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Emotional reactivity to incentive downshift as a correlated response to selection of high and low alcohol preferring mice and an influencing factor on ethanol intake

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ABSTRACT

Losing a job or significant other are examples of incentive loss that result in negative emotional reactions. The occurrence of negative life events is associated with increased drinking (Keyes, Hatzenbuehler, & Hasin, 2011). Further, certain genotypes are more likely to drink alcohol in response to stressful negative life events (Blomeyer et al., 2008; Covault et al., 2007). Shared genetic factors may contribute to alcohol drinking and emotional reactivity, but this relationship is not currently well understood. We used an incentive downshift paradigm to address whether emotional reactivity is elevated in mice predisposed to drink alcohol. We also investigated if ethanol drinking is influenced in High Alcohol Preferring mice that had been exposed to an incentive downshift. Incentive downshift procedures have been widely utilized to model emotional reactivity, and involve shifting a high reward group to a low reward and comparing the shifted group to a consistently rewarded control group. Here, we show that replicate lines of selectively bred High Alcohol Preferring mice exhibited larger successive negative contrast effects than their corresponding replicate Low Alcohol Preferring lines, providing strong evidence for a genetic association between alcohol drinking and susceptibility to the emotional effects of negative contrast. These mice can be used to study the shared neurological and genetic underpinnings of emotional reactivity and alcohol preference. Unexpectedly, an incentive downshift suppressed ethanol drinking immediately following an incentive downshift. This could be due to a specific effect of negative contrast on ethanol consumption or a suppressive effect on consummatory behavior in general. These data suggest that either alcohol intake does not provide the anticipated negative reinforcement, or that a single test was insufficient for animals to learn to drink following incentive downshift. However, the emotional intensity following incentive downshift provides initial evidence that this type of emotional reactivity may be a predisposing factor in alcoholism.

Introduction

The occurrence of negative life events is associated with problematic drinking (Keyes, Hatzenbuehler, & Hasin, 2011). Alcohol consumption to alleviate a negative emotional state has also been consistently cited as a drinking motive (Adams, Kaiser, Lynam, Charnigo, & Milich, 2012; DeMartini & Carey, 2011). Other recent studies have related certain genotypes with increased alcohol consumption in the face of stressful negative life events (Blomeyer et al., 2008; Covault et al., 2007). Predisposition for emotional reactivity may be associated with a propensity to drink alcohol, though in human studies, it is often unclear if emotional reactivity precedes or follows problematic drinking.

Successive negative contrast, reward downshift, or incentive downshift procedures have been widely used to model emotional reactivity in rodents (Crespi, 1942; Flaherty, 1996). During pre-shift sessions, controls have access to a low magnitude reward and shifted animals have access to a high magnitude reward. During post-shift sessions, all of the animals have access to the low reward, that is, the reward magnitude is decreased in the shifted group, but not decreased in the unshifted group. Responding or consumption in the shifted group below the level of the control group is called a negative contrast effect, and is driven by the relative change in reward magnitude, rather than its current absolute value. The

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behavioral, pharmacological, and neuroanatomical data on incentive downshift suggest that contrast behavior is affectively motivated (Flaherty, 1996; Papini, Wood, Daniel, & Norris, 2006). Contrast effects have also been demonstrated using human lab tasks, making successive negative contrast (SNC) a translatable procedure (Anderson, Munafo, & Robinson, 2012; Specht & Twining, 1999).

High Alcohol Preferring (HAP) and Low Alcohol Preferring (LAP) mice were bi–s during 4 weeks of free-choice ethanol access, with the highest HAP intakes exceeding 20 g/kg/day (Grahame, Li, & Lumeng, 1999; Oberlin, Best, Matson, Henderson, & Grahame, 2011). All HAP lines drink above the rate of their alcohol metabolism and reach pharmacologically relevant blood ethanol concentrations during free-choice access, thus constituting a relevant rodent model of alcoholism (Matson & Grahame, 2013). Alleles determining alcohol preference may also affect other phenotypes, providing information about mechanisms underlying differences in alcohol drinking (Flint & Mackay, 2009).

Reactivity to reward downshifts is a relatively universal phenomenon that likely evolved to support foraging behavior, and may be a major source of affective reactions in humans and other species (Papini, 2003). Certain individuals may react more strongly to and/or be less likely to recover from incentive downshift events. One example exists in the preclinical literature of reactivity to incentive downshift being related to an addictive phenotype. Lewis rats exemplify an addictive phenotype compared to Fisher rats (Kosten & Ambrosio, 2002), and Lewis rats also demonstrate a larger and longer-lasting contrast effect compared to Fisher rats (Freet, Tesche, Tompers, Riegel, & Grigson, 2006). However, Lewis and Fisher rats are two inbred strains, and in order to establish a true genotypic correlation, 8 inbred strains or outbred selected lines should be compared (Crabbe, Phillips, Kosobud, & Belknap, 1990). An alternative strategy, pursued here, is to examine replicated selected lines. We hypothesized that reactivity to an incentive downshift would be positively correlated with selection for high alcohol preference.

Alcohol has anxiolytic properties (Becker & Flaherty, 1983; Kliethermes, Finn, & Crabbe, 2003), and may act to reduce frustration occurring because of an incentive downshift event. Ethanol may also inhibit a negative affective state, allowing for negative reinforcement. This idea is similar to the "tension reduction hypothesis," which maintains that individuals consume alcohol to alleviate anxiety or negative feelings (Sher, 1987; Sinha, 2001). Early preclinical consummatory incentive downshift data suggest that ethanol administration during recovery from contrast, after the initial reaction on post-shift day 1, attenuates contrast (Becker & Flaherty, 1982, 1983). Two additional instrumental contrast studies by Cox and colleagues (Cox, 1988; Cox, Klinger, & Kemble, 1987) suggest that ethanol reduces contrast during all post-shift days. Cox (1988) showed that alcohol consumption prior to incentive downshift also prolonged recovery from incentive downshift. It is possible the different results were due to use of different downshift procedures (Flaherty, 1996). Cox et al. (1987) also investigated activity levels immediately following contrast in animals that had consumed alcohol. Alcohol increased activity levels in both shifted and unshifted animals, but the shifted group that consumed alcohol had higher activity levels than the unshifted group that consumed alcohol, suggesting alcohol reduced the suppressive effects of contrast on locomotion. When alcohol was administered on post-shift day 2, contrast was attenuated, but it returned in shifted animals on post-shift day 3, showing that alcohol's attenuating effects are temporary. It is possible that reactivity to incentive downshift confers an increased drinking risk for individuals with a predisposition to drink because drinking transiently reduces frustration.

An additional aim was to assess whether contrast would alter subsequent ethanol consumption. The crossed HAP (cHAP) line is a cross of the HAP1 and HAP2 replicate lines, which was selectively bred with the idea that a cross of the parent lines would fix a higher number of alleles relevant for alcohol preference. The cHAP line drinks more alcohol than either parent line, achieving mean intakes in excess of 25 g/kg/day and blood ethanol concentrations (BEC) greater than 250 mg/dL (Matson & Grahame, 2013; Oberlin et al., 2011). Therefore, the cHAP line is an excellent genetic model of excessive alcohol consumption. In experiment 2, we measured alcohol consumption in cHAP mice immediately following an incentive shift. We hypothesized that if alcohol provides negative reinforcement, incentive downshift would increase subsequent alcohol consumption in cHAP mice.

Methods

Subjects and apparatus

In experiment 1, subjects included HAP2 (12 males, 12 females) and LAP2 (10 males, 12 females) mice from the 46th generation, and HAP3 (12 males, 12 females) and LAP3 (12 males, 12 females) mice from the 20th generation of selection. In experiment 2A, subjects included cHAP (16 males, 16 females), and experiment 2B subjects included cHAP (12 males, 12 females) mice from the 25th generation of selection. Mice were aged 67–89 days at the beginning of training and were alcohol-naive. Mice were maintained on a reverse light–dark cycle (lights on from 8:00 PM to 8:00 AM) for at least 2 weeks prior to testing, and were individually housed 1 week prior to testing and throughout the experiments.

Twelve identical operant boxes were used in all of the experiments, 21.6 × 19.7 × 12.7 cm inside, with 2 sides constructed of clear acrylic and 2 sides of aluminum (Med Associates, St. Albans, VT). Each operant box was contained in a sound- and light-attenuating chamber equipped with a fan for ventilation and background noise. An LED nose-poke light was used as the house light, and was centered on the 19.7 cm side, 6.3 cm above the floor. Below it was a retractable sipper tube with a 10 mL graduated pipette readable to ±.05 mL that was used to measure sucrose and ethanol intakes. Lick-o-meters were used to start the 5 min testing session. During behavioral testing, Cell-Sorb™ bedding was placed under wire grid flooring and was changed bi-weekly; the operant boxes were also cleaned with 70% ethanol at this time. Boxes were wiped down to remove sucrose and droppings after each session using a wet sponge, and clean sipper tubes were used daily. Mice were run daily during the dark cycle between 10:00 AM and 4:00 PM, using red illumination. Control of the operant boxes and collection of data was performed via the MedPC IV software and MedPC interface cards on a computer (Med Associates, St. Albans, VT). Statistical analyses were performed using SPSS (Chicago, IL).

Experiment 1

Successive negative contrast

Mice were food-restricted to 85% ± 5% of their baseline weight (as described in the Supplementary Materials). Half of the mice in each selected line were then assigned to the shifted 32%–4% sucrose (32-4) group; the remaining mice were assigned to the unshifted 4% sucrose to 4% sucrose (4-4) group. Subjects were assigned to treatment groups counterbalanced for sex and family of origin. The day prior to testing, mice received 1 mL of their training concentration of sucrose in the home cage in order to habituate the mice to sucrose. On days 1–10 of training, mice were placed in operant boxes with the sipper tube available, which descended at the same time each mouse was placed in its assigned box. The 5 min