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Alcohol intake in two different mouse drinking models after recovery from the lipopolysaccharide-induced sickness reaction

Mira Lainiola, Anni-Maija Linden*

Department of Pharmacology, Faculty of Medicine, University of Helsinki, Finland

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ABSTRACT

Neuroinflammation may play an important role in the development of alcohol addiction. Recent preclinical reports suggest that enhanced innate immune system signaling increases consumption of alcohol. Our aim was to study whether consequences of lipopolysaccharide (LPS)-induced sickness reaction increase long-term alcohol intake. Adult male C57BL/6J mice, housed in individually ventilated cages, were injected with LPS intraperitoneally (i.p.) and allowed to recover from an acute sickness reaction for 1 week before analysis of their alcohol intake in two different drinking models. Effects of LPS challenge were tested in a continuous two-bottle free choice test with increasing concentrations of alcohol and in a drinking in the dark (DID) binge model. In addition, the effect of repeatedly administered LPS during abstinence periods between binge drinking was analyzed in the DID model. In addition, the DID model was used to study the effects of the microglia inhibitor minocycline (50 mg/kg/day, 4 days) and purinergic P2X7 receptor antagonist Brilliant Blue G (75 mg/kg/day, 7 days) on alcohol intake. In contrast to previous findings, pretreatment with a 1-mg/kg dose of LPS did not significantly increase ethanol consumption in the continuous two-bottle choice test. As a novel finding, we report that increasing the LPS dose to 1.5 mg/kg reduced consumption of 18 and 21% (v/v) ethanol. In the DID model, pretreatment with LPS (0.2–1.5 mg/kg) did not significantly alter 15% or 20% ethanol consumption. Neither did repeated LPS injections affect binge alcohol drinking. Minocycline reduced alcohol, but also water, intake regardless of LPS pretreatment. No data on effects of P2X7 antagonists on alcohol consumption have been previously published; therefore, we report here that subchronic Brilliant Blue G had no effect on alcohol intake in the DID model. As a conclusion, further studies are needed to validate this LPS model of the interaction between immune system activation and alcohol consumption.

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Introduction

Increased expression of innate immune signaling molecules may play an important role in the development of alcohol addiction as well as in the neuropathological problems caused by chronic alcohol use (Crews, Zou, & Qin, 2011; Hutchinson & Watkins, 2014). Increasing evidence, gathered from both rodent models and post mortem human studies, indicates that chronic high-dose alcohol exposure increases, through high-mobility group box 1 (HMGB1) and Toll-like receptor 4 (TLR4) signaling and nuclear factor-kappa B (NF-κB) activation, brain expression of proinflammatory cytokines, including tumor necrosis factor-α (TNFα), interleukin (IL)-1β, IL-6, and chemokine monocyte chemotactic protein-1 (MCP-1), as well as oxidases and proteases (reviewed in Crews et al., 2015). However, less is known about what role this neuroinflammation plays in regulation of alcohol consumption, reward, and alcohol addiction.

Several immune system molecules are linked to regulation of alcohol drinking in rodent models (Harris & Blednov, 2013). For example, genetic deletions of various immune signaling molecules reduced alcohol consumption in knockout mice (Blednov et al., 2012). Mice overexpressing IL-6 showed increased alcohol preference (Harris & Blednov, 2013), and an infusion of an IL-1 receptor antagonist into the mouse basolateral amygdala reduced alcohol intake (Marshall et al., 2016). Moreover, decreasing abnormally high expression of TLR4 or MCP-1 in the central amygdala or ventral tegmental area reduced alcohol self-administration in alcohol-preferring P rats (June et al., 2015). The role of immune signaling in regulation of alcohol consumption in humans is

* Corresponding author. Department of Pharmacology, Faculty of Medicine, University of Helsinki, POB 63 (Haartmaninkatu 8), 00014 University of Helsinki, Finland.
E-mail address: anni-maija.linden@helsinki.fi (A.-M. Linden).

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suggested by genetic studies showing that polymorphisms of NF-κB subunits, IL1β and IL10 are associated with susceptibility to alcoholism (Edenberg et al., 2008; Marcos, Pastor, González-Sarmiento, & Laso, 2008; Pastor, Laso, Romero, & González-Sarmiento, 2005). Additionally, variants of a purinergic P2X7 receptor gene have been linked to alcoholism with co-morbid mood and anxiety disorders (Mantere et al., 2012; Soronen et al., 2011). Moreover, Leclercq and others found that in non-cirrhotic alcoholics, increased intestinal permeability and blood cytokine levels correlated with alcohol craving scores (Leclercq et al., 2012, 2014). Enhanced gut permeability also led to the increased levels of blood lipopolysaccharide (LPS) in alcohol-dependent subjects.

Systemic administration of LPS, an endotoxin from gram-negative bacteria, elicits an innate immune response in the periphery and central nervous system, which has been widely used to study the role of immune signaling in depression, and has been used at high doses to model consequences of sepsis in animals (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Hoogland, Houbolt, van Westerloo, van Gool, & van de Beek, 2015). An acute sickness reaction induced by LPS is characterized by endocrine, autonomic, and behavioral changes including reduced locomotor activity, reduced food and water intake, social withdrawal, and anhedonia. Although these typical behavioral symptoms last one or two days, neuroinflammation and its consequences on neuronal functions appear to persist in the brain longer. For example, moderate doses of LPS (0.3–3 mg/kg, i.p.) produced increases in TNFα, MCP-1, and IL-1β levels in the mouse brain, which lasted at least 1 week (Qin et al., 2008). Moreover, Blednov and others (2011) have shown that pretreatment with LPS (1 mg/kg, i.p.) enhanced alcohol consumption 1 week later in mice.

Our aim here was to utilize the model of enhanced alcohol intake by pretreatment with LPS described earlier (Blednov et al., 2011), in search for an *in vivo* test for studies of interactions between inflammation and alcohol consumption. Because we did not observe the expected enhancement of alcohol drinking in the continuous two-bottle choice model, we next tested the putative effects of LPS challenge in the drinking in the dark (DID) binge model. Finally, although alcohol consumption was not enhanced after LPS treatments, the capacity of two drugs known to modulate neuroinflammation (the microglia inhibitor minocycline and the purinergic P2X7 receptor antagonist Brilliant Blue G) was also tested in the DID model.

Materials and methods

Animals

Male C57Black/6J (Jax®) mice were purchased via Scanbur (a distributor of Charles River, Germany) and transferred at least 2 weeks before experimentation to the animal facility (specific pathogen-free) of the University of Helsinki. Mice were housed in individually ventilated cages (Greenline, Tecniplast, Italy; polysulfone cage, polysulfone/stainless-steel grid top) lined with aspen chip bedding under 12:12-h light:dark cycles (lights on from 6:00 a.m. to 6:00 p.m., unless otherwise noted), at 21–23 °C and a relative humidity of 45 ± 10%, and received standard rodent pellets (Harlan Teklad 2918, Envigo, Madison, WI, USA) and tap water *ad libitum* (unless otherwise noted). The cages were equipped with a wood block (aspen, 1 × 1 × 5 cm) and four sheets (6 × 6 cm) of thin tissue paper (cellulose wadding) as enrichment, which were changed once every 2 weeks at the same time as cages were changed, and scheduled on days when alcohol drinking was not analyzed. The numbers of animals used in the treatment groups are shown in the figures. All efforts were made to minimize animal suffering and reduce the number of animals used. All animal procedures were approved by the Southern Finland Provincial Government.

Drugs

LPS (*E. coli* strain 0111:B4, L4391) was obtained from Sigma (St. Louis, MO, USA). Minocycline hydrochloride and Brilliant Blue G were obtained from Abcam (Cambridge, UK). All drugs were freshly dissolved in pyrogen-free, sterile saline. The pH of minocycline hydrochloride solution was adjusted close to 7 with sodium hydroxide. All other drugs were administered (i.p.) at a volume of 10 mL/kg, except minocycline, which was injected (i.p.) at a volume of 20 mL/kg. For alcohol drinking, ethanol (96% v/v, GPR Rectapur, VWR Chemicals, France) was diluted with tap water into 3–21% (v/v) concentrations.

LPS treatment and recovery

Mice were housed in single cages before LPS pretreatments, which were given at the age of 12 weeks, except in the second continuous two-bottle choice test, when the mice were 7 weeks old, and during repeated LPS injections when the mice were 18–22 weeks old. LPS doses (i.p.) were in the continuous two-bottle choice model at 1–1.5 mg/kg and in the DID models at 0.2–1.5 mg/kg. Body weights and water consumption were monitored daily a few days before LPS and during the recovery period; otherwise, the mice were let undisturbed. Alcohol drinking was started 7 days after LPS injections in other experiments, except when testing the effects of repeated LPS injections, when alcohol drinking was started 4 days after LPS.

LPS pretreatment in the continuous two-bottle choice drinking model

The continuous 24-h two-bottle choice drinking model was performed essentially as described earlier (Blednov et al., 2011). Mice were single-housed in larger individually ventilated cages (30 × 30 × 17 cm) with two holes on the top for placement of drinking bottles or tubes. A water bottle was replaced by a water tube 3 days before LPS treatment. Tubes were used thereafter. Both water and ethanol were delivered from graduated 20-mL tubes affixed to double-ball bearing metal sippers. The position of ethanol and water tubes were changed daily after reading the volume at approximately 4 h after lights were turned on. Tap water was always available.

A single LPS injection (1–1.5 mg/kg) was given in the morning (between 9:00 and 11:00 a.m.). Alcohol drinking was started 1 week after LPS treatment, first at 3% concentration that was available for 2 days, after which increasing concentrations (6%, 9%, 12%, 15%, 18%, and 21%) were offered each for 48 h during a 14-day period. Mice were weighed every other day. After a 1-week alcohol deprivation period, the same drinking procedure was repeated twice. The volume measurement was done by reading from the graduated scale on the drinking tube to the nearest 0.2 mL. Estimates of spillage and evaporation obtained from water and ethanol control tubes, placed in the empty cages, were subtracted from daily ethanol and water intakes. A final daily intake (g/kg/24 h) was a mean of 2 days.

LPS pretreatment in the binge-drinking model (DID 15% ethanol)

The limited-access binge drinking model was adapted from a DID procedure described earlier (Rhodes, Best, Belknap, Finn, & Crabbe, 2005). Mice were single-housed in small individually ventilated cages (16 × 30 × 12 cm, with one hole on the top for a

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