Behavioural Brain Research 320 (2017) 186–194

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Voluntary ethanol consumption changes anticipatory ultrasonic vocalizations but not novelty response

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HIGHLIGHTS

- Response to novelty decreases with age.
- Anticipatory ultrasonic vocalizations are changed after voluntary ethanol exposure.
- Natural reward-associated contexts are recalled after prolong ethanol exposure.
- Contexts associated with natural reward increase anticipatory ultrasonic vocalization after ethanol exposure.
- Ethanol exposure does not affect tickling ultrasonic vocalizations.

ARTICLE INFO

Article history:
Received 16 June 2016
Received in revised form 3 December 2016
Accepted 5 December 2016
Available online 9 December 2016

Keywords:
Novelty seeking
Intermittent access
Ethanol
Ultrasonic vocalizations
Reward processing

ABSTRACT

Novelty and sensation seeking (NSS) and affective disorders are correlated with earlier ethanol (ETOH) consumption, and sustained drinking into adulthood. Understanding the NSS response and affective response before and after voluntary ETOH consumption could elucidate important individual differences promoting sustained ETOH consumption. This study determined that NSS and affective response to rewarding stimulation—measured by ultrasonic vocalizations (USVs)—change after adolescent ETOH voluntary drinking. Rats were tested for their NSS response using the inescapable novelty test. Then rats were tested for their affective response to a natural reward and USVs were measured. The natural reward was experimenter-induced play behavior. Rats were exposed to ETOH for 8 weeks using an intermittent two bottle paradigm. After 8 weeks of voluntary consumption, rats were retested for their response to NSS and affective response to natural reward. Results indicate that voluntary ETOH consumption did not change the response to novelty. Control and ETOH exposed rats decreased their novelty response equally after ETOH consumption, suggesting the decrease was due to age. Importantly, voluntary ETOH consumption changed affective USVs. Compared to water-drinking control rats, ETOH-consuming rats elicited greater anticipatory trill USVs to a natural reward-associated context during a post-drinking probe test. Tickle-induced trill USVs did not change differently between ETOH and control rats. These results provide evidence that voluntary intermittent ETOH exposure increases the anticipation of reward and may represent a form of incentive salience. We postulate these diverging effects could be due to differences in incentive salience or reward processing. Together, these results suggest that voluntary ETOH consumption changes the affective response to conditioned and unconditioned natural rewards and offers a behavioral mechanism for studying affective reward processing after ETOH consumption.

1. Introduction

Alcoholism affects over 16.6 million adults and over 650,000 youth, ages 12–17 in the United States, while only 10–15% are treated for alcohol use disorder (AUD) (National Institute on Alcohol Abuse and Alcoholism, 2013). AUDs are widespread, however, the specific traits contributing to these addictive behaviors vary between individuals. Individual differences moderate the development of AUD [1], but what individual difference traits change after chronic alcohol use is not clearly understood. Determining initial individual differences that promote the development of AUD is important, but determining what individual differences change

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http://dx.doi.org/10.1016/j.bbr.2016.12.004
0166-4328/

after chronic ethanol (ETOH) exposure could aid in determining key traits that promote the development of AUDs.

Animal and clinical studies have reported a strong comorbidity between alcohol abuse and anxiety disorders. People who binge drink alcohol excessively are more likely to display depressive behaviors even after consumption had ceased [2]. In order to measure the effect of binge drinking on affect and other behaviors rodent models of binge drinking have been developed. Previous literature indicates successful preclinical binge drinking models incorporate an intermittent access two bottle choice paradigm (IAE). Rats drink significantly more within the first 30 min and in a 24 h period when alcohol is available on intervening days compared to continuous access [3,4]. The IAE successfully models the binge and withdrawal cycles that contributes to dysregulation of hypothalamic-pituitary-adrenal axis, which may result in emotional or affective disorders [5]. The choice to drink ETOH is important in modeling binge drinking and AUD in rodents. In humans, the development of AUD occurs after voluntary drinking, suggesting that individual differences in consumption or response to ETOH play a significant role in AUD. Therefore, a rodent model of voluntary binge ETOH consumption is important for determining what individual differences promote high levels of drinking. Specifically, determining how novelty and sensation seeking (NSS) and emotional stability are related to the development of AUD or determining how they change after chronic ETOH exposure is paramount to understand individual vulnerabilities to AUD contributing to addictive behavior in humans.

In humans, high NSS individuals report earlier ETOH experimentation, greater overall consumption, and sustained drinking behavior into adulthood [6,7]. Sustained levels of escalated ETOH consumption can lead to depressive behavior, and a decrease in positive affect in response to once hedonic stimuli [7,8]. To date, rodent models of NSS have determined that rodent NSS is complex and may be multidimensional as evidenced by unique uncorrelated behavioral responses [9–12]. Novelty *choice* is measured with the novelty place preference test. Higher novelty *preferring* rats show a propensity to transition to compulsive cocaine self-administration and are resistant to aversive consequences associated with drug reinforcement [1,11,13]. Novelty *response* is tested in the inescapable novelty test. Higher novelty *responders* show faster rates of stimulant self-administration acquisition [9,14]. Therefore, data indicate that novelty choice is important for compulsive drug taking and forced novelty response is important for experimentation and acquisition of drug taking [13]. However, stimulant and depressant addiction show separate neurobiological adaptations and behaviors [15]. Despite both of these novelty tests' relation to addiction, the tests are uncorrelated, suggesting that the inescapable novelty test and novelty place preference test are measuring different aspects of the NSS response. One research group hypothesizes that unlike the novelty place preference test, the inescapable novelty test is measuring the stress response, as evidenced by elevated corticosterone levels [14]. Higher ETOH drinking on an intermittent access schedule results in greater changes to plasma corticosterone levels, and is highly correlated with dysfunctional corticotropin-releasing factor regulation. [5]. Since the IEN test could be used to determine rats' stress response, we aimed to understand how the IEN response changed after intermittent access to ETOH. Alternatively, other research has found that high novelty responders show less preference for ETOH, drink less ETOH, and show a greater ethanol-induced response in locomotor activity when compared to low novelty responders [16,17].

Given that there is a relationship between the IEN and ETOH responses, we focused on determining if the IEN response changes after ETOH consumption [1,11,13,14,18,19]. While the relationship between NSS and drug reward has been researched extensively, determining how natural rewards change after chronic ETOH drinking has not been established. Our lab recently determined that subjective drug value may change differently as a function of the IEN response, such that higher and lower IEN responding rats show different rates of ultrasonic vocalizations (USVs) after repeated non-contingent amphetamine injections [20]. Given that USVs change as a function of amphetamine dose and IEN response, we aimed to understand if 50 kHz USV in response to natural reward change differently after voluntary ETOH consumption.

USVs show large individual differences across rats but remain stable across time, indicating they can be used to study trait-like characteristics in affective and motivational states in rodents [21,22]. Fifty kHz USVs are emitted in response to appetitive stimuli and are indicative of positive affect [23–27]. Trill and frequency modulated (FM) USVs are types of 50 kHz USV that is highly correlated with reward [10,23,28–31]. Twenty-two kHz USVs are emitted when presented with aversive stimuli, during drug withdrawal, and are indicative of negative affect [32–35]. Experimenter-induced tickling is designed to mimic juvenile rodent play behavior. Rats emit high rates of 50 kHz USVs when being tickled; lending support that rats find experimenter tickling rewarding [36]. When USVs are recorded to measure reward that results from psychomotor stimulants or food reinforcement, different USVs are emitted in either optimal or suboptimal reinforcement conditions [32,37]. Previous research has determined that 50 kHz USVs are emitted not only in response to self-administration of psychostimulants, but in anticipation of receiving amphetamine [30], cocaine [28] and ETOH reinforcement [38]. In summary, USVs can be used to interpret positive and negative states in rodents in response to various rewards and affective states.

Our previous research shows that anticipatory USVs change differently in the context associated with natural reward (experimenter-induced tickling), and with actually receiving natural rewards [10]. The present study aimed to determine if voluntary ETOH drinking changes the IEN and USV responses differently. To determine how these individual difference traits change, we measured the IEN response and USV response before and after the intermittent ETOH exposure phase. Since 50 kHz USVs are a reliable measure of rodent positive affect [21,26,39,40], we designed the USV test to probe for 50 kHz USVs because our objective was to determine how the response to naturally rewarding stimulation changes after ETOH drinking. We hypothesized that rats would decrease their locomotor activity in the IEN test after ETOH exposure. Lastly, given that anticipatory USVs increase after associative reward learning, we hypothesized that higher ETOH consumption would result in greater anticipatory 50 kHz trill USVs, while 50 kHz trill USVs in response to receiving a natural reward would decrease.

2. Methods

2.1. Animals

Thirty-eight male Long Evans rats arrived in the lab from Charles River Laboratories at 30 days old. Rats were housed individually in an opaque shoebox cage with pine chip bedding in a temperature and humidity controlled colony room on a reverse 12:12-h light dark cycle with lights off at 10:00A.M. All experimentation occurred in the dark cycle. Food and water were available ad libitum throughout the experiment. Rats habituated to their homecages for one week. During that first week, rats were handled for approximately one minute daily to facilitate experiment handling procedures. Experimentation began 10 days after arrival. All behavioral procedures were approved by Kansas State University Institutional Animal Care and Use Committee and were in accordance with the National Institute of Health guidelines for the Human Use and Care of Laboratory Animals (National Research Council, 2011).