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Research report

Prior alcohol consumption does not impair go/no-go discrimination learning, but causes over-responding on go trials, in rats

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HIGHLIGHTS

- Withdrawal from alcohol did not impair the ability to learn a go/no-go discrimination.
- Withdrawal from alcohol led to over-responding to a reinforced response option that provided limited reinforcement.
- Alcohol injections decreased voluntary consumption of alcohol.

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ABSTRACT

Prior alcohol use is associated with impaired response inhibition in humans, including in laboratory go/no-go discrimination tasks. In two experiments, we determined whether chronic intermittent access to alcohol would alter go/no-go discrimination learning. Rats received 4–6 weeks of chronic intermittent access to 20% alcohol (alone or accompanied by saline or 1.5 g/kg alcohol injections) or water. Rats then began discrimination training 4–5 days after the end of the alcohol access. Each lever was available for 40 s with one lever intermittently reinforced ("active lever") and the other lever non-reinforced ("inactive lever"). The rats given access to alcohol without concurrent alcohol injections drank ~10 g/kg/24-h on average during the last three weeks of alcohol access. The groups given alcohol injections (Alcohol + Injection groups) exhibited suppressed drinking, but the Alcohol + Injection groups exhibited higher blood alcohol spikes than all other alcohol groups (195 vs. 85–90 mg/dl, respectively). We found no evidence for impaired go/no-go discrimination learning in either experiment. However, the alcohol access groups with moderate-to-high average alcohol consumption (>3 g/kg/24-h) exhibited over-responding to the active lever compared to the water-only groups. One group given alcohol injections (Alcohol + Injection group) that exhibited very low voluntary drinking (<1 g/kg/24-h) did not exhibit the over-responding effect, suggesting that the total 24-h alcohol dose matters more than short-lived blood alcohol spikes. Our findings are in accord with previous research showing that repeated alcohol withdrawal causes over-responding for responses that lead to limited reinforcement. Future work will determine the psychological and neurobiological basis of this behavioral change.

1. Introduction

Alcohol exposure can lead to several long-term cognitive problems that persist after intoxication and acute withdrawal. Detoxified alcoholics exhibit many cognitive deficits suggestive of prefrontal cortex dysfunction when tested three weeks to a month after the last alcohol exposure [10,13], with some symptoms remaining for up to two months or even beyond [5]. One domain that appears to be impaired after the cessation of alcohol is impulsivity/inhibitory control [15]. These inhibitory control problems can be seen in the laboratory in go/no-go discrimination tasks. In go/no-go tasks, one cue (the go cue) indicates that a response should be made and another cue (the no-go cue) indicates that responding is unnecessary or punished through administration of some aversive stimulus or loss of reinforcement. Human alcohol use is associated with impaired go/no-go discrimination learning. Detoxified alcoholics, heavy drinkers and people with higher alco-

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hol use disorder scores exhibit impaired performance or abnormal patterns of reaction times in these tasks [1,6].

It is unclear whether go/no-go discrimination impairments can be seen in rodents given prior access to alcohol. We have previously investigated the effects of 6 weeks of alcohol access on reversal learning in a go/no-go task. In this task, the S+/active lever and S−/inactive levers were available for 40 s regardless of responding (although active lever-presses could only earn 2 pellets/trial), while lever-presses on the inactive lever earned no food reward but were not punished by loss of food reward that would otherwise be available. In rats that received discrimination training before alcohol access and then received reversal learning after alcohol access, we found that alcohol access had no effect on reversal learning, but rats given alcohol access exhibited over-responding to the new active lever and inactive levers [11]. However, it is unclear whether alcohol access before all training would lead to impairments in learning the initial go/no-go discrimination or lead to over-responding in the discrimination training.

Here, we examined the effects of 4–6 weeks of CIA on go/no-go discrimination learning in this go/no-go discrimination task. We also investigated whether alcohol injections would cause a higher peak of blood alcohol levels than voluntary drinking and whether these higher peak blood alcohol levels might cause behavioral changes not seen after voluntary drinking. Experiment 1 investigated the effects of 4 weeks of alcohol access or 1.5 g/kg alcohol injections paired with alcohol access 3 times/week on discrimination learning in this task. Experiment 2 investigated the effects of 6 weeks of alcohol access, 1.5 g/kg alcohol injections paired with alcohol access, or saline injections paired with alcohol access (as a control for injection stress) 3 times/week on behavior on discrimination learning in this task.

2. Methods

2.1. Subjects

Male Long-Evans rats (n = 52), weighing 150–250 g upon arrival in the facility, were used for the experiments. All animals were individually housed and maintained on a 12-h reverse light-dark cycle with lights off at 07:30 am in a temperature and humidity controlled room. Once the rats had acclimated to the facility, they were food-restricted to 85% of their free feeding weights by daily feedings with a minimum of 5 g of food chow per day. Once rats reached their 85% target weights, their target body weight was increased by 1 g/day for the remainder of the experiment and rats were fed to maintain them at their target weights. Water was available *ad libitum*. All procedures and animal care were in accordance with the Kansas State University Institutional Animal Care and Use Committee guidelines, the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals, and United States federal law.

2.2. Behavioral apparatus

Experiments were conducted in standard self-administration chambers (Med Associates, St. Albans, VT). The chambers had two retractable levers on either side of the food cup at approximately one third of the total height of the chamber, with a white stimulus light located above each lever. A red house light was mounted on the top-center of the back wall. A speaker for delivering auditory stimuli was located on the left side of the back wall of the chambers, on the opposite wall from the food cup. A Dell Optiplex computer was equipped with Med-PC for Windows. This computer controlled the equipment and recorded lever-presses.

2.3. Procedure

2.3.1. Alcohol access

Once the rats had stabilized on the food restriction conditions, they then received 4–6 weeks of CIA. There were 3 groups in Exp. 1 (n = 8/group): a Water group that only received water in both bottles, an Alcohol group that received alcohol in one of the 2 bottles 3×/week, and an Alcohol + Injection group that received alcohol in one of the 2 bottles 3×/week and 1.5 g/kg injections of alcohol at the beginning of each 24-h alcohol access period. There were 4 groups in Exp. 2 (n = 7/group): a Water group that only received water in both bottles, an Alcohol group that received alcohol in one of the 2 bottles 3×/week, an Alcohol + Injection group that received alcohol in one of the 2 bottles 3×/week and 1.5 g/kg injections of alcohol (9.5 ml/kg solution per injection) at the beginning of each 24-h alcohol access period, and an Alcohol + Saline group that received alcohol in one of the 2 bottles 3×/week and 9.5 ml/kg injections of saline at the beginning of each 24-h alcohol access period.

During the CIA period, all rats had 2 bottles on their cages on all days, with at least one of the bottles containing tap water at all times (a permanent water bottle). In both experiments, the animals in the Water group received no alcohol during the experiment, and had tap water in both bottles for the duration of the access period. These rats had two bottles on the cages during all days of the access period. In both experiments, the Alcohol, Alcohol + Injection and Alcohol + Saline groups had 20% alcohol (v/v) in one of the bottles for a 24-h period every other day (3 days/week) and water in both bottles on the other days. In these groups, the alcohol bottle was placed onto the rats' cages on Monday, Wednesday, and Friday. The location of the alcohol bottle was randomized to avoid side preference. In addition, the Alcohol + Injection group received 1.5 g/kg intraperitoneal (i.p.) injections of 20% alcohol in sterile saline (v/v) at the beginning of each 24-h alcohol access period before being placed back into the cage with the alcohol and water bottles. The Alcohol + Saline group received 9.5 ml/kg i.p. injections of sterile saline at the beginning of each 24-h alcohol access period before being placed back into the cage with the alcohol and water bottles. The alcohol and water bottles were weighed and exchanged between 9 and 10:30 am each morning. The Alcohol + Injection and Alcohol + Saline groups received their injections when the alcohol bottles were placed on the cages (Monday, Wednesday, and Friday mornings). Two grams were subtracted from the daily weight change for all bottles in the calculation of consumption, in order to account for spillage and evaporation.

2.3.2. Operant discrimination training

At the conclusion of the CIA period, all rats were given a single water bottle for the remainder of the experiment. Three days (Experiment 1) or four days (Experiment 2) after the end of the final alcohol exposure period, all rats began behavioral training. First, rats were given 1 session of magazine training. This magazine training session allows the rats to learn the location of food delivery, and also provides an exposure to the food pellets and should prevent neophobia to the food pellets during the beginning of discrimination training. This session was 40 min long with delivery of a 45-mg food pellet (Catalogue # 1811155, TestDiet, Richmond, IN) every 125 s. Next, rats were trained in successive sessions of a go/no-go lever discrimination task. The rats received 4 days of training in Experiment 1 and 10 days of training in Experiment 2. In this task, the right and left lever were extended one at a time in alternating order for 40 s each, with a cue-light illuminated above the extended lever. The left lever was extended with a cue-light steadily illuminated above it and the right lever was extended with the cue-light above it illuminated in a flashing pattern (2 Hz). For each rat, one of the two lever-light compounds was designated as the active lever/S+ and responses on this lever were rewarded on an inter-