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Review

Assessing appetitive, aversive, and negative ethanol-mediated reinforcement through an immature rat model

Ricardo M. Pautassi [a,b,*], Michael E. Nizhnikov [a], Norman E. Spear [a]

[a] Center for Development and Behavioral Neuroscience, State University of New York at Binghamton, Binghamton, NY 13902-6000, USA
[b] Instituto de Investigaciones Medicas M. y M. Ferreyra (INIMEC-CONICET), Friuli 2434, Cordoba, Cba, 5016, Argentina

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ABSTRACT

The motivational effects of drugs play a key role during the transition from casual use to abuse and dependence. Ethanol reinforcement has been successfully studied through Pavlovian and operant conditioning in adult rats and mice genetically selected for their ready acceptance of ethanol. Another model for studying ethanol reinforcement is the immature (preweanling) rat, which consumes ethanol and exhibits the capacity to process tactile, odor and taste cues and transfer information between different sensorial modalities. This review describes the motivational effects of ethanol in preweanling, heterogeneous non-selected rats. Preweanlings exhibit ethanol-mediated conditioned taste avoidance and conditioned place aversion. Ethanol's appetitive effects, however, are evident when using first- and second-order conditioning and operant procedures. Ethanol also devalues the motivational representation of aversive stimuli, suggesting early negative reinforcement. It seems that preweanlings are highly sensitive not only to the aversive motivational effects of ethanol but also to its positive and negative (anti-anxiety) reinforcement potential. The review underscores the advantages of using a developing rat to evaluate alcohol's motivational effects.

Contents

* Corresponding author at: Instituto de Investigaciones Medicas M. y M. Ferreyra (INIMEC-CONICET), Friuli 2434, Cordoba, Cba, 5016, Argentina.
Tel.: +1 54 351 4681465x218; fax: +1 54 351 4695163.
E-mail address: rpautassi@gmail.com (R.M. Pautassi).

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1. Introduction

1.1. Preliminary considerations

Ethanol is arguably the most consumed psychoactive drug in the world. Controlled drinking may be common, but for many individuals ethanol consumption leads to severe psychiatric disorders, with estimates of lifetime prevalence of alcohol dependence reaching 20 and 8% of men and women in the United States, respectively (Enoch, 2003). Genetic factors have been traditionally considered as the main determinants of ethanol affinity (Tyndale, 2003). The level of heritability for alcohol dependence has been claimed to be approximately 50% (Ducci and Goldman, 2008; Enoch, 2003). Indeed, a positive family history for alcoholism is strongly associated with later alcohol abuse or dependence. Male adults with a family history of alcoholism (in first-degree and either second- or third-degree relatives) exhibit a threefold greater incidence of alcoholism than subjects without a family history of alcoholism (Dawson et al., 1992). However, a family history of alcoholism has long been acknowledged to encompass the shared influences of both genetic and environmental influences (National Institute on Alcohol Abuse and Alcoholism, 1993). In the past two decades, the paramount role usually ascribed to genetics in alcohol research has been somewhat tempered by epidemiological and experimental preclinical research indicating that early prenatal or postnatal ethanol experience is significantly associated with later responsiveness to the drug (for a review, see Spear and Molina, 2005). Additionally, ethanol initiation during certain ontogenetic stages, notably adolescence, constitutes a risk factor for the development of later problems with the drug. Specifically, people who begin drinking at age 15 are four-times more likely to become alcohol-dependent than those who start at age 21 (Grant and Dawson, 1997). Ethanol intake usually begins during adolescence, with a decrease in the average age of initiation in the United States from 17.8 years in 1987 to 15.9 years in 1996 (Windle, 2003). A recent study suggests that the peak year for alcohol initiation is even earlier (13–14 years, Faden, 2006). Heavy drinking in this population is also widespread; with 30% of 12th graders reporting that they had been drunk at least once in the last 30 days (Johnston et al., 2007). The insights derived from this and related research (Spear and Molina, 2005; Abate et al., 2008) have added to the conceptualization of alcohol abuse and dependence, which now is considered a developmental disorder with etiological onset at childhood and adolescence (National Institute on Alcohol Abuse and Alcoholism, 2008).

Therefore, understanding the experiential factors that can interact with genetic predisposition to promote high alcohol consumption is important. Ethanol is a complex psychopharmacological agent that exerts a wide array of behavioral effects. Ethanol is a nutrient rich in calories (7 kcal/g; Molina et al., 2007) with a distinctive flavor and taste characterized by a combination of sweet and bitter qualities. These orosensory features can serve as signals (conditioned stimulus, CS) for the upcoming presence of biologically relevant situations (unconditioned stimulus, US) (Molina et al., 1986). For example, contingent experience with the scent of alcohol and aversive stimulation resulted in conditioned avoidance toward the ethanol odor and reduced ethanol intake measured in 21-day-old rats (Serwatka et al., 1986). Ethanol also can act as an interoceptive context that, when present during the acquisition and retrieval phases of a given learning situation, regulates the storage and expression of memories. State dependency mediated by ethanol has been reported in infant, adolescent, and adult rats (Fernandez-Vidal et al., 2003; Hunt et al., 1990; Bruins Slot et al., 1999).

Caloric, orosensory, and state-dependent properties of ethanol play important roles in the regulation of alcohol-seeking and consumption. Initial acceptance of oral ethanol in humans and in non-initiated genetically heterogeneous rats is modulated by these species' apparent dislike for the flavor of ethanol. Ethanol's sensory features have been proposed to constitute a "taste barrier," precluding substantial intake of the drug (Pautassi et al., 2008b). Ethanol intake in two-bottle choice tests decreases sharply as ethanol concentration increases. If faced with a forced choice between water and a relatively low concentration of ethanol (1–5%), heterogeneous non-selected rats may show a modest preference for the drug, but ethanol consumption decreases dramatically as higher concentrations are employed (Kiefer et al., 1987; Samson et al., 1988). Consistent with the hypothesis of a "taste barrier," Kiefer et al. (2005) found that naive rats displayed aversive orofacial reactions when intraorally stimulated with ethanol.

However, beyond caloric or sensory effects, environmental vulnerability to alcohol abuse is mostly influenced by the balance between the contrasting motivational effects of ethanol (Lynch and Carroll, 2001; Roma et al., 2008). Rather than being peripheral constructs, motivational concepts are at the core of all major modern theories of drug abuse and dependence. The compulsive pattern of drug-seeking and -taking found in dependent subjects has been suggested to result from the sensitization of a motivational system responsible for providing incentive salience to environmental stimuli (Robinson and Berridge, 2004; Berridge and Robinson, 1998). Koob and Le Moal (2001, 2008) proposed that drug dependence involves a deviation from the normal reward set point of the organism. Alcohol abuse and dependence are no exceptions to these considerations—motivational properties of ethanol represent critical factors in the modulation of drug-seeking and -taking. Appetitive and aversive consequences of ethanol increase and decrease, respectively, the subsequent probability of such ethanol-focused behaviors (Cunningham, 1998). These factors seem to be particularly important for understanding why certain individuals progress rapidly from controlled use of alcohol to abuse and dependence, while others continue controlled drinking despite continuous exposure to the drug. These subpopulations, consisting of controlled users and those that abuse the drug, may exhibit differential sensitivity to the motivational effects of ethanol. For example, some Asian subjects exhibit an impaired ability to metabolize acetaldehyde, a toxic by-product of ethanol metabolism, because of the lack of one or more alleles for aldehyde dehydrogenase. These persons have increased sensitivity to the aversive peripheral effects of ethanol, a fact that could explain their lower rates of alcohol abuse and dependence (Duranceaux et al., 2006). In contrast, subjects who are at risk for developing alcohol dependence exhibit aldehyde dehydrogenase allelic variations as well as a differential pattern of heart rate activation when given ethanol (Conrod et al., 1997, 1998; Montano Loza et al., 2006; Mulligan et al., 2003). Ethanol-induced changes in heart rate are considered an index of the affective effects of ethanol.