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The peroxisome proliferator-activated receptor alpha agonist fenofibrate attenuates alcohol self-administration in rats

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ABSTRACT

Fibrates are a class of medications used to treat hypercholesterolemia and dyslipidemia that target nuclear peroxisome proliferator-activated receptors (PPARs). Studies have shown the PPARα agonist fenofibrate decreases voluntary EtOH consumption however its impact on the reinforcing and motivational effects of EtOH is unknown. We evaluated the ability of fenofibrate (25, 50 and 100 mg/kg), to alter EtOH (10%, w/v) and sucrose (2%, w/v) operant self-administration in rats under a FR2 schedule of reinforcement over four days and under a progressive ratio (PR) schedule on day five of treatment. Results showed fenofibrate dose-dependently decreased EtOH self-administration under both schedules of reinforcement with the greatest effects seen after four to five days of treatment. Fenofibrate decreased responding for sucrose only under the PR schedule of reinforcement and this effect was not dose-dependent. These findings provide further evidence for fenofibrate as a potential treatment for alcohol use disorder in humans.

1. Introduction

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins that regulate gene expression via their actions as ligand-activated transcription factors (Michalik et al., 2006). Activated PPARs regulate gene expression after heterodimerizing with the retinoid X receptor and bind to PPAR response elements located in target gene promoters. Three PPAR isoforms (α, β, and γ) have been identified to date (Berger and Moller, 2002). PPARα in particular, is involved in energy homeostasis by influencing gluconeogenesis, peripheral triglyceride levels and the breakdown of fatty acids and cholesterol. Accordingly, PPARα receptors are located in organs involved in fatty acid catabolism (e.g. brown adipose tissue, liver, intestines). PPARα receptors are also present throughout the central nervous system (Heneka and Landreth, 2007; Moreno et al., 2004). Commonly known endogenous ligands for PPARα include oleoylethanolamide (OEA), palmitoylethanolamide (PEA), and anandamide (Sun et al., 2006).

Distribution of PPARα in brain and the observation that these receptors may play a role in modulating dopamine (DA) neurotransmission and thus, drug reinforcement, has led to increased attention on ligands targeting PPARs as potential treatments for substance use disorders (Le Foll et al., 2013; Melis et al., 2013a). Indeed, PPARα's are found within limbic structures and expressed on tyrosine-hydroxylase positive neurons (tyrosine-hydroxylase positive) (Moreno et al., 2004; Plaza-Zabala et al., 2010). Administration of the endogenous PPARα ligand, OEA, decreases food consumption and reinforcement that is mediated by central DA neurotransmission (Fu et al., 2003; Plaza-Zabala et al., 2010; Rodriguez de Fonseca et al., 2001; Tellez et al., 2013). Further, increasing endogenous levels of ligands for PPARα or administration of agonists decrease activation of the mesolimbic DA system and attenuate the behavioral effects of nicotine and morphine (Fernandez-Espejo et al., 2009; Luchicchi et al., 2010; Mascia et al., 2011; Melis et al., 2010, 2008, 2013b; Panlilio et al., 2012). Accordingly, evidence indicates that PPARα agonists reduce voluntary ethanol (EtOH) self-administration in rodents; however,

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results have not been consistent.

The fibrates are a drug class of synthetic ligands for PPARs indicated for the treatment of hypercholesterolemia and dyslipidemia. Recent studies have shown the PPARα agonist fenofibrate (a pro-drug for fibrinic acid) decreases voluntary EtOH consumption in mice (Blednov et al., 2016a; Ferguson et al., 2014) and rats (Karahanian et al., 2014). Similarly, gemfibrozil, a PPARα partial agonist, also decreases voluntary EtOH intake in rats (Barson et al., 2009). Yet an earlier report showed that the prototypical PPARα agonist, clofibrate, dramatically increased voluntary EtOH drinking (Schlicht, 1987) whereas another study showed the opposite effect (Lamboeuf and De Saint Blanquat, 1980).

The aforementioned studies used 2-bottle choice and voluntary drinking tests. There have been no studies assessing the effects of fenofibrate on operant oral self-administration, a behavioral paradigm that can better assess EtOH's reinforcing and motivational properties. To achieve this, we tested various doses of fenofibrate on oral operant EtOH self-administration using a fixed ratio (FR) schedule of reinforcement where the response requisite is kept fixed throughout testing. We also used a progressive ratio (PR) schedule of reinforcement where the response requisite is progressively increased over the test session. Potential effects of fenofibrate were similarly assessed under both schedules of reinforcement in rats self-administering a sucrose solution.

2. Materials and methods

2.1. Animals and housing

A total of 14 Wistar rats (Charles River, Wilmington, MA) were housed two to a cage in standard polypropylenle, shoe-box cages with wire tops located within a temperature- and humidity-controlled vivarium that was maintained on a 12:12 light/dark cycle (lights on at 6 a.m.). Rats weighed about 350 g at the start of the experiment and were at least 100 days old. Food and water were available *ad libitum* except for 1–2 days in which.

Water access was restricted for 23-h in order to induce lever pressing for fluids in the operant chamber at the beginning of the training period (see below).

Fig. 1 depicts the experimental procedure followed in the present study. One group of rats (EtOH group; $N = 7$) was housed individually in EtOH vapor chambers (La Jolla Alcohol Research, La Jolla, CA) for 6-weeks prior to operant training using a chronic intermittent exposure (CIE) inhalation schedule known to induce EtOH-dependence (i.e., alcohol vapors were on for 14-h and off for 10-h, 5 days per week) (O'Dell et al., 2004). This CIE inhalation schedule continued throughout the duration of the study. Another group of rats served as sucrose responding controls (SUCROSE group; $N = 7$). All procedures were approved by the Institutional Animal Care and Use Committee in accordance with the National Institutes of Health Guidelines.

2.2. Drugs

The two fluids available for delivery in the operant chambers, sucrose (Calbiochem, La Jolla, CA) and alcohol (ethyl alcohol, 190 Proof, USP grade, Koptec, King of Prussia, PA), were made at concentrations of 2% (sucrose; w/v) and 10% (alcohol; w/v) using tap water. Fenofibrate was purchased from Sigma (St. Louis, MO) and was dissolved in H_2O with 50 μL of Tween-80 added. The three doses of fenofibrate (25, 50, and 100 mg/kg) were prepared in a volume of 1 ml and administered intra-gastrically (PO) on a mg/kg basis 1-hr prior to the onset of test sessions. Each dose was given for five consecutive days in a non-systematic order across rats with at least 1 week intervening between dose presentations.

2.3. Behavioral apparatus

Seven, standard operant chambers (Coulbourn Instruments, Allentown, PA) enclosed in sound-attenuating cubicles (Coulbourn Instruments) were used in the present study. Each chamber was equipped with two levers located on either side of an access area into which a dipper (0.1 mL capacity) could protrude. Prior to activation, the dipper was maintained in a small reservoir of fluid (sucrose or EtOH). Infrared sensors located in the dipper access area provided the means to tabulate numbers of head entries. A house light, a dipper access area light, and two sets of three, colored cue lights, one above each lever, were located within the operant chamber. Stimulus parameters and data tabulation were programmed using Graphic State Notation (version 4.0).

2.4. Operant self-administration training

Rats were put on fluid restriction prior to the first day of training. Training sessions (1-hr in length) began with the illumination of the house light. Initially, a head entry into the dipper access area triggered the protrusion of the dipper for 15-s with a 5-s inter-trial interval. The dipper access light would be illuminated for the entire length of the dipper presentation time. Dipper presentation times were gradually reduced over a week of training, based on each animal's performance, until they were 3-s in duration. Levers were retracted during this phase of training. During the next phase of training, the levers protruded at the start of the session, signaled by the illumination of the house light, and two “primes” (dipper presentations) were given. Then, when the rat pressed the active lever, the house light would turn off, the dipper would protrude, and the access area light and the triple cue light above this lever became illuminated. Presses on the inactive lever had no programmed consequences. Once a rat emitted 25 active lever presses with 20% variability or less in response levels over 2-days, the ratio requirement was raised to fixed-ratio 2 (FR2), the schedule used for the rest of the training. Stable response levels under the FR2 schedule ($\leq$20% variability over 2-days) were required for the animal to move into the testing phase.

2.5. Operant self-administration testing

Test sessions were conducted 5-days a week, 7–8 h s after CIE to EtOH vapor. On Monday-Thursday, a 1-hr session under the FR2 schedule was conducted. The Friday test session was conducted under a progressive ratio (PR) schedule (e.g. 1, 1, 2, 2, 3, 3, 4, 4, 5, 5, 7, 7, 9, 9, 11, 11, 13, 13, 15, 15, 18, 18, 21, 21, 24, 24, etc.) and was 3-h in duration as described previously (Kosten, 2011; Walker and Koob, 2007). Each dose of fenofibrate and its vehicle were administered 1 h prior to the test sessions over these 5-days of testing. At least 1-wk intervened between dose test weeks in order to ensure that response levels had returned to pre-drug, baseline levels.

2.6. Statistical analysis

Data from the FR and PR tests for both groups were analyzed separately and included numbers of active and inactive lever presses and reinforcers earned (dipper presentations). The four days of FR2 tests were analyzed using a 4×4 ANOVA representing factors of fenofibrate dose (0, 25, 50, 100 mg/kg) with repeated measures on Day. Significant main effects were followed by post-hoc pairwise multiple comparisons using Bonferroni *t*-test. Data from the PR test sessions for active and inactive lever presses and reinforcers earned were analyzed using ANOVA with fenofibrate dose (0, 25, 50, 100 mg/kg) as the factor. Significant main effects were followed by post-hoc pairwise multiple comparisons using