Physiology & Behavior 97 (2009) 503–506

Contents lists available at ScienceDirect

Physiology & Behavior

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

Brief communication

Lobeline, a nicotinic partial agonist attenuates alcohol consumption and preference in male C57BL/6J mice

Justin M. Farook [a,*], Ben Lewis [a,1], Justin G. Gaddis [a,1], John M. Littleton [b], Susan Barron [a]

[a] Department of Pharmaceutical Science, University of Kentucky, Lexington, Kentucky 40536, USA
[b] Department of Psychology, University of Kentucky, Lexington, Kentucky 40506, USA

ARTICLE INFO

Article history:
Received 10 January 2009
Received in revised form 22 February 2009
Accepted 26 February 2009

Keywords:
Alcohol
Consumption
Nicotine
C57BL/6J mice
Acetylcholine receptors

ABSTRACT

Lobeline is a partial nicotinic agonist and is currently being investigated as a therapeutic drug for several addictive disorders particularly for smoking cessation. The present study evaluated the effects of repeated (continuous and recurring) administration of lobeline on alcohol consumption (10% alcohol vs. water) and alcohol preference using a 2-bottle choice test procedure. Male C57BL/6J mice were individually housed and acclimatized to 10% alcohol. Immediately following the last day of alcohol acclimatization and attainment of consistent drinking pattern, mice ($n = 5$/group) received subcutaneous injections of lobeline (3, 5, or 10 mg/kg) or saline. Groups received either repeated–recurring (3 injections, given every other day) or repeated–continuous (daily injections for 5 days) subcutaneous injections of lobeline. Fluid consumption (alcohol and water) was recorded daily. Results showed that lobeline significantly reduced alcohol consumption and alcohol preference during the repeated (recurring and continuous) administration phases, while total fluid consumption remained unchanged. These results provide support that nicotinic receptor based drugs may be useful as potential treatments for alcoholism.

1. Introduction

The co-occurrence of alcohol consumption and cigarette smoking is well documented [1]. It has been reported that the tendency to consume alcohol is 10 times more prevalent in smokers than in nonsmokers, and therefore a strong correlation exists between alcohol consumption and cigarette smoking [2]. Although an exact mechanism for this relationship is not clear, it is postulated that either drug may increase the rewarding effects [3], or may decrease the toxic or aversive effects of one another [4]. One possible scenario is that alcohol could stimulate the pleasurable effects of nicotine thereby inducing people to smoke more when drinking alcohol [5]. Thus, a clearer understanding of the neurochemical interaction between alcohol and nicotine is essential towards the development of new pharmacotherapies for preventing and/or reducing consumption, or craving for these drugs.

Acetylcholine receptors, or nAChRs in the central nervous system (CNS) represents a common point of action for both nicotine and alcohol since both these drugs are able to stimulate the mesolimbic dopaminergic system, which is an important part of the brain reward system [6,7]. Nicotine is the primary constituent found in cigarettes that is known to reinforce the pleasure of cigarette smoking [8]. The reinforcing effects of alcohol could be partially mediated by nicotinic receptors, which modulate neurotransmitter release [9]. Repeat administration of low doses of nicotine increases, and higher doses suppress, alcohol consumption in rats [10]. Mecamylamine, a nAChR antagonist, significantly reduces alcohol consumption in rats [6]. Therefore, nAChRs could be considered as a potential receptor target for pharmacological interventions for alcoholism [11].

Lobeline is a natural alkaloid derived from *Lobelia inflata* that binds to nAChRs with high affinity, displaying agonist–antagonist activity [12,13], thus leading to its pharmacological classification as a partial agonist. The pharmacology of lobeline is complex since studies show that it interacts with nicotine receptors in a manner that is different from nicotine [12]. The therapeutic potential of lobeline is currently being investigated for smoking cessation [14], as well as for amphetamine [15] and cocaine addictions [16]. The precise mechanism of action of lobeline is unknown, and its potential effects on alcohol consumption are only beginning to emerge. To the best of our knowledge, no studies have been published that investigated the effects of lobeline on alcohol consumption. The reported plasma half-life of lobeline is 50 min [13], and it is of interest to test if lobeline could have a carry over effect from injections administered on a previous day.

Considering its efficacy in other addictive behaviors, the present study was designed to test the effects of repeated administration (continuous, or recurring for 5 days) of lobeline on alcohol consumption and alcohol preference in a high alcohol preferring strain of mice such as the C57BL/6J. The C57BL/6J mice were chosen because they

* Corresponding author. Tel.: +1 859 257 6122; fax: +1 859 323 1979.
E-mail address: justinfarook@uky.edu (J.M. Farook).
[1] Equal contribution.

0031-9384/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.physbeh.2009.02.031

consume large quantities of alcohol, they are widely available and established literature on the pharmacological, behavioral and genetic properties is well documented [17]. A 2-bottle choice procedure that used this strain was recently used in our laboratory to test the therapeutic potential of novel drugs in treating alcoholism [18]. In the 2-bottle choice procedure, animals were placed in single cages, and two bottles containing water or alcohol were made available continuously as a free choice to the animals.

2. Materials and methods

2.1. Animals

Male C57BL/6J mice weighing 28–32 g (Jackson Laboratory, ME) were housed 1/cage in a room maintained on a 16/8 light/dark cycle (lights on at 06:00 AM and off at 09:00 PM) and kept at a constant temperature with free access to food and water for 7 days upon their arrival. All research was conducted in accordance with the guidelines of the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996 and approved by the University of Kentucky Institutional Animal Use and Care Committee.

2.2. Drug

Lobeline *(2-[6-(2-Hydroxy-2-phenylethyl)-1-methyl-2-piperidinyl]-1-phenylethanone hydrochloride (−) Lobeline hydrochloride; $C_{22}H_{27}NO_2 \cdot HCl$)* was obtained from Sigma-Aldrich, USA. The drug was freshly prepared and then injected subcutaneously(s.c.) at doses of 3, 5 and 10 mg/kg (injection volume 10 ml/kg). The various doses of lobeline were chosen based on previous literature [19]. Control animals received s.c. saline injections in a similar injection volume.

2.3. Behavioral procedure

Two-choice test procedure: alcohol priming: Prior to the start of the experiment, mice were given 24 h access to water and alcohol for 7 days using 2 feeding tubes (Dyets Inc, PA) inserted directly into the animal cage. Over these 7 days, the concentration of alcohol was gradually increased using the following schedule: days 1–2: 3%; days 3–5: 6%; days 6–7: 10%. The position of water and alcohol tubes was changed on alternate days in order to avoid potential position bias. Repeated–recurring and repeated–continuous administration phases were considered separate experiments and involved separate batch of animals. Repeated–recurring drug administration involved 3 drug injections (on days 1, 3 and 5), whereas repeated–continuous drug administration involved drug injections on all 5 days. Everyday between 1400 and 1600 h , the amount of alcohol and water consumed was measured for 5 days (every 24 h). Subsequently the drug injections took place after which animals were put into clean cages with fresh alcohol and water. For repeated–recurring drug exposure group, during days when animals do not receive drug injections, animals are then put into clean cages with fresh alcohol and water immediately after measuring the amount of alcohol and water consumed. Alcohol preference was calculated by using the following equation: preference (%) = alcohol intake × 100/total fluid intake.

Statistical analysis: All statistical analysis was performed using SPSS for Windows (v12). The multiple dose determination studies were analyzed using two-way analysis of variance (ANOVA) followed

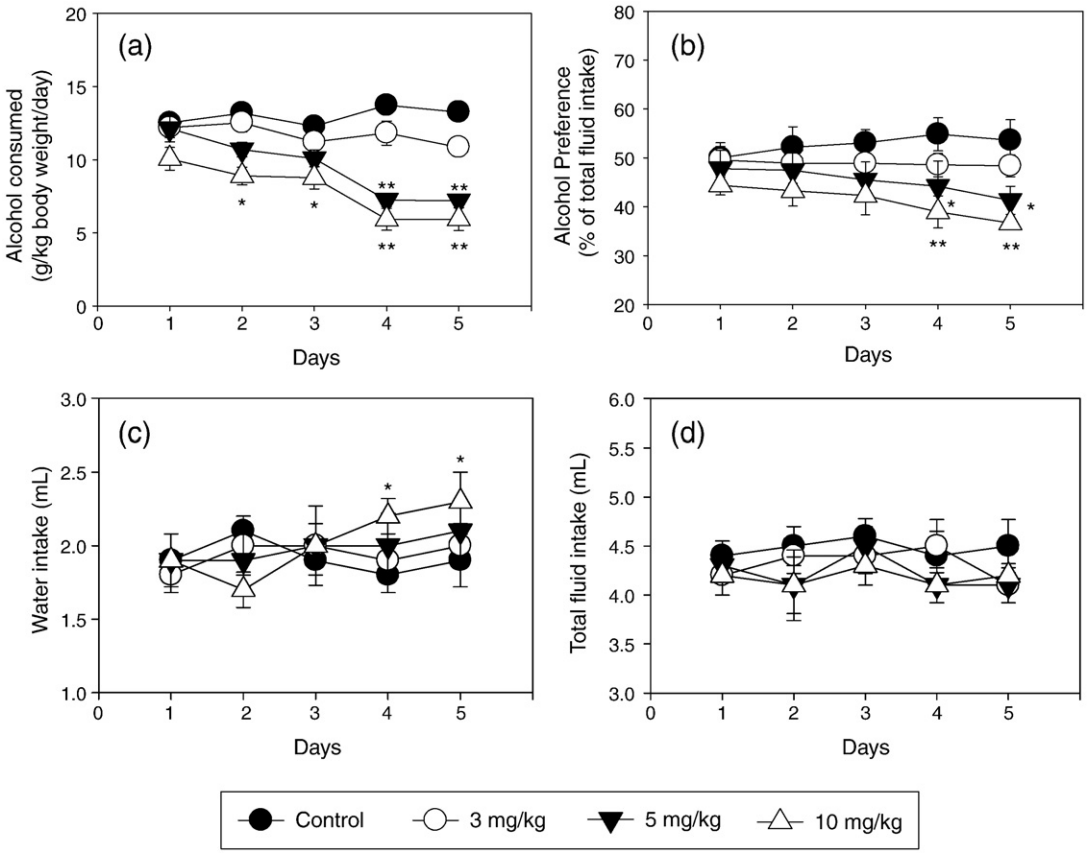

Fig. 1. Effects of subcutaneous repeated (recurring) administration of lobeline (doses of 3, 5, and 10 mg/kg) in the 2-bottle choice procedure test using male C57BL/6 J mice ($n = 5$/group). a) corresponds to alcohol consumption (g/kg); b) corresponds to alcohol preference (% of total fluid intake); c) corresponds to water intake (ml); d) corresponds to total fluid intake (mL). *$p<0.05$, or **$p<0.001$ by post hoc tukey HSD against the appropriate control group across days.