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Invited review

Rat animal models for screening medications to treat alcohol use disorders

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ABSTRACT

The purpose of this review is to present animal research models that can be used to screen and/or repurpose medications for the treatment of alcohol abuse and dependence. The focus will be on rats and in particular selectively bred rats. Brief introductions discuss various aspects of the clinical picture, which provide characteristics of individuals with alcohol use disorders (AUDs) to model in animals. Following this, multiple selectively bred rat lines will be described and evaluated in the context of animal models used to screen medications to treat AUDs. Next, common behavioral tests for drug efficacy will be discussed particularly as they relate to stages in the addiction cycle. Tables highlighting studies that have tested the effects of compounds using the respective techniques are included. Wherever possible the Tables are organized chronologically in ascending order to describe changes in the focus of research on AUDs over time. In general, high ethanol-consuming selectively bred rats have been used to test a wide range of compounds. Older studies usually followed neurobiological findings in the selected lines that supported an association with a propensity for high ethanol intake. Most of these tests evaluated the compound's effects on the maintenance of ethanol drinking. Very few compounds have been tested during ethanol-seeking and/or relapse and fewer still have assessed their effects during the acquisition of AUDs. Overall, while a substantial number of neurotransmitter and neuromodulatory system targets have been assessed; the roles of sex- and age-of-animal, as well as the acquisition of AUDs, ethanol-seeking and relapse continue to be factors and behaviors needing further study.

This article is part of the Special Issue entitled “Alcoholism”.

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1. Background from a clinical perspective

1.1. Societal burden of alcohol abuse and dependence

Approximately half of all Americans have at least one relative with an alcohol use disorders (AUD), with some of these individuals having this trait across multiple generations (Research Society on Alcoholism [RSA], 2011, 2015). Half of individuals meeting a lifetime diagnosis for an AUD do so by age 21 with two-thirds doing so by age 25 (Hingson et al., 2006). This is especially troubling given between 15% and 25% of individuals in the military have AUDs (Bray and Hourani, 2007; Bray et al., 2006; RSA, 2011; 2015). There has been a narrowing of the gender gap recently, especially among youth and the elderly (Brienza and Stein, 2002; Nelson et al., 1998; Substance Abuse and Mental Health Services Administration (SAMHSA), 2012; Wilsnack et al., 1991). In the US, the cost of AUDs approaches a quarter of a trillion dollars each year (Harwood et al., 2000; RSA, 2015), with close to 100,000 people dying due to alcohol-related causes every year (RSA, 2011; 2015). The Centers for Disease Control and Prevention (CDC) considers AUDs the third leading cause of preventable death (Mokdad et al., 2004) and is a major factor in the top three leading medical causes of death (RSA, 2011; 2015). Moreover, a direct association has been found between alcohol (ethanol, the primary form of alcohol abused, will be used instead of alcohol in the rest of the paper) use and 50 different medical conditions (Reed et al., 1996; Rehm et al., 2003).

1.2. (Endo)Phenotypic associations with ethanol abuse and dependence

For the present discussion, an endophenotype (sometimes called intermediate phenotype) is defined as a characteristic (a) having relative specificity for the psychiatric disorder being studied, (b) a trait vs state characteristic such that it predates overt expression of symptoms, (c) having significant heritability and is associated with familial density of the disorder, and (d) has biological and clinical plausibility (e.g., Ray and Heilig, 2013). Preclinical and clinical research indicates the following endophenotypes are directly related to the development of ethanol dependence (a) lower initial sensitivity to ethanol's aversive effects (c.f., Bell et al., 2006b, 2012; Colombo et al., 2006; Draski and Deitrich, 1996; Le et al., 2001b; Schuckit and Gold, 1988), (b) greater levels and/or quicker development of ethanol-induced tolerance (c.f., Costin and Miles, 2014; Lê and Mayer, 1996), (c) anxiety-like and/or depressive behavior including during ethanol withdrawal (c.f., Ciccocioppo et al., 2006; Heilig et al., 2010; Kirby et al., 2011; Overstreet et al., 2006; Pautassi et al., 2010; Sjoerds et al., 2014; Thorsell, 2010), (d) stress reactivity (c.f., Barr and Goldman, 2006), and (e) sweet liking/preference (c.f., de Wit and Richards, 2004; Kampov-Polevoy et al., 2014; Lange et al., 2010; Pepino and Mennella, 2007; Perry and Carroll et al., 2008).

Endophenotypes also include ethanol-associated physiological and behavioral stimulation (Trim et al., 2010) [which is modeled in rodents by increased motor activity and/or approach behavior (Chappell and Weiner, 2008; Faria et al., 2008; Wise and Bozarth, 1987), aggression (Chiavegatto et al., 2010), and social facilitation (Varlinskaya and Spear, 2009, 2010)]. Interestingly, there appears to be pharmacological validity for ethanol-associated stimulation as well as reward, with histaminergic (Panula and Nuutinen, 2011 and references therein) and ghrelin (Jerlhag et al., 2011 and references therein) systems implicated in ethanol-induced motor activation, ethanol-induced conditioned place preference, ethanol-preference