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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 PPAR α 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 100mg/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). PPAR α in particular, is involved in energy homeostasis by influencing gluconeogenesis, peripheral triglyceride levels and the breakdown of fatty acids and cholesterol. Accordingly, PPAR α receptors are located in organs involved in fatty acid catabolism (e.g. brown adipose tissue, liver, intestines). PPAR α receptors are also present throughout the central nervous system (Heneka and Landreth, 2007; Moreno et al., 2004). Commonly known endogenous ligands for PPAR α include oleoylethanolamide (OEA), palmitoylethanolamide (PEA), and anandamide (Sun et al., 2006).

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Distribution of PPAR α 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, PPAR α '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 PPAR α 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 PPAR α 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; Melis et al., 2008; Melis et al., 2013b; Panlilio et al., 2012). Accordingly, evidence indicates that PPAR α agonists reduce voluntary ethanol (EtOH) self-administration in rodents; however, 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 PPAR α agonist fenofibrate (a pro-drug for fibrinic acid) decreases voluntary EtOH consumption in mice (Blednov et al., 2016; Ferguson et al., 2014) and rats (Karahanian et al., 2014). Similarly, gemfibrozil, a PPAR α partial agonist, also decreases voluntary EtOH intake in rats (Barson et al., 2009). Yet an earlier report showed that the prototypical PPAR α 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 polypropylene, 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 AM). 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)

Figure 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 H₂O with 50 μ L 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 (< 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, 7–8hrs 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 hour 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.

2.7 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, 100mg/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, 100mg/kg) as the factor. Significant main effects were followed by post-hoc pairwise multiple comparisons using Student-Newman-Keuls Method. *P*-value considered significant was set at <0.05.

3. Results

3.1 Alcohol and sucrose self-administration

3.1.1 FR2 tests—The numbers of active and inactive lever presses emitted over the four days of tests conducted under the FR2 schedule of reinforcement are shown in Table 1 for both EtOH and sucrose groups. Analysis of active lever presses emitted by the EtOH group revealed a significant main effect for fenofibrate Dose ($F_{(3,111)}=42.696$; $P<0.001$) and Day ($F_{(3,111)}=15.990$; $P<0.001$) and a Dose $\times$ Day interaction ($F_{(9,111)}=3.403$; $P=0.002$). Post-hoc analysis of active lever presses following the main effect for Dose indicated a significant difference between all fenofibrate doses ($P's<0.05<0.001$). Post-hoc analysis following the main effect for Day showed the numbers of active lever presses significantly differed between all days ($P's<0.05$) except Day 1 vs. Day 2 and Day 2 vs Day 3 ($P's>0.05$). Post-hoc analysis following the significant Dose $\times$ Day interaction showed comparisons for factor Day within Dose revealed significantly lower active lever presses on Day 4 compared to Days 1 and 2 ($P's<0.01$) following 25 mg/kg fenofibrate. Further, active lever presses were significantly lower ($P's<0.05$) on Days 3 and 4 compared to Day 1 following both 50mg/kg and 100mg/kg fenofibrate. Post-hoc comparisons for factor of Dose within Day for the EtOH group revealed lower active lever presses following 100mg/kg compared to the 25mg/kg fenofibrate dose ($P<0.01$) across all days. Moreover, active lever presses were significantly lower following all fenofibrate doses (25, 50, 100mg/kg) compared to 0mg/kg on days Days 3 and 4 ($P's<0.05$). Analysis of inactive lever presses revealed a significant

main effect for fenofibrate dose ($F_{(3,111)}=4.430$; $P=0.017$) but not Day ($F_{(3,111)}=0.982$; $P=0.423$) and no interaction ($F_{(9,111)}=1.018$; $P=0.438$). Post-hoc comparisons following the main effect for fenofibrate dose revealed overall decreases in inactive lever presses following 50 and 100mg/kg fenofibrate compared to 0mg/kg ($P's<0.05$).

Analysis of active lever presses for the FR tests in rats self-administering sucrose revealed no main effects for fenofibrate dose ($F_{(3,111)}=0.214$; $P=0.886$) nor Day ($F_{(3,111)}=2.947$; $P=0.061$). Analysis of inactive lever presses revealed a significant main effect for fenofibrate dose ($F_{(3,111)}=12.510$; $P<0.001$) but not for Day ($F_{(3,111)}=1.66$; $P=0.210$) and no interaction ($F_{(9,111)}=1.259$; $P=0.280$). Post-hoc analysis following the main effect for fenofibrate dose revealed significant decreases in inactive lever presses 25mg ($P<0.05$) and 100mg/kg ($P<0.01$) compared to 0mg/kg and 100mg/kg compared to 50mg/kg ($P<0.01$).

The number of reinforcers earned under the FR tests across days for the EtOH and sucrose groups is presented in Figure 2A and B respectively. For the EtOH group, analysis revealed a significant main effect for fenofibrate dose ($F_{(3,111)}=47.969$; $P<0.001$), Day ($F_{(3,111)}=15.384$; $P<0.001$) and a fenofibrate dose $\times$ Day interaction ($F_{(9,111)}=3.216$; $P=0.003$). Post-hoc analysis of reinforcers earned following the main effect for Dose indicated a significant difference between all fenofibrate doses ($P's<0.02$ - <0.001). Post-hoc analysis following the main effect for Day showed the numbers of reinforcers earned significantly differed between all days ($P's<0.05$) except Day 1 vs. Day 2 and Day 2 vs Day 3 ($P's>0.05$). Post-hoc analysis following the significant Dose $\times$ Day interaction showed comparisons for factor Day within Dose revealed significantly lower numbers of reinforcers earned on Day 4 compared to Day 1 ($P<0.001$) and Day 2 ($P=0.005$) following 25 mg/kg fenofibrate. Further, reinforcers earned were significantly lower ($P's<0.05$) on Days 3 and 4 compared to Day 1 following both 50mg/kg and 100mg/kg fenofibrate. Post-hoc comparisons for factor of Dose within Day revealed lower numbers of reinforcers earned following 100mg/kg compared to the 25mg/kg fenofibrate dose ($P<0.01$) across all days. As shown in Figure 2A, reinforcers earned were significantly lower following all fenofibrate doses (25, 50, 100mg/kg) compared to 0mg/kg on days Days 3 and 4 ($P's<0.05$).

Reinforcers earned across days for the sucrose group are presented in Figure 2B. Analysis revealed no main effect for fenofibrate dose ($F_{(3,111)}=0.132$; $P=0.940$) nor Day ($F_{(3,111)}=2.872$; $P=0.065$).

3.1.2 PR Tests—Data generated from the PR tests are presented in Table 2. Analysis of active lever presses for the EtOH group revealed a significant main effect for fenofibrate dose ($F_{(3,27)}=46.895$; $P<0.001$). Post-hoc comparisons following the significant main effect for fenofibrate dose indicated significant differences between all doses ($P's<0.01$). There was no main effect for fenofibrate dose ($F_{(3,27)}=1.079$; $P=0.377$) on inactive lever presses.

Analysis of active lever presses in rats self-administering sucrose under the PR schedule of reinforcement revealed a main effect for fenofibrate dose ($F_{(3,27)}=9.880$; $P<0.001$). Post-hoc analysis following the main effect for fenofibrate dose revealed significant decreases in active lever presses following 25mg, 50mg and 100mg/kg fenofibrate compared to 0mg ($P's<0.01$). A significant main effect for fenofibrate dose was also found following analysis

of inactive lever presses elicited by the sucrose group ($F_{(3,27)} = 8.168$; $P < 0.001$). Post-hoc analysis following the main effect for fenofibrate dose revealed significant decreases in inactive lever presses following 25mg, 50mg and 100mg/kg fenofibrate compared to 0mg (P 's < 0.01).

Reinforcers earned under the PR tests for both EtOH and sucrose groups are presented in Figure 3A and B respectively. Analysis of reinforcers earned for the EtOH group revealed a significant main effect for fenofibrate dose ($F_{(3,27)} = 36.361$; $P < 0.001$). Post-hoc pairwise multiple comparisons revealed significant differences between all fenofibrate doses (P 's < 0.01) in a dose-response manner (Figure 3A). Analysis of reinforcers earned for the sucrose group revealed a significant main effect for fenofibrate dose ($F_{(3,27)} = 12.472$; $P < 0.001$). Post-hoc pairwise multiple comparisons revealed significant differences between 0mg/kg and 25, 50 and 100mg/kg fenofibrate doses (P 's < 0.01).

4. Discussion

The results of the present study show that administration of fenofibrate, a preferential PPAR α agonist, led to a dose-dependent decrease in the reinforcing and motivational effects of EtOH with the greatest impact seen after about three to four days of treatment. Fenofibrate did not alter responding for sucrose under a FR2 schedule of reinforcement however it did decrease responding under a PR schedule of reinforcement. Unlike the effects of fenofibrate seen on EtOH self-administration, altered responding for sucrose was not dose-related and appeared non-selective. Nonetheless, the present study is the first to show fenofibrate decreases operant oral EtOH self-administration in rats under two schedules of reinforcement. These data are consistent with a majority of previous studies assessing fenofibrate on oral voluntary EtOH self-administration in rodent.

Results from the present study are largely congruent with previous studies assessing the impact of PPAR α agonists on the behavioral effects of EtOH. For example, Ferguson et al. showed pretreatment with fenofibrate (150mg/kg/8 days, PO) decreased EtOH (15%) consumption in mice using a continuous access two-bottle choice drinking procedure (Ferguson et al., 2014). A more recent study showed similar results following fenofibrate (100 and 150mg/kg, PO) administration in mice using continuous and intermittent 2-bottle choice EtOH (15%) drinking tests (Blednov et al. 2016a). In that same study, fenofibrate administration in mice lacking PPAR α did not alter EtOH consumption but did in wild-type mice thus showing specificity. Similarly, at a dose of fenofibrate that significantly reduced EtOH self-administration in the present study, Karahanian et al. showed fenofibrate (50mg/kg/14 days, PO) decreased voluntary EtOH (10%) consumption in high-drinker UChB rats (Karahanian et al., 2014). Further, the PPAR α partial agonist gemfibrozil (50mg/kg, PO), decreased EtOH intake in rats voluntarily consuming a 7% alcohol solution (Barson et al., 2009). In contrast to these and the present study, Schlicht showed that daily administration of the prototypical PPAR α agonist clofibrate (300mg/kg/day) in food fed to Spontaneously Hypertensive Rats dramatically *increased* voluntary consumption of a high concentration of EtOH (30%) compared to controls (Schlicht, 1987). These contradictory findings may be attributed to a number of methodological differences including dose, administration route of the PPAR α agonist, rat strain, and uncommonly high concentration

of EtOH used. Nevertheless, results of the present study are in line and extend previous studies assessing the impact the PPAR α agonist fenofibrate on EtOH-reinforced behavior in rodents.

Our data indicate that the effect of fenofibrate on sucrose reinforcement appears to be non-specific. In contrast to dose-related effects seen in rats self-administering EtOH under a FR2 schedule of reinforcement, fenofibrate did not decrease active lever presses (Table 1) nor reinforcers earned (Figure 2B) in rats self-administering sucrose. This finding is consistent with a recent study in mice (2-bottle choice test 24-hour access) showing fenofibrate did not alter saccharin intake (Blednov et al 2016b). Fenofibrate did however decrease active as well as inactive lever presses and reinforcers earned under a PR schedule of reinforcement for sucrose (Table 2 and Figure 3B). Yet this effect was not dose-related as was the case with fenofibrate's effects on both FR and PR schedules of reinforcement for EtOH. That the effects of fenofibrate on number of active lever presses emitted and reinforcers earned under both FR and PR schedules in the EtOH group implies that decreases in EtOH-reinforced behavior are specific to fenofibrate. This effect was also dose-related. Because fenofibrate did decrease sucrose self-administration under the PR schedule may reflect differences in the sensitivity between the schedules of reinforcement utilized to detect drug effects on reinforced behavior. Given the role of PPAR α in lipid metabolism, satiety and food consumption however, it is not surprising that fenofibrate significantly decreased sucrose reinforcement (Michalik et al., 2006). Indeed, endogenous PPAR α ligands, such as OEA, and synthetic PPAR α agonists (e.g. WY14643, GW7647) decrease food consumption and body weight in wild-type and obese mice but not in PPAR α knock-out mice (Fu et al., 2003; Tellez et al., 2013). In accord with our results, numerous studies using a variety of rat and mouse obesity models have consistently shown fenofibrate decreases food consumption (Jeong and Yoon, 2009; Lee et al., 2002; Park et al., 2012). The present study extends this effect of fenofibrate to the motivational aspects of sucrose self-administration.

The mechanism(s) responsible for the ability of fenofibrate to decrease EtOH reinforcement are presently unknown, however, both central and peripheral targets have been proposed. EtOH is metabolized into acetaldehyde and then to acetate by the liver through three primary enzymatic reactions involving alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), and catalase. Drugs that increase activity of these enzymes augment EtOH metabolism into acetate. For example, blockade of ALDH increases systemic levels of acetaldehyde that may be aversive and presumably, contribute to the marginally successful use of the ALDH inhibitor disulfiram, for the treatment of alcohol use disorder in humans. It appears however that disulfiram's therapeutic effects are likely due to it acting centrally (Gaval-Cruz and Weinshenker, 2009). Nevertheless, evidence indicates PPAR agonists can alter EtOH elimination. For example, consistent with facilitation of ethanol elimination, bezafibrate and clofibrate, increase ALDH and peroxisomal beta-oxidation activity that results in decreased blood EtOH and acetaldehyde levels and increased acetate concentrations following EtOH (Hawkins et al., 1974; Kramar and Kremser, 1984; Lamboeuf and De Saint Blanquat, 1980; Tsukamoto et al., 1996). Another report shows that fenofibrate increased blood acetaldehyde levels and liver catalase activity following voluntary alcohol drinking (10%), but does not alter liver ALDH levels (Karahanian et al., 2014). Although these data suggest that fenofibrate facilitates EtOH clearance, blood EtOH

levels were not assessed (Karahanian et al., 2014). A recent study using mice evaluated the effects of fenofibrate (150mg/kg) on EtOH clearance following an IP injection of EtOH (4.0g/kg) measured over 5 time points (30, 60, 120, 180 and 240 min)(Blednov et al., 2016b). Results indicate that fenofibrate facilitated EtOH clearance. It would stand to reason that if fenofibrate facilitated the metabolism of EtOH, rats would have compensated by increasing responding for EtOH. Our data would appear to be consistent if EtOH elimination was delayed since fenofibrate decreased EtOH self-administration in the present study. Moreover, the PPAR α / γ / β mixed agonist bezafibrate, which has been shown to decrease blood EtOH levels, does not reduce voluntary EtOH self-administration (Ferguson et al., 2014; Tsukamoto et al., 1996). Nevertheless, it is unlikely that the impact of fenofibrate on EtOH self-administration found in the present study was due strictly to altered EtOH elimination, although studies are needed to directly assess this possibility.

It has been proposed that fenofibrate's ability to decrease voluntary EtOH consumption may be due to its ability to act peripherally by enhancing liver catalase activity in turn, increasing systemic acetaldehyde levels that are presumably aversive (Karahanian et al., 2014; Karahanian et al., 2015). Evidence suggests however, that acetaldehyde is reinforcing on its own. For example, studies have shown it is self-administered orally, intravenously, directly into the ventricles and into the VTA (Muggirone et al., 2013). Further, drugs that prevent the formation of acetaldehyde and acetaldehyde chelators block EtOH's rewarding effects (Font et al., 2006a, b; Peana et al., 2008). In addition to EtOH, we found that fenofibrate also decreased sucrose reinforcement, an effect not likely attributed to increases in systemic acetaldehyde levels. A more likely mechanism underlying fenofibrate's effects on EtOH self-administration is action through the PPAR α (Blednov et al., 2016) influencing DA neurotransmission within the mesolimbic system (Melis et al., 2013a). It is more plausible however that fenofibrate, and PPAR α agonists in general, block EtOH's behavioral effects through multiple mechanisms (Ferguson et al., 2014).

5. Conclusions

The present study demonstrated that the preferential PPAR α agonist fenofibrate decreased operant oral EtOH self-administration in a dose-dependent manner. Fenofibrate also decreased sucrose reinforcement but this was not dependent upon dose and observed only under a PR schedule of reinforcement. Our results are consistent with other studies assessing the effects of fenofibrate on voluntary alcohol consumption and extend its effects to contingency-dependent EtOH reinforcement. Fenofibrate is presently approved for the treatment of hypercholesterolemia and dyslipidemia. Results from our study and others support the notion that fenofibrate should also be assessed for the treatment of alcohol use disorder in humans.

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Highlights

- Fenofibrate reduced self-administration of EtOH under two reinforcement schedules
- The effects of fenofibrate on EtOH self-administration were dose-dependent
- The effects of fenofibrate on sucrose self-administration were not dose-dependent
- First study to test fenofibrate on operant oral EtOH self-administration in rats

Fig 1.

Experimental procedure timeline of rats orally self-administering EtOH (ethyl alcohol). Rats were exposed to chronic intermittent exposure (CIE) to EtOH vapor prior to being trained to lever-press for EtOH. CIE inhalation continued throughout the duration of the study (5 days on, 2 days off). Following acquisition, rats were administered a test dose of fenofibrate (0, 25, 50, 100 mg/kg, PO) for 5 consecutive days. Testing occurred under both fixed (FR2) and progressive ratio (PR) schedules of reinforcement. One week of maintenance of EtOH separated each fenofibrate test dose. Another group of rats were trained to self-administer a sucrose solution that were not exposed to EtOH vapor.

Fig 2.

Effects of various doses of fenofibrate on reinforcers earned (mean+SEM) in rats self-administering ethanol (A., EtOH, 10%, N=7) or sucrose (B., 2%, N=7) under a FR2 schedule of reinforcement. Rats were administered various doses of fenofibrate for four days. Fenofibrate decreased reinforcers earned in rats self-administering EtOH but not sucrose. Compared to control (0mg/kg), decreases in reinforcers earned following fenofibrate were more prominent for all doses on Days 3 and 4. ** $P<0.01$.

Fig 3.

Effects of various doses of fenofibrate on reinforcers earned (mean+SEM) in rats self-administering ethanol (A., EtOH, 10%, N=7) or sucrose (B., 2%, N=7) under a PR schedule of reinforcement. Rats were administered various doses of fenofibrate for five days. Fenofibrate decreased reinforcers earned in both groups. Fenofibrate dose-dependently decreased reinforcers earned in rats self-administering EtOH, but not sucrose. ** $P < 0.01$.

Table 1

Fixed-Ratio tests: active and inactive lever presses.

Fenofibrate Dose (mg/kg)	EtOH [^] #				Sucrose			
	0	25 ^{**}	50	100 ^{**}	0	25	50	100
Day								
Active	1	38.14±4.42	44.71±3.95	37.86±4.76	29.71±2.61	80.71±15.44	99.71±9.60	102.57±11.42
	2	42.71±5.31	39.57±3.18	31.43±4.37	22.00±2.55	89.00±13.73	90.86±8.90	86.86±10.02
	3	47.00±7.30	33.86±4.16	25.14±4.28	16.43±2.30	92.57±18.91	79.43±8.26	79.43±7.45
	4	42.00±6.91	23.14±2.92	21.14±2.70	11.86±1.68	99.14±12.65	73.29±7.80	73.71±5.78
EtOH [^]								
Inactive	1	2.00±0.72	2.14±0.80	1.14±0.46	0.57±0.20	7.71±1.94	6.86±1.20	5.00±1.51
	2	2.43±1.62	1.14±0.51	1.00±0.38	1.71±0.61	9.00±1.69	3.57±0.69	5.71±0.42
	3	3.14±1.06	0.86±0.34	0.43±0.20	0.71±0.36	6.00±1.60	4.57±1.70	5.29±1.30
	4	1.14±0.55	0.86±0.40	0.57±0.30	0.43±0.30	5.57±1.59	3.43±1.39	5.71±1.73

Significant main effect for [^]fenofibrate dose, #day and ¥ dose X day interaction

Bolded measures:

^{**} Significant difference from 0mg/kg, P<0.01

[†] Significantly different from 0mg/kg, P<0.05

Table 2

Progressive-Ratio tests: active and inactive lever presses.

		EtOH^				Sucrose^			
Fenofibrate Dose (mg/kg)		0	25	50	100	0	25	50	100
Active		46.43±3.12 **	31.29±2.88 **	18.00±1.95 *	8.57±1.1 **	103.57±9.07	69.14±9.91 **	59.86±6.00 **	48.71±3.26 **
Inactive		2.00±0.58	2.00±0.58	2.00±0.65	1.15±0.34	8.43±1.78	4.86±0.91 *	2.57±0.65 *	1.43±0.48 *

Significant main effect for ^fenofibrate dose

EtOH group: all fenofibrate doses differed from each other, **p<0.01, *p<0.05

Sucrose group:

* significant difference from Omg/kg, p<0.01,

** significant difference from Omg/kg, p<0.01