., 1986, 2002; Rodd et al., 2003)
4. Ethanol is self-administered intragastically (Murphy et al., 1988; Waller et al., 1984) and intracranially (Engleman et al., 2009; Toalston et al., 2014) indicating taste and calories are not the primary motivators for this behavior
5. Ethanol is consumed and self-administered despite ethanol-induced motor impairment (Bell et al., 2011; McBride, Kimpel, McClintick, Ding, Hauser, et al., 2013)
6. Ethanol drinking and self-administration induce autonomic (heart rate) and/or behavioral (motor) activation (Bell, Rodd, Toalston, et al., 2008; Bell et al., 2002; Melendez et al., 2002)
7. Ethanol is operantly self-administered, without using fading/adaptation techniques (i.e., P rats work for access to ethanol) (Files et al., 1998; Murphy et al., 1989; Rodd et al., 2003; Rodd-Henricks et al., 2002a, 2002b; Rodd-Henricks, McKinzie, Shaikh, et al., 2000; Samson et al., 1998; Toalston et al., 2008)
8. Chronic home-cage, free-choice ethanol consumption leads to metabolic (Lumeng & Li, 1986) and functional (Gatto et al., 1987; Stewart et al., 1991; 1996) tolerance
9. Chronic home-cage, ethanol consumption leads to dependence (e.g., decreased seizure thresholds) (Kampov-Polevoy et al., 2000; Waller et al., 1982)
10. Relapse behavior is displayed under home-cage and operant conditions [e.g., expression of an alcohol deprivation effect (ADE) is observed] (Rodd et al., 2003; Rodd-Henricks et al., 2001; Rodd-Henricks, McKinzie, Shaikh, et al., 2000)
11. Serve as an animal model of adolescent binge alcohol abuse by exceeding ethanol intakes seen during adulthood, with motor impairment and BACs exceeding 80 mg

%, under both continuous and limited access conditions (Bell et al., 2011, 2014; McBride et al., 2005; McBride, Rodd, et al., 2014)

12. Self-administer or consume drugs of abuse by (a) orally consuming nicotine-adulterated solutions (Hauser et al., 2012); (b) operantly self-administering nicotine both orally (Hauser et al., 2014) and intravenously (Le et al., 2006); and (c) intracranially self-administering cocaine (Katner et al., 2011), nicotine (Deehan et al., 2015; Hauser et al., 2014), and nicotine + ethanol (Truitt et al., 2015).

9. Some Family History Positive (FHP) Correlates

The above survey of the literature concerning neurobehavioral and neurobiological phenotypes found in these selectively bred high vs. low alcohol-consuming rat lines indicates that many phenotypes present in alcohol abusing or dependent individuals are also present in these lines. For example, similar to the animal literature, clinical studies of FHP subjects (i.e., with a family history of alcoholism) report an inverse relationship between low level responsivity to ethanol and risk for the development of AUDs (c.f., Crabbe et al., 2010; Schuckit, 1994, 2009, 2014). Thus, after an ethanol challenge young adult FHP females (Eng et al., 2005; Lex et al., 1988) and males (Schuckit, 1985; Schuckit & Gold, 1988) display less body sway than family history negative (FHN) controls. An individual's level of response (low vs. high) to ethanol also influences brain regional activation following an acute ethanol challenge (Trim et al., 2010). Moreover, an individual's level of response to ethanol is associated with the long- vs. short-allele for the 5-HT transporter (*5htt*) gene and this association has significant predictive validity for alcohol intake by adolescents (Hinckers et al., 2006). As discussed earlier, the FHP, P, rat displays lower levels of ethanol-induced behavioral and physiological changes compared with FHN, NP, rats (Bell et al., 2001; Stewart et al., 1992).

Alcohol dependence is a chronic relapsing disorder, with craving and relapse often precipitated by physiological and behavioral responses (i.e., cue-reactivity) to environmental and interoceptive cues associated with alcohol and/or drugs of abuse consumption (Childress et al., 1993; Drummond et al., 1990; Greeley et al., 1993; Kaplan et al., 1983, 1985; O'Brien et al., 1992; Rajan et al., 1998; Stormark et al., 1998). In addition, ethanol's effects on heart rate-reactivity are associated with level of genetic density in FHP individuals as well dissociating FHP from FHN subjects, such that persons that are FHP display greater sensitivity to ethanol reward and display sensation-seeking behavior (Assaad et al., 2003; Conrod, Pihl, & Vassileva, 1998; Finn, Earleywine, & Pihl, 1992; Peterson, Pihl, Seguin, Finn, & Stewart, 1993). This has also been shown in cross-sensitivity by stimulant users displaying a characterisitic alcohol-reward heart rate response (Brunelle, Barrett, & Pihl, 2006). It is noteworthy that both male (Bell et al., 2002) and female (Bell, Rodd, Toalston, et al., 2008) P rats display increased heart rate during ethanol drinking. In addition, this autonomic reactivity can be conditioned to the environment associated with ethanol consumption (Bell, Rodd, Toalston, et al., 2008; Bell et al., 2002). Thus, monitoring autonomic reactivity in P rats may be an important model system for testing compounds targeting craving, especially in the context of cue-reactivity.

10. Some Neurochemical, Neuropharmacological as well as Neurogenetic Correlates

The Cholinergic System

Acetylcholine is released from neurons projecting to a broad range of cortical and subcortical structures and influences cellular physiology and neuronal function throughout the brain (Newman, Gupta, Climer, Monaghan, & Hasselmo, 2012). There are two classifications of cholinergic receptors: nicotinic and muscarinic. The neuronal nicotinic acetylcholine receptors (nAChRs) belong to the family of ligand-gated ion channel receptors (Albuquerque, Pereira, Alkondon, & Rogers, 2009; Gotti et al., 2009). Nicotinic acetylcholine receptors (nAChRs) consist of 11 neuronal subunits, which are divided into 8 alpha subunits (α2–α10) and 3 beta subunits (β2–β4). nAChR subtypes with diverse subunit combinations are distributed across multiple brain regions, including the mesocorticolimbic and extended amygdala reward circuitry, where they regulate dopaminergic function. A notable difference among the receptor subtypes is that the homomeric α7 nAChR does not desensitize to nicotine stimulation as the heteromeric nAChRs (e.g., α4β2 nAChR) do. The α7 nAChRs are located presynaptically on glutamatergic projections from the mPFC to the NAcbSh. Therefore, activation α7 nAChRs may enhance glutamatergic excitatory drive and promote DA release in the NAcb after α4β2 receptors are desensitized. Muscarinic acetylcholine receptors (mAChRs) are G-protein coupled receptors that are widely distributed in the brain. There are 5 mAChRs neuronal subunits (M1–M5) (Bymaster, McKinzie, Felder, & Wess, 2003; Wess, 2003; Wess et al., 2003; Yamada et al., 2003). Studies examining the striatum indicated that M1 receptors are expressed on spiny projection neurons (Wang et al 2006), whereas M2/M4 receptors are primarily presynaptic autoreceptors (Yan & Surmeier, 1996, Zhang et al., 2002). As autoreceptors, M2/M4 receptors inhibit ACh release and subsequent nAChR-dependent DA release in the striatum (Shin et al., 2015). In addition, M2 receptors are located on glutamatergic terminals which inhibit its release (Hersch, Gutekunst, Rees, Heilman, & Levey, 1994). The M5 receptor is the only mAChR subtype found on midbrain DA neurons (Vilaró et al., 1990; Palacios, & Mengod, 1990; Weiner, Levey, & Brann, 1990) and these receptors modulate DA and DA/glutamate projections from the midbrain (Shin et al., 2015).

Substantial research indicates that nAChR activity mediates, in part, the rewarding effects of drugs of abuse (Chatterjee & Bartlett, 2010; Corrigall & Coen, 1994; Ericson, Blomqvist, Engel, & Soderpalm, 1998; Hendrickson, Guildford, & Tapper, 2013; McGehee & Role, 1995; Nisell, Nomikos, & Svensson 1994; Rahman, 2013; Rahman et al., 2015, 2016; Rahman & Prendergast, 2012; Sajja, Dwivedi, & Rahman, 2010). For example, both alcohol (Brodie, Pesold, & Appel, 1990; Brodie, Shefner, & Dunwiddie, 1999) and nicotine (Calabresi, Lacey, & North, 1989; Nisell et al., 1994) activate VTA DA projection neurons and stimulation of nAChRs within the VTA modulate, at least in part, the reinforcing effects of nicotine (Corrigall & Coen, 1994; Nisell et al., 1994) and alcohol (Blomqvist, Ericson, Johnson, Engel, & Soderpalm, 1996; Ericson, Molander, Lof, Engel, & Soderpalm, 2003; Soderpalm et al., 2000). Additonally, a number of reports indicate that pre-exposure to nicotine significantly increases operant or free-choice ethanol self-administration and reinstates ethanol-seeking behavior in animal models (Bito-Onon, Simms, Chatterjee,

Holgate, & Bartlett, 2011; Hauser et al., 2012; Le et al., 2003). Moreover, co-administration of ethanol and nicotine produces an additive effect on their reinforcing effects and associated dopamine release in the nucleus accumbens (NAcb, Ericson, Lof, Stomberg, & Soderpalm, 2009; Tizabi, Bai, Copeland, & Taylor, 2007; Sajja et al., 2010).

Emerging preclinical evidence indicates that a number of ligands targeting nAChRs modulate ethanol drinking behavior. For example, mecamylamine, a non-selective nAChR antagonist or varenicline, a partial agonist at α4β2* nAChRs, reduces ethanol drinking behavior by targeting nAChRs in the mesocorticolimbic dopamine system (Ericson et al., 1998; Le et al., 2000; Steensland, Simms, Holgate, Richards, & Bartlett, 2007). In addition, nAChR ligands such as cytisine, a partial agonist at α4β2*, and lobeline, a non-selective antagonist, were found to reduce ethanol self-administration or nicotine-induced ethanol drinking in rodents (Bell, Eiler, Cook, & Rahman, 2009; Chatterjee, Steensland, Rollema, & Bartlett, 2011; Hendrickson, Zhao-Shea, & Tapper, 2009; Sajja & Rahman, 2011, 2012, 2013). Overall, brain nAChRs have emerged as important therapeutic targets for the rewarding effects of ethanol in numerous animal models. Regarding P rats, sazetidine-A, a novel ligand that desensitizes α4β2 nAChRs with partial agonistic activity reduces ethanol drinking by P rats (Rezvani et al., 2010). In addition, pretreatment with nicotine increases operant ethanol-self administration and relapse behavior in P rats (Hauser et al., 2012). Furthermore, P rats have higher sensitivity to the reinforcing effects of nicotine in the pVTA compared with outbred Wistar rats (Hauser et al., 2014). These reinforcing effects of nicotine can be blocked by mecamylamine, an nAChR antagonist, when injected simultaneously into the pVTA of P rats (Hauser et al., 2014), indicating that mesolimbic cholinergic activity modulates the reinforcing effects of ethanol and nicotine. More recent findings indicate that P rats will also co-administer ethanol + nicotine into the pVTA (Truitt et al., 2015) and self-administer nicotine into the NAcbSh (Deehan et al., 2015). In addition, oral binge ethanol + nicotine self-administration by P rats induces greater sensitivity to the reinforcing effects of nicotine in the NAcbSh by shifting the self-administration dose-response curve to the left (Deehan et al., 2015).

Receptor binding studies have shown that P rats have lower striatal α7 nAChR expression than NP rats (Tizabi et al., 2001). Additonally, there is higher expression of *Chat* (choline acetyltransferase), *Chrm3* (mACh3R), *Slc5a7* (transporter uptake for acetylcholine synthesis), *Slc18a3* (vesicular amine transport into secretory vesicles) in the NAcbSh of adult P rats compared with NP rats, whereas adult P rats have lower expression of *Chrm4* (mACh4R) in the NAcbSh than NP rats (McBride, Kimpel, McClintick, Ding, Hauser, et al., 2013, McBride, Kimpel, McClintick, Ding, Hyytia, et al., 2013). These findings suggest that the accumbal cholinergic system may be more active in P rats than NP rats. Clinical research indicates individuals with AUDs have lower ChAT activity and mAChR density in the hippocampus (Antuono, Sorbi, Bracco, Fusco, & Amaducci, 1980; Nordberg, Larsson, Perdahl, & Winblad, 1983) as well as ChAT protein expression in the basal forebrain (Ventreno, Broadwater, Liu, Spear, & Crews, 2014). However, these clinical findings do not necessarily indicate that basal levels are different from control subjects. Our microarray findings indicate that ethanol drinking by adult P rats increased *Chrn7a* expression in the NAcb (Bell, Kimpel, et al., 2009), but reduced its expression in the CeA (McBride et al., 2010) and the DRN of ethanol-drinking adolescent P rats (McClintick et al., 2015). Overall,

a modest number of differences in ACh--associated gene expression levels have been detected between P and NP rats (data for the pVTA came from McBride et al., 2012; data for the CeA and NAcbSh came from McBride, Kimpel, McClintick, Ding, Hyytia, et al., 2013). Similalry, few changes in ACh-associated gene expression levels have been detected following binge-drinking in adult or adolescent P rats (adult data for the whole NAcb came from Rodd et al., 2008; adult data for the NAcbSh came from Bell, Kimpel, et al., 2009, McBride et al., 2010; adult data for the CeA came from McBride et al., 2010; adult data for the pVTA came from McBride, Kimpel, McClintick, Ding, Hyytia, et al., 2013; adolescent data for the CeA came from McBride, Kimpel, et al., 2014; adolescent data for the DRN came from McClintick et al., 2015) thus far (Figure 1). Taken together, these data indicate that brain cholinergic activity regulates behaviors associated with alcohol abuse and alcoholism and the P rat displays some treatment characteristics seen in the clinical population. For instance, varenicline has modest effects on reducing ethanol intake by P rats. However, the tests done in P rats thus far have not incorporated ethanol and nicotine co-abuse, which appears to be necessary to observe efficacy with varenicline in the clinical setting.

The Dopaminergic System

DAergic projections (Figure 2) emanating from the tegmentum [especially the ventral tegmental area (VTA)] and terminating in limbic, forebrain and cortical regions (e.g., the mesocorticolimbic and extended amygdala reward circuitry), are involved in the appetitive and consummatory behaviors associated with, as well as the positive and negative reinforcing properties of, addictive drugs. DA activates metabotropic receptors ($D_{1–5}$) that are generally classified as D_1-like (D_1 and D_5) and D_2-like ($D_{2–4}$) (Cooper, Bloom, & Roth, 2002). D_1-like receptors are typically coupled to the activation of adenylyl cyclase whereas D_2-like receptors are coupled to the inhibition of adenylyl cyclase (Cooper et al., 2002). DA neurotransmission is terminated via clearance by uptake through the high affinity DA transporter (DAT) (Cooper et al., 2002). The DAergic system plays a central role in the processing of natural-, alcohol- and drug of abuse-associated reward and reinforcement (e.g., Di Chiara & Imperato, 1988; McBride & Li, 1998; Melendez et al., 2002; Nogueira, Kalivas, & Lavin, 2006; Palmer, Low, Grandy, & Phillips, 2003; Volkow & Morales, 2015), with imaging studies indicating D2/3 receptor dysfunction in subjects addicted to several different drugs of abuse (Cosgrove, 2010). When an individual or animal ingests alcohol and/or other drugs of abuse, DA efflux is increased in several key mesocorticolimbic brain reward centers (e.g., Brodie et al., 1990; Franklin et al., 2009; Gessa, Muntoni, Collu, Vargiu, & Mereu, 1985; Imperato & Di Chiara, 1986; Smith & Weiss, 1999; Yoshimoto & McBride, 1992). This change in DAergic activity and other associated neuroplastic changes promote further alcohol and drug taking behavior. Following prolonged alcohol and/or drug abuse, individuals may display tolerance to these DA-elevating properties. Thus, the requirement for more alcohol and/or drug taking to get the same level of initial response moves the individual further through the addiction cycle, which starts out as impulsive use for intoxication and progresses to compulsive use to avoid or reduce the negative consequences of alcohol/drug withdrawal.

Regarding P rats, these animals exhibit reduced basal NAcb tissue DA levels and/or enhanced ethanol-induced extracellular DA efflux, compared to outbred rats or their alcohol non-preferring counterparts (Engleman, Ingraham, McBride, Lumeng, & Murphy, 2006; McBride, Chernet, Dyr, Lumeng, & Li, 1993; Murphy, McBride, Lumeng, & Li, 1982, 1987; Smith & Weiss, 1999; Strother, Lumeng, Li, & McBride, 2005; also see Bell et al., 2012b; Murphy et al., 2002 for reviews). DAergic neuronal activity from the VTA appears to play a major role in these alterations of mesocorticolimbic DAergic tone either basally or under ethanol-induced conditions (e.g., Engleman et al., 2011; Morzorati, 1998; Morzorati & Marunde, 2006; Morzorati, Marunde, & Downey, 2010), which is modulated in part by glutamatergic activity in the pVTA (Fitzgerald, Liu, & Morzorati, 2012). In addition, chronic or binge-like alcohol drinking by P rats reduces D_2 autoreceptor function (Engleman, McBride, Li, Lumeng, & Murphy, 2003; Engleman et al., 2000), elevates extracellular DA levels (Thielen et al., 2004) and increases DA reuptake (Sahr et al., 2004) in the NAcb. Sari and colleagues (2006) also reported that long-term ethanol consumption by P rats increased D_1 and D_2 exprssion levels in the NAcb core (NAcbCo) with D_2 expression also increased in NAcb shell (NAcbSh). These authors indicated that intermittent periods of ethanol deprivation increased D_1 receptor expression in the amygdala and D_2 receptor expression in the caudate putamen as well.

Given the evidence for differences in, and ethanol-induced changes of, DAergic activity, it is not surprising that a number of DA-associated compounds have been tested for their effects on ethanol drinking or self-administration by this line. Systemic administration of the DA agonist ibogaine (Rezvani et al., 1995) and DAT inverse modulator amphetamine (McBride, Murphy, Lumeng, & McBride, 1990) reduced ethanol drinking. Ethanol drinking by P rats also was disrupted by systemic administration of the D_2 agonist bromocriptine (Mason et al., 1994; McBride et al., 1990; Weiss et al., 1990) and the D_3 agonist 7-OH-DPAT (Mason et al., 1997) as well as intra-VTA infusion of the D_2 agonists quinpirole (Hauser et al., 2011; Nowak, McBride, Lumeng, Li, & Murphy, 2000) and quinelorane (Nowak et al., 2000). Both systemic administration (Mason et al., 1997) and intra-bed nucleus of the stria terminalis (BNST) infusion (Eiler, Seyoum, Foster, Mailey, & June, 2003) of the D_1 antagonist SCH23390 reduced ethanol drinking and self-administration by P rats. Similarly, both systemic administration (Mason et al., 1997) and intra-BNST as well as intra-VTA infusion (Eiler et al., 2003) of the D_2 antagonist eticlopride reduced ethanol drinking and self-administration by P rats. Additonally, ethanol drinking by P rats was reduced by microinfusion of the D_2 antagonist sulpiride into the VTA (Nowak et al., 2000), NAcb (Levy et al., 1991) and ventral pallidum (Melendez et al., 2005). Finally, systemic administration of the D_3 antagonist SB-277011-A (Thanos et al., 2005) as well as the DAT inhibitors GBR 12909 (McBride et al., 1990) and DOV 102,677 (Yang et al., 2012) reduced ethanol intake by this line of rats.

It is noteworthy that P rats have lower levels of D_2 receptors than NP rats in the VTA, NAcb and caudate putamen (McBride, Chernet, Dyr, et al., 1993; Strother, Lumeng, Li, & McBride, 2003) and smaller subpopulations of DA projections from the VTA compared with NP rats (Zhou, Zhang, Lumeng, & Li, 1995), but no differences in D_1 or D_3 receptor levels have been detected thus far (McBride et al., 1997). Finally, differences in both mRNA and protein expression levels of alpha-synuclein (SNCA, often associated with DAergic

function) have been found between P and NP rats, such that hippocampal levels were twice as high in inbred P rats compared with inbred NP rats (Liang et al., 2003). Interestingly, clinical research indicates that *Snca* expression is associated with alcohol craving, hazardous alcohol-drinking and Post Traumatic Stress Disorder (PTSD) symptomology in hazardous drinkers (Foroud et al., 2007; Guillot, Fanning, Liang, Leventhal, & Berman, 2015; Guillot, Pang, Leventhal, Liang, & Berman, 2015). Regarding gene expression differences, similar to the cholinergic system, only a modest number of DA-associated differences have been detected between P and NP rats so far (data for the pVTA came from McBride et al., 2012; data for the CeA and NAcbSh came from McBride, Kimple, McClintick, Ding, Hyytia, et al., 2013). This paucity of findings was also true for DA-associated changes following ethanol drinking, usually binge-like, by P rats (adult data for the whole NAcb came from Rodd et al., 2008; adult data for the NAcbSh came from Bell, Kimpel, et al., 2009; McBride et al., 2010; adult data for the CeA came from McBride et al., 2010; adult data for the pVTA came from McBride, Kimpel, McClintick, Ding, Hauser, et al., 2013; adolescent data for the CeA came from McBride, Kimpel, et al., 2014; McBride, Rodd, et al., 2014; adolescent data for the DRN came from McClintick et al., 2015) (Figure 2). In summary, whenever ethanol-induced changes were detected, the direction of change was generally an up-regulation of mRNA expression. Overall, the DAergic system is the center of the mesocorticolimbic reward circuit and it appears that effective medications for alcoholism modulate the circuit, rather than impacting the DA-system directly.

The GABAergic System

GABA is the primary inhibitory neurotransmitter in the CNS. Thus, it and its receptors are found throughout the brain (e.g., Benham, Engin, & Rudolph, 2014). In addition, there are four GABA transporters: GAT1 and GAT3 located pre-synaptically; GAT2 and GAT3 located post-synaptically; GAT1, GAT2, GAT3 and GAT4 on glia (c.f., Clausen et al., 2006; Gonzalez-Burgos, 2010; Madsen, White, & Schousboe, 2010). The GABA receptors are classified as either $GABA_A$ or $GABA_B$. There are multiple subunit isoforms for $GABA_A$ receptors [(alpha1–6), (beta1–3), gamma1–3), delta, (rho1–3), epsilon, pi and theta], but the most common in the CNS is a pentamer comprising $(\alpha1)2(\beta2)2(\gamma2)$. The receptor itself is a ligand-gated chloride channel that has binding sites for GABA, benzodiazepine, picrotoxin, steroids and anesthetics. Activation of the $GABA_A$ receptor opens the chloride channel for influx, which induces a hyperpolarized state that decreases the probability of an action potential resulting in an inhibitory state (c.f., Fritschy, Panzanelli, & Tyagarajan, 2012; McCarson & Enna, 2014). $GABA_A$ receptors are located extra- and post-synaptically, whereas $GABA_B$ receptors are located both pre- and post-synaptically (Hanchar, Dodsen, Olsen, Otis, & Wallner, 2005; Lovinger & Roberto, 2013). $GABA_B$ receptors are G-protein coupled, heteromer, receptors with two known subunits R1 and R2, where it appears the R1 subunit binds GABA and the R2 subunit interacts with the G-protein (Gaiarsa, Kucweski, & Porcher, 2011; Terunuma et al., 2014).

Several research groups have reported significant associations between GABA gene variants, expression levels, and activation in brain regions such as the mesocorticolimbic system and the extended amygdala (which includes substructures of the bed nucleus of the stria terminalis, amygdala, nucleus accumbens and prefrontal cortex), with high alcohol-

consuming phenotypes and risk for developing alcohol dependence in alcoholics as well as alcohol-preferring rats (Dick & Bierut, 2006; Enoch et al., 2012; Herman et al., 2012; Korpi & 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, GABAergic activity regulates, in part, other neuromodulator systems in the mesocorticolimbic reward circuit (Eiler & June, 2007; Melis, Camarini, Ungless, & Bonci, 2002; Rahman & McBride, 2002), supporting the role of GABA in DA-associated responses to reward. Given there are genetic differences, between P and NP rats, in these other neuromodulator systems of the mesocorticolimbic reward circuit as well (e.g., Bell et al., 2012, 2016; Franklin et al., 2014; Rahman et al., 2014, 2016 and discussed herein), this gene-by-gene interactional effect may serve as another contributing factor for the development of alcohol abuse and dependence (e.g., Saba et al., 2015; Tabakoff et al., 2009). Acute alcohol experience potentiates GABA signaling and facilitates its hyperpolarizing actions (Koob, 2004). And, $GABA_A$ and $GABA_B$ receptors mediate some of the rewarding, reinforcing, and motivational effects of alcohol consumption and alcohol binge drinking (Eiler & June, 2007; Nowak, McBride, Lumeng, Li, & Murphy, 1998; Tanchuck, Yoneyama, Ford, Fretwell, & Finn, 2011; also see Agabio & Colombo, 2014). Systemically, the $GABA_A$ agonist topiramate (Breslin, Johnson, & Lynch, 2010; Lynch, Bond, Breslin, & Johnson, 2011) and $GABA_B$ agonist baclofen (Liang et al., 2006; Maccioni et al., 2012) and $GABA_B$ positive modulators GHB (June et al., 1995), CGP7930 (Liang et al., 2006) and GS39783 (Maccioni et al., 2012) all reduced ethanol drinking and/or self-administration by P rats. Similarly, negative modulators of the benzodiazepine-site Ro 15-4513 (McBride, Murphy, Lumeng, & Li, 1988), Ro 19-4603 (June et al., 1996; June, Murphy, Mellor-Burke, Lumeng, & Li, 1994; June, Torres, et al., 1998), Ru 34000 (June, Eggers, et al., 1998), Ro 15-1788 (June et al., 1994; June, Torres, et al., 1998), CGS 8216 and ZK 93426 (June, Devaraju, et al., 1998; June, Zuccarelli, et al., 1998) all reduced ethanol intake and/or self-administration by P rats. The partial agonist/antagonist βCCt systemically also reduced ethanol self-administration by P rats (June et al., 2003). Centrally, intra-VTA infusion of the $GABA_A$ receptor antagonists bicuculline, picrotoxin (Nowak et al., 1998) and SR95531 (Eiler & June, 2007) reduced ethanol intake or self-administration by P rats. Similarly, intra-VTA infusion of the negative modulator of the benzodiazepine-site Ru 34000 (June, Eggers, et al., 1998) as well as intra-CeA (Foster et al., 2004) and intra-VP (June et al., 2003) infusion of the partial agonist/antagonist βCCt reduced operant self-administration of ethanol by P rats. Also, shRNA-induced reductions of $GABA_A$-α2-subunit and its associated toll-like receptor 4 (*Tlr4*), in the CeA of P rats, significantly reduced alcohol self-administration (Liu et al., 2011).

Previous work indicated that P rats have more $GABA_A$ receptors in the NAcb than NP rats (Hwang, Lumeng, Wu, & Li, 1990), and P rats display a greater response to benzodiazepines in the PFC, NAcbSh, CPU, cingulate gyrus and dorsal lateral septum than NP rats as well (Thielen, McBride, Chernet, Lumeng, & Li, 1997). Additionally, as seen in Figure 3, gene expression for a number of $GABA_A$ and $GABA_B$ receptor subunits differ between P and NP rats (data for the pVTA came from McBride et al., 2012; data for the CeA and NAcbSh came from McBride, Kimpel, McClintick, Ding, Hyytia, et al., 2013). Also seen in Figure 3 are our findings on the role of ethanol drinking, usually in a binge-like manner, on $GABA_A$

and $GABA_B$ receptor subunit gene expression (adult data for the whole NAcb came from Rodd et al., 2008; adult data for the NAcbSh came from Bell, Kimpel, et al., 2009, McBride et al., 2010; adult data for the CeA came from McBride et al., 2010, adult data for the pVTA came from McBride, Kimpel, McClintick, Ding, Hauser, et al., 2013; adolescent data for the CeA came from McBride, Kimpel, et al., 2014; McBride, Rodd, et al., 2014; adolescent data for the DRN came from McClintick et al., 2015). In general, where differences in mRNA expression were detected in the NAcbSh and pVTA, P rats had lower GABAR-associated levels than NP rats. Following ethanol consumption by adult P rats, the majority of detected changes in the NAcbSh represented downregulated gene expression, whereas detected changes in the CeA were approximately equally down- vs up-regulated gene expression. Following ethanol drinking by adolescent P rats, practically all detected changes represented down-regulation of GABA-associated gene expression. These findings suggest lowered GABAergic function in the NAcbSh and DRN following excessive ethanol intake by P rats, which would support increased excitatory/glutamatergic activity as a contributor to excessive ethanol intake (see glutamatergic section directly below).

The Glutamatergic System

The amino acid glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS). Given this, it is not surprising that glutamatergic projections, transporters and receptors are found throughout the brain. As the primary excitatory neurotransmitter, glutamate plays a crucial role in neuroplasticity, learning and memory (c.f., Henley & Wilkinson, 2013; Morris, 2013; Warburton, Barker, & Brown, 2013). Glutamate interacts with both metabotropic (Grm1-Grm8) and ionotropic receptors, which include those that can bind to N-methyl-D-aspartate (NMDA) subunits [Grin1, Grin2a-Grin2d, and Grin3a-Grin3b], α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) subunits [Gria1-Gria4] or kainite subunits [Grik1-Grik4], for excellent reviews see (Danbolt, 2001; Niciu, Kelmendi, & Sanacora, 2010; Traynelis et al., 2010). Because of glutamate's role in excitotoxicity, extracellular glutamate must be tightly controlled (Danbolt, 2001; Sari, 2014; Wang & Qin, 2010). Multiple glutamate transporters have been implicated in this process (Anderson & Swanson, 2000; Danbolt, 2001; Gegelashvili & Schousboe, 1997, Seal & Amara, 1999). Nevertheless, the human excitatory amino acid transporter 2 (EAAT2) and its rodent analog glutamate transporter 1 (GLT1) appear to be the primary transporters performing this function (Danbolt, 2001; Mitani & Tanaka, 2003; Rothstein, Van Kammen, Levey, Martin, & Kunci, 1995; Sari, 2014). However, the glial protein cystine/glutamate exchanger (xCT) appears to exchange extracellular cystine for intracellular (glial) glutamate (Bannai et al., 1984; Bannai & Ishii, 1982), which seems counterintuitive except for the fact that cystine is converted to cysteine, among other things, and reduces oxidative stress (c.f., Ishii & Mann, 2014).

Glutamatergic activity has been shown to mediate natural as well as drug and non-drug associated reward through direct and indirect interactions with other neurotransmitter/neuromodulatory systems within the mesocorticolimbic and extended amygdala reward neurocircuitry (e.g., Carlezon & Wise, 1996; Grace, Floresco, Goto, & Lodge, 2007; Kupila et al., 2012). For instance, research with the P rat has shown that free-choice ethanol drinking results in elevated levels of extracellular glutamate in the NAcb (Das, Yamamoto,

Hristov, & Sari, 2015), as well as its subregion the NAcbSh, and the pVTA (Ding et al., 2013). The latter authors reported that this increase in glutamate was inversely related to decreases in glutamate clearance. Considerable research has examined the hypothesis that sensitized mesocorticolimbic and extended amygdala glutamate neurotransmission mediate in part alcohol and drug dependence. For example, it appears continued alcohol or drug intake results in a hypergluatmatergic state within mesocorticolimbic and extended amygdala reward circuits (Gass & Olive, 2008; Kryger & Wilce, 2010; Vengeliene, Bilbao, Molander, & Spanagel, 2008). Pre-clinical evidence supports clinical findings that alcohol acutely inhibits, and chronically sensitizes and upregulates glutamate neurotransmission, in brain reward regions of the mesocorticolimbic and extended amygdala circuits (e.g., Carlezon & Wise, 1996; Chandler, Newsom, Sumners, & Crews, 1993; Cui et al., 2013; Ding, Engleman, Rodd, & McBride, 2012; Floyd, Jung, & McCool, 2003; Gass & Olive, 2008; Kapasova & Szumlinski, 2008; Nevo & Hamon, 1995; Nie, Madamba, & Siggins, 1994; Nie, Yuan, Madamba, & Siggins, 1993; Tabakoff & Hoffman, 2013; Weitlauf & Woodward, 2008), which may be due, in part, to changes in glutamate clearance (Ding et al., 2013; Kapasova & Szumlinski, 2008; Othman, Sinclair, Haughey, Geiger, & Parkinson, 2002; Parks et al., 2002; Rao, Bell, et al., 2015; Sari et al., 2011; Smith, 1997; Smith & Zsigo, 1996; Thoma et al., 2011). Moreover, recent data showed that 10 weeks of operant binge-like self administration of solutions containing both ethanol and nicotine resulted in elevation of extracellular glutamate levels in the PFC (Deehan, et al., 2015).

The role of glutamate in alcohol consumption is prominent in binge-drinking as well (c.f., Bell et al., 2016; Rao, Bell, et al., 2015). Genetic animal models of alcoholism, the P rat in this case, engaging in binge-like drinking, which results in BACs of 80 mg% and higher (c.f., Bell et al., 2011, 2014), display numerous changes in glutamate receptor and/or subunits, transporters, scaffolding proteins as well as other associated gene expression levels in discrete brain regions of the mesocorticolimbic and extended amygdala circuits (Bell et al., 2016; Bell, Kimpel, et al., 2009; Coleman et al., 2011; McBride, Kimpel, et al., 2014; McBride et al., 2009, 2010; McBride, Rodd, et al., 2014; McClintick et al., 2015; Rodd et al., 2008). These changes in glutamatergic neurotransmission include enhanced receptor activation and intracellular downstream signaling cascades (Cozzoli et al., 2009; Szumlinski et al., 2007; Tabakoff et al., 2009). In support of this contention, glutamate receptor antagonists such as acamprosate and MPEP reduce binge-like drinking dose-dependently (Grace et al., 2007; Gupta et al., 2008). Increases in excitatory neurotransmission may be greater during periods of acute ethanol withdrawal, which is commonly associated with binge drinking, compared to more protracted withdrawal periods (Ward et al., 2009). This may support the hypothesis that binge alcohol abuse increases susceptibility to alcohol-induced excitotoxic brain damage to a greater extent than continuous excessive drinking (e.g., Hunt, 1993; see also discussion and references in Bell et al., 2013). Overall, it is likely that glutamatergic neuroadaptations following repeated binge-like drinking behavior lead to a glutamate-GABA functional imbalance (Enna, 1997; Fadda & Rossetti, 1998; Szumlinski et al., 2007), and are responsible, in part, for withdrawal symptomology when ethanol access is terminated. This withdrawal symptomology in turn increases the negative reinforcement-associated properties of continued binge drinking (Everitt & Robbins, 2005; Koob & LeMoal, 2008; Robinson & Berridge, 2008). These effects are consistent with a proposed

transition from binge/impulsive alcohol drinking to habitual/compulsive drinking to dependence (c.f., Koob, 2013; Koob & Volkow, 2010).

Systemically, the GRM1 antagonist CPCCOEt did not affect operant self-administration (Schroeder, Overstreet, & Hodge, 2005a, 2005b), whereas the GRM1 antagonist JNJ 16259685 (Besheer, Faccidomo, Grondin, & Hodge, 2008a, 2008b) did significantly reduce operant self-administration by P rats. Slight procedural and/or motor effect differences may explain the difference between the former and latter findings from the same laboratory. The GRM2/3 antagonist LY404039 significantly reduced ethanol-seeking behavior as well as relapse, but did not affect the maintenance, of ethanol self-administration by P rats (Rodd et al., 2006). The GRM5 antagonists MPEP (Schroeder et al., 2005a, 2005b) and MTEP (Cowen, Djouma, & Lawrence, 2005) both reduced operant self-administration of ethanol by P rats. Intra-NAcb infusion of the GRM2/3 agonist LY379268 and GRM5 antagonist MPEP both significantly reduced operant ethanol self-administration by P rats (Besheer et al., 2010). Much more research has been done exploring the effects of manipulating GLT1 transporter levels, within subregions of the mesocorticolimbic reward circuit, on ethanol intake by P rats, to which we turn next.

The P rat has been very useful in assessing the efficacy of beta-lactam antibiotic, and similar, molecules in reducing alcohol intake, which appears to be due to a reversal of ethanol-induced down-regulation of GLT1 levels and the concomitant increase in extracellular glutamate. For example, chronic free-choice drinking by P rats reduced GLT1 expression in the NAcb but not in the PFC, although xCT (the glutamate-cystine antiporter) was reduced in both regions (Alhaddad, Das, & Sari, 2014; Sari & Sreemantula, 2012; Sari, Sreemantula, Lee, & Choi, 2013). Ceftriaxone administered peripherally reversed ethanol-induced downregulation of GLT1 (both isoforms GLT1a and GLT1b) in the PFC and NAcb as well as xCT in the NAcb, PFC and Amyg (Alhaddad, Das, et al., 2014; Rao & Sari, 2014a, 2014b). Similarly, ceftriaxone reversed ethanol-induced increases in extracellular glutamate of the NAcb (Das et al., 2015). Research with other beta-lactam antibiotics in P rats has shown that amoxicillin, augmentin and ampicillin, which have the potential to be orally administered, reduced alcohol intake and increased GLT-1 expression in PFC and NAcb of P rats (Goodwani, Rao, Bell, & Sari, 2015; Rao, Goodwani, et al., 2015). Non-antibiotic compounds with a putative ability to upregulate GLT1 expression and/or activity have been tested in P rats as well. For example, GPI-1046, an analog of FK506, significantly reduces free-choice alcohol intake by male P rats with a concomitant increase in GLT1 expression levels in the NAcb and PFC (Sari & Sreemantula, 2012). Similar results were found for MS-153 with significant decreases in ethanol intake paralleling reversals of ethanol-induced GLT1 downregulation in the NAcb, Amyg and hippocampus (Aal-Aaboda, Alhadad, Osowik, Nauli, & Sari, 2015; Alhadad, Kim, et al., 2014). Finally, it has been demonstrated that upregulation of GLT1 (including both isoforms) and xCT by ceftriaxone and MS-153 involves NF-kB and Akt signaling pathways (Alhaddad, Kim, et al., 2014; Rao, Saternos, Goodwani, & Sari, 2015).

An early study found that, globally, CNS *Grm3* and *Grm7* and the glycine-α1 subunit mRNA levels are lower in inbred P rats compared with inbred NP rats (Kimpel et al., 2007). More recently, Zhou and colleagues (2013) reported that P rats are homozygous for a *Grm2*

stop codon (Grm2*407) that essentially renders them a functional KO of *Grm2*. At the same time, Meinhardt and colleagues (2013) published their own work indicating GRM2 deficits are inversely related to drug-seeking behavior. As highlighted in Bell et al. (2016), a number of site-specific differences in glutamate-associated mRNA expression levels (see Figure 4) have been observed between P and NP rats (data for the pVTA came from McBride et al., 2012; data for the CeA and NAcbSh came from McBride, Kimpel, McClintick, Ding, Hyytia, et al., 2013). As with differences between P and NP rats, a number of glutamate-associated gene and/or protein expression changes are observed after ethanol drinking by P rats (adult data for the whole NAcb came from Rodd et al., 2008; adult data for the NAcbSh came from Bell, Kimpel, et al., 2009; McBride et al., 2010; adult data for the CeA came from McBride et al., 2010; adult data for the pVTA came from McBride, Kimpel, McClintick, Ding, Hauser, et al., 2013; adolescent data for the CeA came from McBride, Kimpel, et al., 2014; McBride, Rodd, et al., 2014; adolescent data for the DRN came from McClintick et al., 2015) (Figure 4). The protein changes after ethanol drinking in the NAcb and amygdala are from Obara et al. (2009). In general, differences, between P and NP rats, in accumbal ionotropic-associated glutamate receptor subunits are equally greater or lesser than that observed in the other line. However, metabotropic glutamate receptors are, for the most part, expressed lower in the P rat than in the NP within this brain region. Following ethanol consumption by adult P rats, expression levels for metabotropic glutamate receptors remained unchanged, whereas gene expression for ionotropic-associated glutamate receptor subunits are equally up- and down-regulated in the NAcb. In the CeA, the only observed difference was lower expression of *Grm2* and *Grm3* in P vs NP rats. However following ethanol drinking, all detected ionotropic subunit-associated and metabotropic glutamate receptor gene expression changes reflected up-regulation. This would suggest a strong neuroplastic response associated with ethanol-induced elevations in glutamate, such that substantial, enhanced glutamatergic neurotransmission is occurring in this brain region of the P rat. Similar observations have been seen in glutamate-associated protein levels of P rats (Obara et al., 2009) and electrophysiological activity in Marchigian sP rats (Herman et al., 2016). As discussed in our recent glutamate review (Bell et al., 2016), the findings from P rats support the hyperglutamatergic hypothesis of alcohol and drug dependence. Given this, the P rat serves as a genetic animal model of alcoholism with characteristics of glutamatergic function paralleling clinical observations including the efficacy of topirmate in significantly reducing ethanol intake.

The Serotonergic System

The neurotransmitter serotonin (5-HT) is associated with addictive behaviors, appetite regulation, behavioral inhibition, mood, and cognitive functions. Thus, dysregulation of the 5-HT system is implicated in the development of alcohol dependence. The serotonin transporter (SERT) clears 5-HT from the synapse through reuptake into the presynapse. There are seven families of 5-HT receptors (5-$HT_{1–7}$) and at least 14 distinct 5-HT receptor subtypes (Barnes & 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 & Segal 1978; Halliday & Tork,

1989; Herve, Pickel, Joh, & Beaudet, 1987; Parent, Descarries, & Beaudet, 1981; Van Bockstaele, Cestari, & Pickel, 1994). For example, 5-HT activates VTA-DA neurons (Pessia, Jiang, North, & Johnson, 1994), induces DA release in VTA slices (Beart & McDonald 1982), enhances DA release in NAc when locally applied to the VTA (Guan & McBride 1989) or the dorsal raphe is activated (Yoshimoto & McBride, 1992), potentiates the excitatory actions of alcohol on VTA-DA neurons (Brodie, Trifunovic, & Shefner, 1995), and increases extracellular DA release in the PFC (Iyer & Bradberry, 1996).

Acute alcohol exposure appears to increase 5-HT activity (McBride, Chernet, Rabold, Lumeng, & Li, 1993; Smith & Weiss, 1999), whereas chronic exposure to alcohol may result in the development of tolerance to this effect (Smith & 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 (Pivac, Muck-Seler, Mustapic, Nenadic-Sviglin, & Kozaric-Kovacic, 2004; Schmidt, Dufeu, Heinz, Kuhn, & Rommelspacher, 1997) and genetically selected alcohol-preferring rats (McBride, Chernet, Rabold, et al., 1993; Murphy et al., 1987; Strother, Chernet, Lumeng, Li, & McBride, 2001; Zhou, Bledsoe, Lumeng, & Li, 1991a, 1991b). Moreover, treatments that reduce 5-HT neurotransmission can elevate self-administration of alcohol (Ciccocioppo, Angeletti, Colombo, Gessa, & Massi, 1999; Lyness & Smith, 1992). 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) and alcoholic individuals with a polymorphism of the 5-HT transporter can respond favorably to certain medication combinations (Johnson, 2010). 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 2005, 2010; Wrase, Reimoid, Puls, Kienast, & Heinz, 2006). Research on the involvement of 5-HT in binge alcohol drinking has been limited, with some evidence that binge drinking induces a blunted 5-HT response in the Scheduled High Alcohol Consumption (SHAC) mouse binge drinking model (Szumlinski et al., 2007). Additionally, acute withdrawal from alcohol after binge-like exposure leads to a wide-spread reduction in 5-HT and other neurotransmitters in several brain regions including those associated with the mesocorticolimbic system (Smith, Co, Mcintosh, & Cunningham, 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. However, actual efficacy of 5HT manipulation to treat alcohol dependence in the clinic has been rather modest and may be relevant only in certain subpopulations of alcoholics.

Systemically, the 5HT precursor, D1L-5-HTP (McBride et al., 1990), reverse SERT modulator, fenfluramine (McBride et al., 1990); as well as agonists for the $5HT_1$, TFMPP (McBride et al., 1990), $5HT_{1A}$, 8-OH-DPAT (McBride et al., 1990), $5HT_2$, DOI (McBride et al., 1990), all reduced ethanol intake by P rats. However, most work has examined receptor antagonists, including WAY 100,635 (Zhou, McKinzie, Patel, Lumeng, & Li, 1998) which targets the $5HT_{1A}$ receptor; amperozide/FG 5606 (Lankford, Bjork, & Myers, 1996; Overstreet, McArthur, Rezvani, & Post, 1997), and FG 5974 (Lankford et al., 1996; Overstreet et al., 1997; Piercy, Bjork, & Myers, 1996) which target $5HT_2$ receptors; as well as MDL 72222 (Rodd-Henricks, McKinzie, Edmundson, et al., 2000) and ICS 205-930 (Rodd et al., 2010; Rodd-Henricks, McKinzie, Edmundson, et al., 2000) which target $5HT_3$

receptors, all of which reduce ethanol intake or the acquisition of operant ethanol self-administration by P rats. Additionally, the SERT inhibitors fluoxetine (Murphy et al., 1985, 1988; Rezvani et al., 2000; Zhou et al., 1998), fluvoxamine (Murphy et al., 1985) and DOV 102,677 (Yang et al., 2012) all reduced ethanol intake by P rats. The last compound also inhibits the norepinephrine and dopamine transporters.

A number of differences in serotonin-associated protein (Ciccocioppo, Ge, Barnes, & Cooper, 1998; McBride, Chernet, Raboid, et al., 1993; McBride et al., 1997; McBride, Guan, Chernet, Lumeng, & Li, 1994; Murphy et al., 1987; Pandey, Lumeng, & Li, 1996) and mRNA expression levels (see Figure 5) have been reported between P and NP rats (data for the pVTA came from McBride et al., 2012; data for the CeA and NAcbSh came from McBride, Kimpel, McClintick, Ding, Hyytia, et al., 2013). Observed ethanol drinking-induced changes in gene expression have come mainly from our work with adolescent bingeing P rats and in the DRN, from which all 5HT projections emanate (adult data for the whole NAcb came from Rodd et al., 2008; adult data for the NAcbSh came from Bell, Kimpel, et al., 2009, McBride et al., 2010; adult data for the CeA came from McBride et al., 2010; adult data for the pVTA came from McBride, Kimpel, McClintick, Ding, Hauser, et al., 2013; adolescent data for the CeA came from McBride, Kimpel, et al., 2014; McBride, Rodd, et al., 2014; adolescent data for the DRN came from McClintick et al., 2015) (Figure 5). For the most part, P rats have lower levels of central 5HT, 5HIAA, and 5HT receptors than NP rats. Following ethanol drinking by both adult and adolescent P rats, usually in binge-like form, nearly all detected changes in 5HT-associated gene expression represented down-regulation. These findings provide strong evidence that serotonergic deficits predispose an individual to abuse ethanol and, without intervention, foster continued excessive drinking.

The Noradrenergic and Corticotrophin Releasing Hormone (CRH) Systems

It is widely established that the central noradrenergic system serves a global function in neuromodulation, controlling vigilance, attention, and the sleep–wake cycle as well as contributing to learning and memory processes. Neuroanatomical evidence indicates that noradrenergic system in the brain arise from the cell bodies in the locus coeruleus and project to different cerebral regions and to the spinal cord (Cooper et al., 2002). Moreover, there is a complex interaction between norepinephrine (NE) and corticotrophin releasing factor (CRF), a neuropeptide strongly associated with central autonomic and stress activity, receptors within the locus coeruleus (Reyes, Bangasser, Valentino, & Van Bockstaele, 2014). In addition to major projections to the frontal cortex, (NE) neurons project to the limbic system (Flavin & Winder, 2013), including amygdala, bed nucleus of the stria terminalis, hippocampus, and hypothalamus where it is implicated in addiction (Becker, 2012; Koob, 2013; Sofuoglu, Rosenheck, Petrakis, 2014; See also Al' Absi, 2007), anxiety (Geiger, Neufang, Stein, & Domschke, 2014), attention (Geiger et al., 2014; Hegerl & Hensch, 2014), cognition (Chandler, Waterhouse, & Gao, 2014), memory, mood (Gold, 2015), pain (Elman, Borsook, & Volkow, 2013; Strobel, Hunt, Sullivan, Sun, & Sah, 2014), post-traumatic stress disorder (PTSD, Sofuoglu et al., 2014; Wimalawansa, 2014), sleep (Zeitzer, 2013), suicide (Elman et al., 2013), and associated physiological processes (Klimek, Rajkowska, Luker, Dilley, et al., 1999; Moret & Briley, 2011).

NE in synaptic vesicles is derived from two sources. The synthesis of NE begins with the synthesis of dopamine from tyrosine and is transported into the vesicle by the vesicular monoamine transporter (VMAT). Once dopamine is synthesized and stored in synaptic vesicles, an enzyme called dopamine-β-hydroxylase further hydroxylates dopamine into NE. The synthesis of NE is different than the other neurotransmitters as they are usually made in the cytoplasm of the terminal buttons, whereas NE's final stage of synthesis occurs in synaptic vesicles. Neurotransmission is initiated by an action potential which triggers the release of NE into the synaptic cleft. Released NE interacts with multiple adrenergic receptors, including presynaptic α2 and postsynaptic α1, β1 and β2 receptors. NE is removed from the synaptic cleft by both selective NE transporter (NET) as well nonselective transporters. NE's stimulation of α2-adrenergic receptors provide's feedback inhibition of further release. Cytoplasmic NE that is not sequestered in synaptic vesicles by VMAT is degraded into its metabolites by the enzyme monoamine oxidase, type a (MAO-A) (Cooper et al., 2002; Golan, Tashjian, Armstrong, & Armstrong, 2012; Krishnan & Nestler, 2008).

Evidence indicates that central NE activity modulates alcohol drinking behavior (Ehrenreich, Schuck, Stender, et al., 1997; Getachew, Hauser, Taylor, & Tizabi, 2010; See also Al' Absi, 2007). For example, selective NE uptake inhibition may normalize the behavioral and negative affective effects of alcohol (Getachew et al., 2010). Similarly, α1-adrenergic antagonists, α2-adrenergic agonists and β-adrenergic antagonists modulate alcohol drinking or associated withdrawal behavior (e.g., Gilpin & Koob, 2010; Riihioja, Jaatinen, Oksanen, et al., 1997; Walker, Rasmussen, Raskind, & Koob, 2008). There have been several studies investigating the adrenergic system's role in excessive ethanol drinking by P rats using peripheral routes of administration. Prazosin, an α1-adrenergic antagonist (Menkes, Baraban, & Aghajanian, 1981), reduces home cage limited access drinking (Rasmussen, Alexander, Raskind, & Froehlich, 2009), relapse drinking (Froehlich, Hausauer, Fischer, Wise, & Rasmussen, 2015), operant self-administration (Verplaetse & Czachowski, 2015, Verplaetse et al., 2012), and operant ethanol-seeking (Verplaetse & Czachowski, 2015, Verplaetse et al., 2012). It also disrupts the acquisition of excessive ethanol drinking by P rats (Froehlich, Hausauer, Federoff, Fischer, & Rasmussen, 2013). Combining prazosin and naltrexone was more effective in reducing ethanol drinking than either compound alone, at least in P rats (Froehlich, Hausauer, & Rasmussen, 2013). Additonally, tolerance did not appear to develop following repeated daily treatments (Rasmussen, Kincaid, & Froehlich, 2015). Another study found that clonidine, an α2-adrenergic receptor agonist, can also reduce ethanol drinking by P rats (Rasmussen, Alexander, Malone, Federoff, & Froehlich, 2014; Rasmussen, Beckwith, Kincaid, & Froehlich, 2014). In addition, the triple monoamine uptake inhibitor (i.e., DAT, NET and SERT) DOV 102,677 reduced ethanol intake by P rats (Yang et al., 2012). Paralleling the preclinical findings, prazosin also has shown promise in the treatment of AUDs in humans (e.g., Simpson, Saxon, Meredith, et al., 2009). Overall, limited data suggest the involvement of the noradrenergic system in AUDs but substantial territory still needs to be explored regarding the role of NE and stress-associated systems in alcohol dependence.

The CRF system is localized, often colocalizing with NE, in multiple brain regions associated with addiction, anxiety, consummatory behavior, sleep, stress, learning and memory (Reul & Holsboer, 2002; Sajdyk, Shekhar, & Gehlert, 2004). These brain regions

include the raphe nucleus (Lukkes et al., 2011), multiple nuclei of the hypothalamus and the amygdala (Blume et al., 2009; Campbell, Grove, & Smith, 2003; Sajdyk et al., 2004; Smialowska, Wieronska, & Wedzony, 2002), pituitary (Stanley et al., 2004), cortex and lateral septum (Miyata, Shiota, Chaki, Okuyama, & Inagami, 2001), bed nucleus of the stria terminalis and hippocampus (Van Pett et al., 2000). Moreover, CRF-R1 receptors colocalize with cholinergic, noradrenergic and DAergic neurons in many of these brain regions as well (Sauvage & Steckler, 2001). There is increasing research into the role of CRH, NPY, glucocorticoids and HPA activity (the endogenous opioid system is discussed next) in alcohol dependence. One important reason for this is the fact that most earlier research on pharmacological treatments was conducted in animal models mimicking early stages of the dependence cycle, rather than the later stages observed in dependence. In the P rat, CRF protein expression levels are lower in the PFC, pyriform cortex, hypothalamus and amygdala compared with NP rats (Ehlers et al., 1992).

A subsequent study revealed that both CRF protein and mRNA are lower in the CeA of P rats compared with NP rats (Hwang, Stewart, Zhang, Lumeng, & Li, 2004). More recent work has shown that P rats have a polymorphism in the promoter region of the CRFR2 gene, which is not present in NP rats (Yong et al., 2014). This polymorpshism is associated with lower *Crfr2* expression, especially in the amygdala; and, similar to innately reduced NPY levels in the amygdala, reduced *Crfr2* expression appears to be directly associated with higher ethanol intake and anxiety in P rats (Yong et al., 2014). Regarding CRF, ligands targeting the CRF1 receptor, such as antalarmin and MPZP, reduce ethanol drinking by P rats but dependence is a requirement to see these effects (Gilpin, Richardson, & Koob, 2008; Gilpin, Stewart, & Badia-Elder, 2008; Heilig & Egli, 2006).

Similar to oservations for the cholinergic and DAergic systems, very few differences in adrenergic and CRF-associated mRNA expression differences (see Figure 6) between P and NP rats (data for the pVTA came from McBride et al., 2012; data for the CeA and NAcbSh came from McBride, Kimpel, McClintick, Ding, Hyytia, et al., 2013). The same is true for ethanol drinking-induced changes in P rats (adult data for the whole NAcb came from Rodd et al., 2008; adult data for the NAcbSh came from Bell, Kimpel, et al., 2009; McBride et al., 2010; adult data for the CeA came from McBride et al., 2010; adult data for the pVTA came from McBride, Kimpel, McClintick, Ding, Hauser, et al., 2013; adolescent data for the CeA came from McBride, Kimpel, et al., 2014; McBride, Rodd, et al., 2014; adolescent data for the DRN came from McClintick et al., 2015) (Figure 6). However, most drinking protocols used for our recent microarray work have been binge-like and limited access in nature. Thus, the animals were probably not physically dependent on alcohol, despite being quite motivated to consume it and achieving BACs greater than 80–100 mg%.

The Opioid System(s)

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 (c.f., Oswald & Wand, 2004). Therefore, it is not surprising that these peptides have been shown to influence the

development of alcohol abuse and dependence. 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, similar to 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. (2012). 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; Charbogne et al., 2014; Roberts et al., 2000).

There is a substantial literature on peripheral administration of opioid-associated ligands to reduce ethanol-drinking by P rats. Essentially, peripheral naltrexone, a pan-opioid antagonist, has been tested repeatedly (Coonfield, Kiefer, Ferraro, & Sinclair, 2004; Dhaher et al., 2012; June, Grey, et al., 1998; Sable, Bell, Rodd, & McBride, 2006) along with a study testing the effects of CeA microinjections (Foster et al., 2004). These publications all reported significant reductions in ethanol intake by male and female, adolescent and adult P rats using both home-cage and operant procedures. Peripheral testing with the pan-opioid antagonists, naloxone (Badia-Elder et al., 1999; June et al., 1991) and nalmefene (June, Grey, et al., 1998), also revealed significant reductions in ethanol intake by male and female, adolescent and adult P rats using both home-cage and operant procedures. Another study reported that nalmefene microinjections into the NAcb, Hipp and VTA significantly reduced operant alcohol self-administration by adult female P rats (June et al., 2004). A study examining the acquisition, maintenance and relapse operant self-administration of ethanol by adult female P rats found that the mu opioid receptor (MOR) antagonist LY255582 significantly reduced all of these behaviors (Dhaher et al., 2012). Other studies examined the role of the delta opioid receptor (DOR) in mediating ethanol intake by adult P rats. Systemic treatment with the DOR antagonists naltriben, naltrindole and ICI 174,864 reduced home-cage ethanol drinking (Krishnan-Sarin, Jing, et al., 1995; Krishnan-Sarin, Portoghese, Li, & Froehlich, 1995) and operant self-administration (June et al., 1999) of the same.

Despite a clear role for the opioid system (including ligand-associated changes in drinking) in alcohol drinking and consummatory behavior across reinforcers, very few changes induced by ethanol and/or differences between P and NP rats have been reported to date (Figure 7). Data of line-dependent differences for the pVTA came from McBride et al., 2012 and data for the CeA and NAcbSh came from McBride, Kimpel, McClintick, Ding, Hyytia, et al., 2013. Data for ethanol drinking-induced changes in P rats (adult data for the whole NAcb came from Rodd et al., 2008; adult data for the NAcbSh came from Bell, Kimpel, et

al., 2009, McBride et al., 2010; adult data for the CeA came from McBride et al., 2010; adult data for the pVTA came from McBride, Kimpel, McClintick, Ding, Hauser, et al., 2013; adolescent data for the CeA came from McBride, Kimpel, et al., 2014; McBride, Rodd, et al., 2014; adolescent data for the DRN came from McClintick et al., 2015) (Figure 7). The findings thus far indicate that multiple opioid systems are involved in excessive ethanol drinking and modulation of this system consistently reduces ethanol intake significantly. Thus, the P rat also displays the relatively robust reduction in alcohol abuse induced by the pan-opioid receptor antagonist naltrexone, let alone similar observations for more selective mu- and delta-opioid antagonists.

The Neuropeptide Y (NPY) system

Neuropeptide Y (NPY) is a 36 amino acid peptide abundantly expressed throughout the central and peripheral nervous systems (Allen, Adrian, Allen, et al., 1983) and acts centrally on target cells through the G-protein, coupled NPY receptors Y1, Y2, and Y5 (Dumont, Satoh, Cadieux, et al., 1993; Fetissov, Kopp, & Hokfelt, 2004; Wolak et al., 2003). NPYir cell bodies have been found in the hypothalamus, hippocampus, amygdala, brain stem nuclei and ganglions of the sympathetic and parasympathetic nervous systems. There is evidence that NPY is locally synthesized (van den Pol, 2012), therefore its expression is not dependent upon projection neurons. For the most part, NPY neurons are interneurons and found in most brain regions except for the thalamus and the cerebellum, although Y-receptors have been detected in the thalamus (e.g., Kaji, 2013). NPY is implicated in food intake and energy balance, anxiety, stress, autonomic function, learning and memory (c.f., Parker, 2013). Given the role of stress and anxiety (at least their comorbidity for the latter) in alcohol and drug dependence, it is not surprising that NPY, and for that matter the interaction of NPY and CRF (e.g., Thorsell, 2010), is implicated in the development and maintenance of alcohol and/or drug dependence (c.f., Al'Absi, 2007). Regarding the NPY-CRF interaction, There appears to be a confluence of activity from multiple systems in the CeA that mediates anxiety and alcohol dependence with a complex interaction of the CRF, GABAergic, glutamatergic and NPY systems (Gilpin, Herman, & Roberto, 2015; Roberto, Gilpin, & Siggins, 2012). Additionally, cAMP response element-binding protein (CREB), brain derived neurotrophic factor (BDNF), activity-regulated cytoskeleton (Arc) associated protein are involved in the modulation of CeA-NPY activity and, by extension, are involved in anxiety and alcohol dependence as well (c.f., Pandey, 2003; Wand, 2005).

Centrally, site-specific injections of NPY point to the amygdala (Gilpin, Richardson, et al., 2008; Gilpin, Stewart, et al., 2008; Pandey, Chartoff, Carlezon, et al., 2005) and hypothalamus (Gilpin, Stewart, Murphy, & Badia-Elder, 2004; Kelley, Nannini, Bratt, & Hodge, 2001) as possible primary neuroanatomical loci for NPY-induced alterations in ethanol drinking. Previous studies suggest that NPY is a major factor which distinguishes the ethanol-drinking behavior of P vs NP rats (Cowen, Chen, & Lawrence, 2004; Pandey, Carr, Heilig, Ilveskoski, & Thiele, 2003; Thiele & Badia-Elder, 2003). P rats display lower levels of NPY immunoreactivity in various regions of the brain, including the CeA, hippocampus and the FC with higher levels in the paraventricular hypothalamic nucleus and arcuate nucleus of the hypothalamus (Ehlers, Li, Lumeng, et al., 1998; Hwang, Zhang, Ehlers, Lumeng, & Li, 1999). Furthermore, decreased levels of NPY are associated with

increased anxiety in P rats (Spence et al., 2005; Stewart et al., 1993), and ICV infusion of NPY has been shown to reduce ethanol intake in the P rat (Gilpin, Stewart, Murphy, Li, & Badia-Elder, 2003) (Fig. 8). Genomically, NPY is localized in an interval that is highly associated with alcohol preference and consumption, mapping to a quantitative trait locus (QTL) with a lod score of 9.2 on rat chromosome 4, using an F2 population bred from iP and iNP rats (Bice, Foroud, Bo, et al., 1998; Carr, Foroud, Bice, et al., 1998).

11. Pharmacogenomics and Alcoholism/Addiction

The interest in using pharmacogenomic research to treat alcohol dependendence spans more than a decade (e.g., Anton et al., 2008; Goldman, Oroszi, O'Malley, & Anton, 2005). Numerous studies have identified a number of single nucleotide polymorphisms that are associated with alcohol dependence and/or drug codependence including (a) CHRM2 (Luo et al., 2005; Wang et al., 2004), CHRNA4 (Kim et al., 2004), CHRNA5 (Saccone et al., 2007; Wang et al., 2009) as well as the CHRNA5-CHRNA3-CHRNB4 cluster and alcohol abuse/dependence (Schlaepfer et al., 2008); (b) DAT (Heinz, Goldman, Gallinat, Schumann, & Puls, 2004; see also Bhaskar & Kumar, 2014 for this and other DA-associated polymorphisms), DA beta hydroxylase (DBH) and alcohol dependence in women (Preuss et al., 2013), DRD3 and alcohol craving (Agrawal et al., 2013) as well as DA dysfunction and Cloninger Type I alcoholism (Leggio & Addolorato, 2008); (c) GABRA1, GABRA2, GABRB3, GABRG3 and alcohol dependence or sensitivity to its intoxicating effects during the ascending slope of the BAC curve (e.g., Bierut et al., 2010; Dick et al., 2004; Dick et al., 2006; Edenberg et al., 2004; Enoch, Schwartz, Albaugh, Virkkunen, & Goldman, 2006; Haughey et al., 2008; Noble et al., 1998); (d) GRIK3 (Grzywacz, Malecka, Suchanecka, Bienkowski, Samochowiec, 2013) and GRIN2A (Domart et al., 2012) with alcohol dependence as well as GRM8 and event-related potential (ERP) theta power and alcohol dependence (Chen et al., 2009); (e) 5HT dysfunction and Cloninger Type II alcoholism (Leggio & Addolorato, 2008), HTR1A and alcohol as well as nicotine co-dependence (Zuo et al., 2013), HTR1B and alcohol as well as multiple drug abuse (Cao, LaRocque, & Li, 2013; Contini et al., 2012), HTR2A and alcohol as well as heroin abuse (Cao et al., 2014), HTR7 and alcohol dependence as wel as electrophysiological measures (Zlojutro et al., 2010; Zuo et al., 2014), alcohol dependence and SERT (e.g., Heinz et al., 2004; c.f., Johnson, 2010; McHugh, Hofman, Asnaani, Sawyer, & Otto, 2010; Plemenitas et al., 2015); (f) OPRM1 and level of response to ethanol in Native Americans (Ehlers, Lind, & Wilhelmsen, 2008), OPRM1 polymorphisms and naltrexone's efficacy for treating alcohol dependence (e.g., Jonas et al., 2014), as well as PDYN and OPRK1 with alcohol dependence (Gerra et al., 2007; Williams et al., 2007; Xuei et al., 2006); (g) CRFR1 polymorphism with P3 ERP and alcohol dependence (Chen et al., 2010); and (h) NPY and its receptor's association with alcohol as well as multiple drug abuse and dependencies (Bhaskar et al., 2013; Frances et al., 2011; Okahisa et al., 2009; Sato et al., 2010; Wetherill et al., 2008). While there is overlap in the ethanol affected neurotransmitter and neuropeptide systems between the clinical alcohol dependent population and the P rat, much more research needs to be done.

12. Conclusions

The present chapter sought to present the existing neuropharmacological findings on P rats in a more holistic manner than done in the past. While previous reviews listed many differences between the P rat and its control line the NP rat, this was mostly done in tabular form or buried in the text. By using figures of the primary neurotransmitter and neuropeptide systems examined thus far in the P rat, our objective was to map the published findings in the context of the projections and/or localization of each respective neuromodulatory system. This chapter also outlines how the P rat has neurochemical, physiological and behavioral characteristics often seen in individuals with alcohol, and in some cases drug, dependence. Finally, it has been proposed that an animal model of alcoholism should display similar pharmacological efficacy as that seen in the alcohol dependent treatment population. Because excessive alcohol is under genetic control, individual differences are expected in animal models just as individual differences prevail in the clinical treatment population. Thus, an animal model of alcoholism also should display some pharmacological treatment validity (Dyr & Kostowski, 2008; Litten et al., 2012; Overstreet, Rezvani, Djouma, Parsian, & Lawrence, 2007).

For the cholinergic system, the P rat displays a modest effect of varenicline on ethanol intake. This parallels the clinical literature in that there are mixed findings for the efficacy of varenicline, especially in the context of smokers vs nonsmokers and/or co-morbid psychaitric conditions. For the DAergic system, findings with the P rat do not match clinical observations; such that whereas manipulations of the DAergic system consistently affect ethanol intake in P rats, this is not true in the treatment setting. For the GABAergic system, the results are mixed. GABAergic modulators are often used during ethanol withdrawal, but cross-tolerance with the effects of ethanol and inherent abuse liability limit their usefulness beyond acute care. One exception should be noted and that is topiramate, which has shown similar efficacy in P rats, other animal models and a tested treatment population. Topiramate, as an anticonvulsant, modulates both GABAergic and glutamatergic activity. Acamprosate, another modulator of the glutamatergic system, has demonstrated modest effects in the clinical treatment population, but only has marginal effects in P rats. Similar to the DAergic system, modulators of the serotonergic system have had limited success in the clinical setting even though robust effects are seen in P rats. Ondansetron is one exception, with mixed findings in both P rats and human laboratory subjects. In addition, it appears that variances in the SERT gene (*5htt*) can determine some pharmacotherapeutic efficacy supporting a role for pharmacogenomics. For the noradrenergic system, prazosin consistently decreases ethanol intake in P rats and promising results are being seen in human clinical studies as well. For the opioid system, naltrexone consistently reduces ethanol intake in P rats and while some clinical studies report robust effects, other clinical studies have reported modest to marginal results. Similar to observations of *5htt* polymorphisms, variances in the OPRM1, and possibly OPRK1, gene appear to have some predictive validity for naltrexone's efficacy in the treatment of alcohol dependence. A final example, which does not fall into any of the systems discussed in this chapter, is ibudilast and more selective inhibitors of phosphodiesterase 4 (PDE4, e.g., Bell et al., 2015; Franklin, Hauser, Lasek, Bell, & McBride, 2015). Robust findings in P rats and multiple other animal models parallel

early results from clinical laboratory studies. Regarding these early findings, it should be noted that in 2015 the Food and Drug Administration (FDA) gave ibudilast a fast-track designation for the treatment of methamphetamine dependence. While considerable progress has been made in the treatment of alcohol and drug dependence, considerable more work needs to be done. One future direction for research with the P rat is to determine if this genetic animal model will self-administer other drugs of abuse. Present work, and some previous work, from our laboratory indicates P rats will readily self-administer nicotine and cocaine into discrete regions of the mesocorticolimbic reward circuit. Intravenous work has not been published yet, but the results look promising for this route of administration as well. These findings suggest that the P rat may be a genetic animal model of polysubstance abuse/dependence.

To date, the vast majority of the genomic information about the P rat has come from microarray and RT-PCR techniques. Future research should use next-generation DNA sequencing to identify genomic signatures of selection between P and NP rats and next-generation RNA sequencing methodologies to analyze allele-specific expression of genes in F1 crosses of these lines (e.g., Farris & Mayfield, 2014; Wang, Kapoor, & Goate, 2012). This will help move the field from QTL analyses to quantitative trait nucleotide [QTN; i.e., (SNPs)] and quantitative trait gene (QTG) analyses (e.g., Ehlers, Walter, Dick, Buck, & Crabbe, 2010; Milner & Buck, 2010; Spence et al., 2009). By doing so, the level of genomic resolution and the power of these analyses will be exponentially increased over the existing techniques. In addition, by localizing genetic variation to genes and SNPs, research on the role of epigenomics/epigenetics (e.g., Moonat et al., 2010; Renthal & Nestler, 2009) in alcohol preference can also be advanced. These advances will allow investigators to combine traditional hypothesis-driven research based on deductive reasoning with unprejudiced genome association studies. These approaches will delineate putative neuromolecular pathways (e.g., intracellular cascades) mediating alcohol dependence and identify possible new drugable targets to prevent and/or treat alcohol abuse and dependence.

Another direction for future research is the use of emerging and evolving neuroscience methodologies to examine the role of second messenger systems, synaptic plasticity, protein-protein interactions, gene-gene interactions, and the role of noncoding RNAs (e.g., Clerget, Bouguignon-Igel, & Rederstorff, 2015; Gedik et al., 2015; Gorini, Bell, & Mayfield, 2011; Gorini, Harris, & Mayfield, 2014; Manzardo, McGuire, & Butler, 2015; Nunez et al., 2013; Ponomarev, Wang, Zhang, Harris, & Mayfield, 2012). Emerging bioinformatic strategies would synthesize the large amounts of data obtained with high throughput gene and/or protein expression techniques (e.g., Gorini et al., 2011; Gorini et al., 2014). Presently, this synthesis has started to reveal the complex neurobiology of alcoholism and the multiple roles of genetics in its development through functional and genetical genomics (e.g., Spanagel et al., 2013; Zuo et al., 2014). We believe that continued research with the P rat using these more advanced genomic, proteomic and bioinformatic techniques will yield new information on molecular substrates to target for repurposing existing FDA-approved medications, or those that are in advanced clinical trials, to treat alcohol and drug abuse/dependence.

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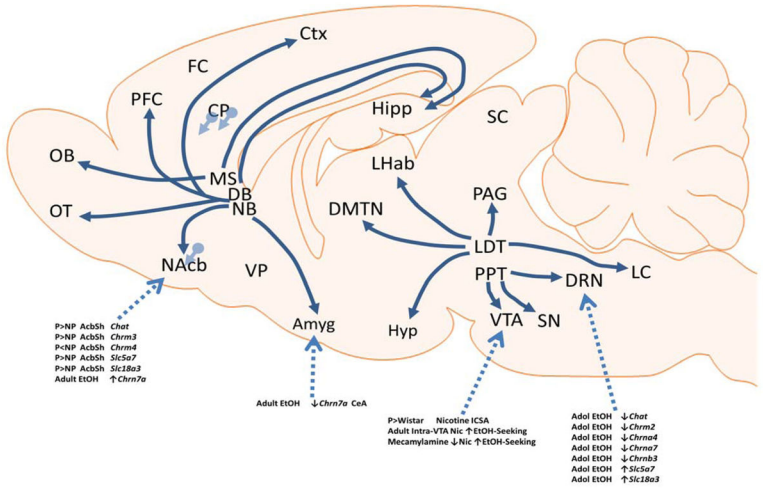

Figure 1.

Innate differences in gene expression between P and NP rats, ethanol-drinking induced changes in gene expression of P rats as well as pharmacological changes in cholinergic activity and/or effects. AcbSh = nucleus accumbens shell; Amyg = amygdala; CeA = central amygdala; Ctx = cortex; CP = caudate-putamen; DB = diagonal band of Broca; DMTN = dorsal medial thalamic nucleus; DRN = dorsal raphe nucleus; FC = frontal cortex; Hipp = hippocampus; Hyp = hypothalamus; LC = locus coereleus; LDT = lateral dorsal tegmentum; LHab = lateral habenula; MS = medial septum; NAcb = nucleus accumbens; NB = nucleus basalis; OB = olfactory bulb; OT = olfactory tubercle; PAG = periaqueductal grey; PFC = prefrontal cortex; PPT = pedunculopontine tegmentum; SC = superior colliculus; SN = substantia nigra; VP = ventral pallidum; VTA = ventral tegmental area. Dark arrows indicate cholinergic projections. Up-arrow indicates an increase, whereas down-arrow indicates a decrease in expression levels, activity or consumption. Short filled arrow = interneuron.

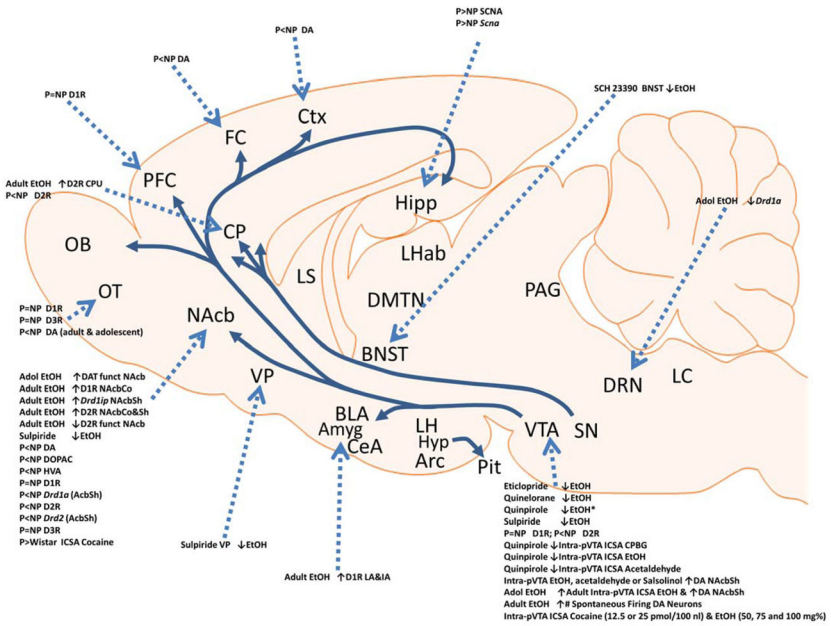

Figure 2.

Innate differences in gene (italics) and/or protein expression between P and NP rats, ethanol-drinking induced changes in gene expression of P rats as well as pharmacological changes in dopaminergic activity and/or effects. Arc = arcuate nucleus of the hypothalamus; BLA = basolateral amygdala; BNST = bednucleus of the stria terminalis; ICSA = intracranial self-administration; IA = intercalated amygdala; LA = lateral amygdala; LH = lateral hypothalamus; NAcbCo = nucleus accumbens core; Pit = pituitary; pVTA = posterior ventral tegmental area. For other abbreviations see Figure 1 legend. Dark arrows indicate dopaminergic projections. Up-arrow indicates an increase, whereas a down-arrow indicates a decrease in expression levels, activity or consumption/self-administration. *, indicates multiple studies.

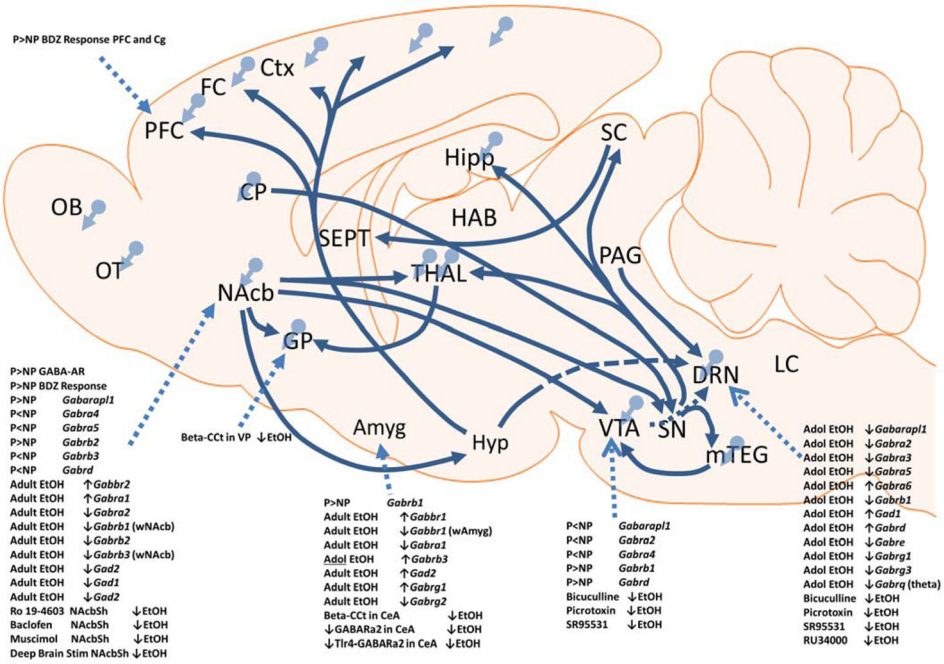

Figure 3.

Innate differences in gene (italics) and/or protein expression between P and NP rats, ethanol-drinking induced changes in gene expression of P rats as well as pharmacological changes in GABAergic activity and/or effects. BDZ = benzodiazepine; Cg = cingulate cortex; GP = globus pallidus; HAB = habenula; mTEG = medial tegmentum; SEPT = septum; THAL = thalamus; wAmyg = whole amygdala; wNAcb = whole nucleus accumbens. For other abbreviations see Figures 1 and 2 legend. Dark arrows indicate GABAergic projections. Up-arrow indicates an increase, whereas a down-arrow indicates a decrease in expression levels, activity or consumption/self-administration. Short filled arrow = interneuon.

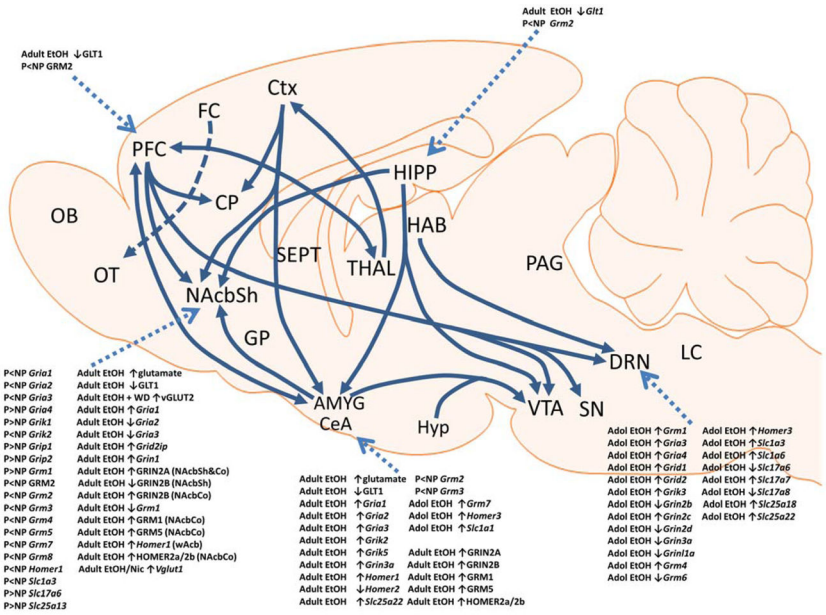

Figure 4.

Innate differences in gene (*Italics*) and/or protein (Upper Case) expression between P and NP rats, ethanol-drinking induced changes in gene expression of P rats as well as pharmacological changes in glutamatergic activity and/or effects. WD = withdrawal. For other abbreviations see Figures 1, 2 and 3 legends. Dark arrows indicate glutamatergic projections. Up-arrow indicates an increase, whereas a down-arrow indicates a decrease in expression levels, activity or consumption/self-administration.

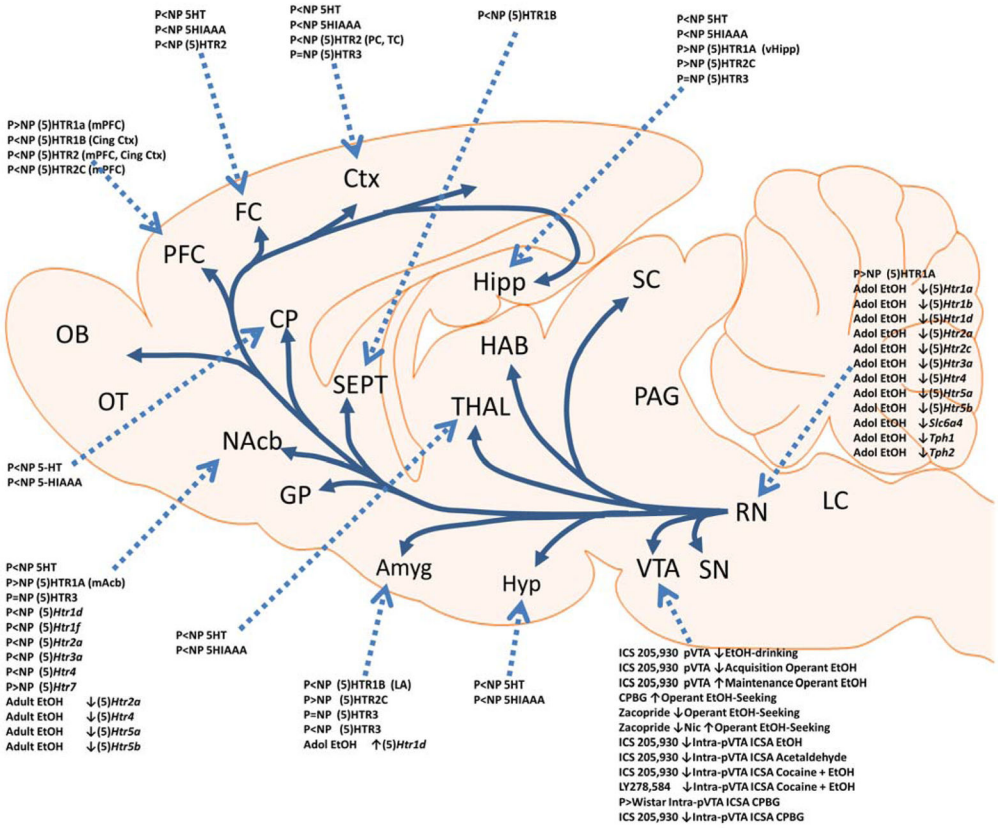

Figure 5.

Innate differences in gene (italics) and/or protein expression between P and NP rats, ethanol-drinking induced changes in gene expression of P rats as well as pharmacological changes in serotonergic activity and/or effects. mAcb = medial nucleus accumbens; LA = lateral amygdala; PC = pyriform cortex cortex; RN = raphe nuclei; TC = temporal cortex; vHipp = ventral hippocampus. For other abbreviations see Figures 1, 2, 3 and 4 legends. Dark arrows indicate serotonergic projections. Up-arrow indicates an increase, whereas a down-arrow indicates a decrease in expression levels, activity or consumption/self-administration.

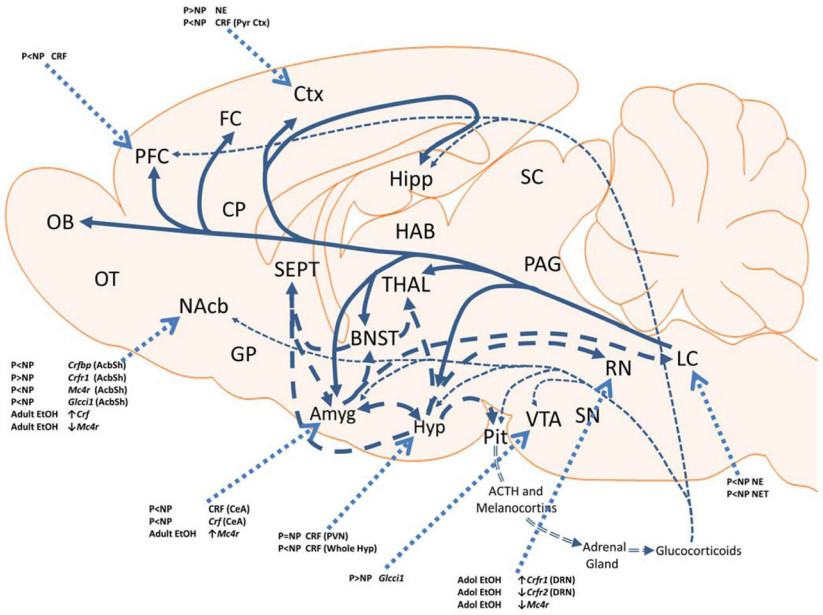

Figure 6.

Innate differences in gene (italics) and/or protein expression between P and NP rats, ethanol-drinking induced changes in gene expression of P rats as well as pharmacological changes in noradrenergic and corticotrophic releasing factor-system activity and/or effects. ACTH = adrenal corticotrophic hormone; MC4R = melanocortin-4 receptor. For other abbreviations see Figures 1, 2, 3, 4 and 5 legends. Dark, solid arrows indicate noradrenergic projections. Dark, thick, dashed arrows indicate CRF projections. Dark, thin, dashed arrows point to nuclei with glucocorticoid binding sites and activity. Up-arrow indicates an increase, whereas a down-arrow indicates a decrease in expression levels, activity or consumption/ self-administration.

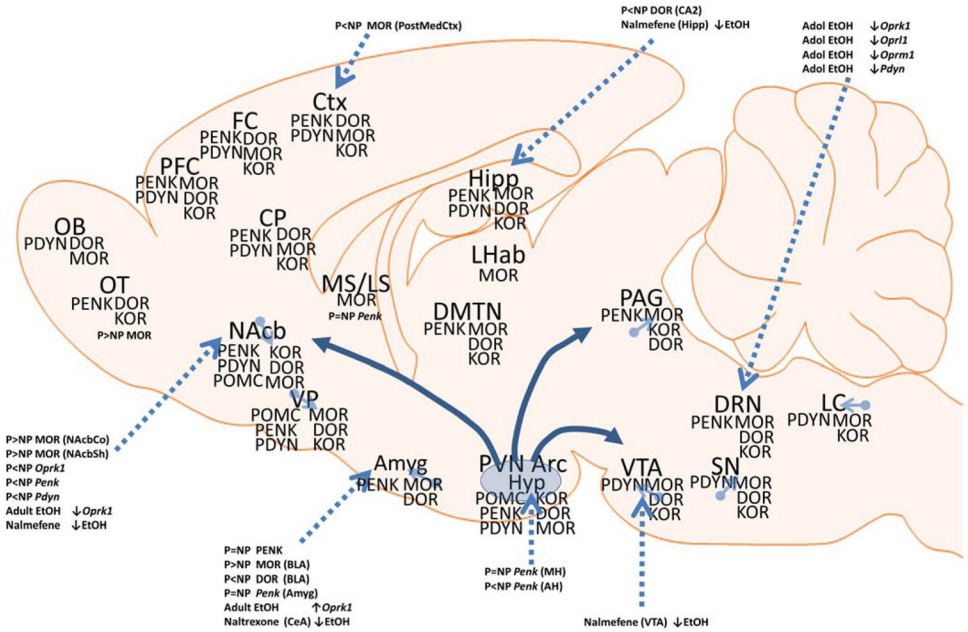

Figure 7.

Innate differences in gene (first letter upper case others lower case and in italics) and/or protein expression between P and NP rats, ethanol-drinking induced changes in gene expression of P rats as well as pharmacological changes in opioid-system activity and/or effects. DOR = delta opioid receptor; KOR = kappa opioid receptor; MOR = mu opioid receptor; Pdyn = prodynorphin; Penk = proenkephalin; POMC = proopiomelanocortin. For other abbreviations see Figures 1, 2, 3, 4, 5 and 6 legends. When multiple opioid precursors (PDYN, PENK or POMC) and/or opioid receptors (DOR, KOR or MOR) are localized in the brain region, the order of density are presented from highest (top) to lowest (bottom). Dark, solid arrows indicate opioid projections. Short light-shaded arrows represent opioid containing interneurons. Up-arrow indicates an increase, whereas a down-arrow indicates a decrease in expression levels, activity or consumption/self-administration.

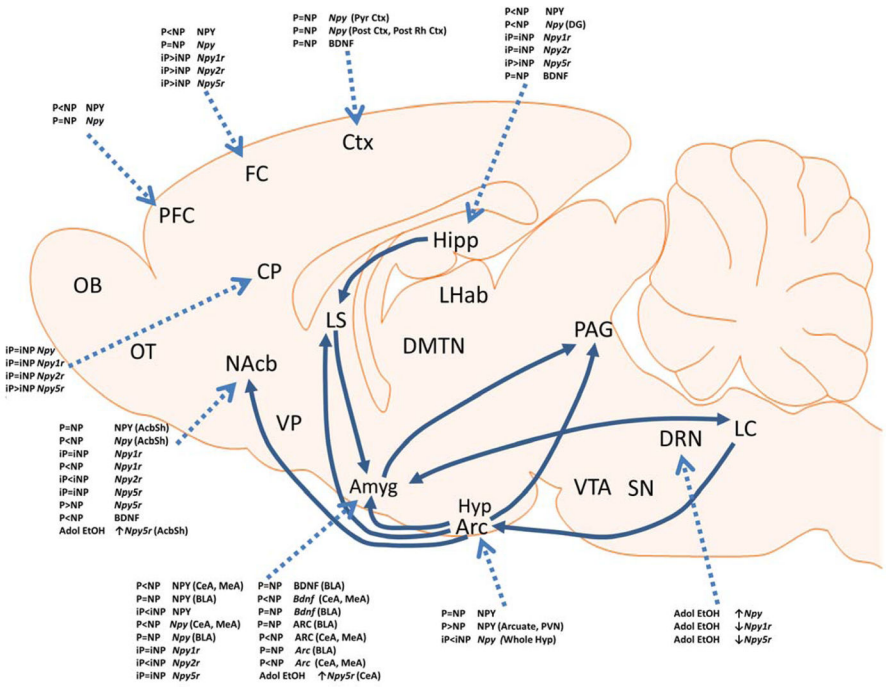

Figure 8.

Innate differences in gene (italics) and/or protein expression between P and NP rats, ethanol-drinking induced changes in gene expression of P rats as well as pharmacological changes in the neuropeptide Y (NPY)-system activity and/or effects. ARC = activity-regulated cytoskelten-associated protein; BDNF = brain derived neurotrophic factor. For abbreviations see Figures 1, 2, 3, 4, 5, 6 and 7 legends. Dark, solid arrows indicate NPY projections. It is important to remember that NPY is also synthesized locally in the brain. Up-arrow indicates an increase, whereas a down-arrow indicates a decrease in expression levels, activity or consumption/self-administration.