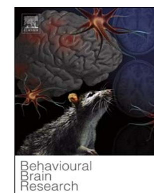
Behavioural Brain Research 339 (2018) 73–78

Contents lists available at ScienceDirect

Behavioural Brain Research

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



Research report

Brain-derived neurotrophic factor (BDNF) determines a sex difference in cue-conditioned alcohol seeking in rats

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ARTICLE INFO

Keywords:
Brain-derived neurotrophic factor
Alcohol seeking
Sex differences
Reinstatement
Extinction

ABSTRACT

Alcohol use disorder is a detrimental addictive disease that develops through prolonged ethanol exposure and regular intoxication. However, the changes in the underlying neurobiology leading to alcohol addiction remain unclear. Brain-Derived Neurotrophic Factor (BDNF) is implicated in substance abuse disorders including alcoholism. As the vast majority of previous animal model studies have concentrated on males only, the aim of this study was to determine whether endogenous BDNF mediates alcohol seeking in a sex-specific manner.

We used an operant self-administration paradigm where the animals were trained in operant chambers to self-administer a 10% ethanol solution, and compared male and female BDNF heterozygous (HET) and wildtype (WT) rats. Over several weeks, the animals progressed through acquisition, progressive ratio, extinction, and reinstatement phases.

There were no significant sex or genotype differences in the number of alcohol-paired lever presses during acquisition, progressive ratio and extinction. However, a significant difference between male and female WT rats following alcohol-primed reinstatement was completely absent in BDNF HET rats suggesting a role of BDNF in sex differences in alcohol seeking after abstinence. Female BDNF HET rats showed significantly higher number of alcohol-paired lever presses during reinstatement than female WT controls.

These findings suggest that BDNF regulatory pathways are involved in sex differences in reinstatement of alcohol intake and emphasize the need to include both male and female animals to explore sex-specific interactions in addiction neurocircuitry.

1. Introduction

Alcoholism is an addictive substance use disorder that often precedes long-term chronic disease. Excessive alcohol consumption causes a variety of primary injuries through liver impairment and neurodegeneration, frequently resulting in public and domestic violence and a broad spectrum of social dysfunction disorders [1]. While alcohol intake in the short term can lead to behaviour-related injury, long-lasting dependence can alter blood pressure, cardiovascular health, mental stability, and is increasingly correlated with liver cancer progression [2]. The prevalence of alcohol abuse is high, with 5.9% of all deaths and 5.1% of the global burden of disease and injury attributed to alcohol in 2012 [3]. Understanding the neurochemical adaptations that lead to alcoholism is of great importance and may lead to amelioration of alcohol addiction though enhanced treatment and diagnosis.

Adaptations to the addiction circuitry of the brain are partially regulated through growth factors. In particular, neurotrophins, growth factors involved in neurodevelopment and neuronal plasticity, have been shown to regulate responses to drug abuse, such as alcoholism [4]. Brain-Derived Neurotrophic Factor (BDNF) is one such neurotrophin, produced in the endoplasmic reticulum and expressed within the central and peripheral nervous systems [5]. The precursor, proBDNF, is proteolytically cleaved to form the mature construct that interacts with the tropomyosin receptor kinase B (TrkB) to initiate downstream signalling on several phosphorylation pathways [1]. These pathways promote neuronal cell growth, maturation, differentiation, synaptogenesis and synapse stability, as well as playing a role in learning and long-term memory consolidation [6]. Alcohol intake has been shown to

Abbreviations: BDNF, brain-derived neurotrophic factor; BEC, blood alcohol concentration; FR3, fixed ratio 3 requirement; HET, BDNF heterozygous (HET) rat; IVC, individually-ventilated cages; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PR, progressive ratio; SEM, standard error of the mean; TrkB, tropomyosin receptor kinase B; WT, wildtype rat

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https://doi.org/10.1016/j.bbr.2017.11.019
Received 28 September 2017; Received in revised form 14 November 2017; Accepted 16 November 2017
Available online 21 November 2017
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reduce BDNF expression over intermittent, repeated, moderate, and chronic exposure in rodents [7,8]. Neuronal networks adapt to recurrent ethanol presence, altering a homeostatic balance that leads to craving in ethanol absence [9] and reducing BDNF expression.

BDNF can also regulate drug sensitization and self-administration, although this regulation appears to be regionally-specific, and differs between addictive drugs. For example, cocaine craving in rats is increased following infusion of BDNF into the nucleus accumbens (NAc) [10], while a reduction of BDNF in the same region is correlated with heightened alcohol preference [11]. BDNF in the medial prefrontal cortex (mPFC) has a similar role with elevated endogenous activity within the mPFC reducing cocaine self-administration [12], while a reduction of levels of the neurotrophin escalates alcohol drinking [13–15]. BDNF in the dorsal striatum may act as a negative regulator for alcohol intake [4] and amygdaloidal BDNF represses anxiety-like behaviour and ethanol intake through increased dendritic spine density [16]. These similarities and variances between brain regions and between addictive substances, infer local specificity of the role of BDNF in reward pathways.

Heterozygous (HET) mutant rodents with a deletion of one BDNF gene allele exhibit a 50% reduction in endogenous protein production [17,18]. These models have been used primarily in the two-bottle choice paradigm where BDNF heterozygous mice develop an increased sensitivity to ethanol exposure [19,20] and a preference for alcohol consumption [19]. Rat models are favourable due to their enhanced learning capabilities and comparable neurocircuitry to humans [21]. More specifically, similar to humans, rats show a strong alcohol deprivation effect which is not as pronounced in mouse models [22]. The role of BDNF within the dorsal striatum has been studied in rats using operant, restricted, and ad libitum ethanol access [23,24]. However, no analyses have been done in BDNF haploinsufficient rats. Furthermore, studies on the role of BDNF in alcoholism have yet to compare and acknowledge potential sex-specific interactions, with previous studies primarily testing male and rarely female animals, but never in parallel. This is despite the suggestion that female rodents have increased sensitivity to BDNF attenuation [19] and accelerated alcohol dependence [25], reflecting potential sex-specific mechanisms in alcohol addiction.

The aim of this study was to compare male and female BDNF HET rats with their WT controls to test the hypothesis that endogenous BDNF negatively regulates alcohol seeking in an operant paradigm in a sex-specific manner.

2. Materials and methods

2.1. Animals

We used BDNF HET rats and WT Sprague-Dawley control littermates obtained from a breeding colony at the La Trobe Animal and Research Teaching Facility, La Trobe University, Melbourne. All rats were genotyped by sending genetic samples to Transnetyx (Cordova, TN, USA). Rats were aged 6–8 weeks at the commencement of behavioural experiments and housed in reverse-light cycle conditions (on 8pm, off 8am) in groups of 2–4 in standard individually-ventilated cages (IVC, Tecniplast, Bugaggiate, Italy). All rats had *ad libitum* access to standard rat chow and water for the duration of the study.

2.2. Ethanol preference − operant self-administration

2.2.1. Overnight training

Initial overnight training and subsequent experiments were conducted in operant chambers (Med Associates, St Albans City, VT, USA) as previously described [26]. A timeline of the experimental paradigm can be found in Fig. 1. Briefly, each chamber was housed within a sound-proof cubicle with a fan to provide airflow and mask external noise. Two retractable levers (visible during operant sessions) were placed below a stimulus light and adjacent to a fluid receptacle. Levers were positioned at opposite corners of the chamber. A single drop of vanilla essence was placed onto a plastic dish under the active lever to act as an olfactory cue and the stimulus light was set to illuminate upon completion of the required number of presses of the active lever only. A controlled liquid dispenser fed each receptacle. Initially, each animal was introduced to the operant chamber for an overnight training session which ran for approximately 16 h. During this session, rats could explore the chamber and learn to lever press for rewards of a solution containing 5% v/v ethanol and 5% w/v sucrose. Pressing the opposite lever resulted in water being dispensed. The levers were set to dispense fluid on a fixed ratio of FR2; 2 lever presses = 100 microliter reward. Rats were provided with food pellets within the chamber to ensure they had adequate access to food overnight.

2.2.2. Sucrose fade

Following overnight training, rats were placed into operant chambers for daily 20 min sessions, five times a week (Monday–Friday). Ethanol and water response levers were alternated between sessions to avoid place-preference, with a small drop of solution (either water or the ethanol-containing solution) left in each receptacle to indicate the current orientation. Similar to the overnight training, both vanilla essence and a stimulus light acted as cues to signal reward availability. A standard 'sucrose fading' protocol was administered (5% sucrose, 5% ethanol 1-5 days, 2.5% sucrose, 10% ethanol from 6 to 8 days). This allowed the aversive taste of ethanol to be overcome through gradual reduction of the concentration of sucrose over a 9-day period. Once sucrose was withdrawn, a 10% ethanol solution was applied to all future sessions.

2.2.3. Fixed ratio responding

Once 9 days of sucrose fade were complete, rats successfully responded to a 10% ethanol solution under a 3:1 fixed ratio requirement (FR3, 3 lever presses equal one reward) within a 20-min daily exposure. Rats that did not lever press were removed from further analysis ($n = 6$). For each session, the total number of ethanol and water responses were recorded. Ethanol availability was again paired with a stimulus light and vanilla essence olfactory cue. Operant responding sessions for ethanol continued up to day 37 until a consistent baseline response was obtained.

2.2.4. Progressive ratio responding

Once a baseline level of responding was achieved, a progressive ratio (PR) reward system was used as previously described [27] to investigate the role of BDNF on "breakpoint". During this phase, the press requirement is progressively increased for each consecutive reward. For example, the first reward is delivered after one press, second reward delivered after three presses, and the third reward delivered after six presses). The water lever followed the same progressive ratio. Breakpoint represents the point during the PR protocol at which the animal ceases to press the active lever the sufficient number of times for a drug reward to be administered. This protocol occurred every second day for a period of one week for a total number of three 90-min PR sessions (Monday, Wednesday, and Friday). The 20-min FR3 condition was conducted in-between PR sessions (Tuesday and Thursday) and resumed after the last PR session for one week prior to commencing extinction testing.

2.2.5. Extinction

Following breakpoint analysis and a further 7 days of FR3 responding to 10% ethanol, extinction training began on day 49 on 10% ethanol. During this phase, both the ethanol solution and water, as well as the conditioned cues (vanilla essence and stimulus light) were withheld from the chamber. Sessions continued daily for 20 min. During the extinction phase lever pressing no longer resulted in a reward, rapidly causing a diminished propensity to lever press. Extinction sessions continued until lever pressing activity reached a low baseline,

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