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Fenofibrate – A lipid-lowering drug – Reduces voluntary alcohol drinking in rats

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A B S T R A C T

The administration of disulfiram raises blood acetaldehyde levels when ethanol is ingested, leading to an aversion to alcohol. This study was aimed at assessing the effect of fenofibrate on voluntary ethanol ingestion in rats. Fenofibrate reduces blood triglyceride levels by increasing fatty acid oxidation by liver peroxisomes, along with an increase in the activity of catalase, which can oxidize ethanol to acetaldehyde. UChB drinker rats were allowed to consume alcohol 10% v/v freely for 60 days, until consumption stabilized at around 7 g ethanol/kg/24 h. About 1–1.2 g ethanol/kg of this intake is consumed in the first 2 h of darkness of the circadian cycle. Fenofibrate subsequently administered (50 mg/kg/day by mouth [p.o.]) for 14 days led to a 60–70% ($p < 0.001$) reduction of 24-h ethanol consumption. When ethanol intake was determined within the first 2 h of darkness, the reduction was 85–90% ($p < 0.001$). We determined whether animals chronically allowed access to ethanol and subsequently treated with fenofibrate, would a) increase liver catalase activity, and b) increase blood acetaldehyde levels after a 24-h ethanol deprivation and the subsequent administration of 1 g ethanol/kg. The oral administration of 1 g ethanol/kg produced a rapid increase in blood (arterial) acetaldehyde in fenofibrate-treated animals versus controls also administered 1 g/kg ethanol (70 μM vs. 7 μM; $p < 0.001$). Liver catalase activity following fenofibrate treatment was increased 3-fold ($p < 0.01$). Other hepatic enzymes responsible for the metabolism of ethanol (alcohol dehydrogenase and aldehyde dehydrogenase) remained unchanged. No liver damage was induced, as measured by serum glutamic-pyruvic transaminase (GPT) activity. The effect of fenofibrate in reducing alcohol intake was fully reversible. Overall, in rats allowed chronic ethanol intake, by mouth (p.o.), fenofibrate administration increased liver catalase activity and reduced voluntary ethanol intake. The administration of 1 g ethanol/kg (p.o.) to these animals increased blood acetaldehyde levels in fenofibrate-treated animals, suggesting the possible basis for the reduction in ethanol intake.

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Introduction

The main route of elimination of ethanol in mammals is via liver oxidation to acetaldehyde followed by the oxidation of acetaldehyde to acetate. These 2 reactions are carried out by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH2), respectively. However, more than 2 decades ago, it was suggested that liver catalase, and to a lesser extent cytochrome P4502E1 (CYP2E1), also play a role in the conversion of ethanol to acetaldehyde (Handler, Bradford, Glassman, Ladine, & Thurman, 1986). Catalase is localized mainly in peroxisomes, and hydrogen peroxide is required for its activity. H_2O_2 is provided by the metabolism of fatty acids via peroxisomal oxidation (Handler & Thurman, 1988a). The role of catalase in ethanol metabolism has been largely underestimated: pioneering experiments where 4-methylpyrazole (a potent inhibitor of ADH) was administered to rats showed a very low rate of ethanol elimination, and it was concluded that ADH, and not catalase, is mainly responsible for the metabolism of ethanol (Blomstrand, Ellin, Löf, & Ostling-Wintzell, 1980). However, it was later discovered that 4-methylpyrazole also inhibits acyl-CoA synthetase (Bradford, Forman, & Thurman, 1993), an enzyme essential to initiate the process of fatty acid oxidation. Thus, by blocking fatty acid oxidation, the generation of H_2O_2 in the peroxisomes is prevented, and thus catalase is inhibited indirectly.

The importance of catalase in ethanol metabolism was demonstrated in experiments where specific substrates for both enzymes were used: butanol for ADH and methanol for catalase (Handler & Thurman, 1988b). Catalase accounts for 25% of ethanol metabolism

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in normal nutritional conditions. However, in fasted rats, the elimination of alcohol attributed to catalase was 65%. This observation may indicate that alcohol metabolism by catalase is dependent on peroxisomal fatty acid oxidation, a process that is increased by fasting. Taken together, these antecedents indicate that catalase plays a role in the metabolism of ethanol, primarily under conditions that promote peroxisomal®-oxidation of fatty acids.

It is well established that elevated systemic acetaldehyde concentrations are aversive, and are the basis for the treatment of alcohol-dependent individuals with disulfiram (an inhibitor of acetaldehyde metabolism). Considering the role of peroxisomal catalase in the metabolism of ethanol to acetaldehyde, it is of interest to examine whether existing mechanisms that increase the activity of this enzyme affect ethanol intake. The peroxisome proliferator-activated receptors (PPARs) are transcription factors that play essential roles in the regulation of cellular differentiation, development, and metabolism of carbohydrates, lipids, and proteins (Berger & Moller, 2002). Three types of PPARs have been identified (Berger & Moller, 2002): α (alpha) – expressed mainly in the liver; γ (gamma) – expressed predominantly in adipose tissue; and β/δ (beta/delta) – expressed in virtually all tissues. An important action of PPARα is the upregulation of peroxisomes. PPARα can be activated pharmacologically by the fibrate drugs, a class of amphipathic carboxylic acids (clofibrate, gemfibrozil, ciprofibrate, bezafibrate, and fenofibrate) (Schoonjans, Staels, & Auwerx, 1996). These were originally indicated for cholesterol disorders (generally as an adjunct to statins) and then widely used for disorders that feature high plasmatic triglycerides (Cignarella, Bellosta, Corsini, & Bolego, 2006; Grundy & Vega, 1987). Among fibrates, fenofibrate showed the safer profile in clinical trials (Brown, 2007; Keech et al., 2005). Due to its lipid-lowering effect, fenofibrate is a drug used for the treating of subjects with hypercholesterolemia as well as with severe hypertriglyceridemia (triglycerides > 1000 mg/dL). Fenofibrate is a synthetic ligand specific for the nuclear receptor PPARα. Fenofibrate binds and activates PPARα, and this regulates the transcription of genes involved in energy metabolism by binding to PPARα response elements in their promoter regions (reviewed by Gervois, Fruchart, & Staels, 2007). Furthermore, fenofibrate was also reported to enhance catalase levels in the liver (Clouet, Henninger, Niot, Boichot, & Bezard, 1990). After 1–2 weeks of oral fenofibrate administration to mice, catalase activity markedly increased in liver (Arnaiz, Travacio, Llesuy, & Boveris, 1995; Henninger, Clouet, Cao Danh, Pascal, & Bezard, 1987; Steinberg, Schladt, Dienes, Timms, & Oesch, 1988). In addition to proliferation of peroxisomes, the increase of catalase activity by fenofibrate treatment can also be attributed to the upregulation of catalase mRNA levels in liver (Harano et al., 2006).

There are very few reports about the effects of fibrates on ethanol metabolism. Rats administrated bezafibrate, clofibrate, or simfibrate showed enhanced ethanol metabolism, higher blood acetate levels, and increased fatty acid β-oxidation in liver peroxisomes after ethanol (2 g/kg) administered orally (Tsukamoto et al., 1996). These results suggest that fibrates induced β-oxidation by peroxisomes and increased H_2O_2 production, which could lead to augmented ethanol metabolism by catalase. In these studies, blood acetaldehyde levels were not measured and, importantly, ethanol intake by rats was not voluntary. In another study, a high-fat diet was simultaneously offered along with ethanol to rats treated with gemfibrozil (Barson et al., 2009). In these studies, blood triglycerides levels were lowered and a simultaneous decrease in voluntary ethanol intake was observed. The authors explained these results by the positive relationship between the circulating triglycerides and the ingestion of alcohol. Yet another possible mechanism is that gemfibrozil caused the reduction in alcohol intake directly, increasing blood acetaldehyde levels, with no relation to the diminution of blood triglycerides.

The aim of our study was to evaluate the effects of fenofibrate on voluntary alcohol consumption on chronically drinking rats and on blood acetaldehyde levels after p.o. administration of 1 g/kg of ethanol.

Materials and methods

Animals

High-drinker UChB rats derived from the Wistar strain and bred selectively for their high alcohol intake were used in this study (Quintanilla, Israel, Sapag, & Tampier, 2006). Two-month-old male rats were housed in individual cages in temperature- and humidity-controlled rooms under a regular 12-h light/12-h dark cycle. For 60 days, rats were offered the choice of a 10% (v/v) ethanol solution and water from 2 graduated tubes. Food was provided *ad libitum* and the volume of water and ethanol solution consumed was recorded daily. After this time, ethanol consumption stabilized at ~7 g ethanol/kg/day. All procedures used in this study were revised by and in compliance with the Animal Experimentation Committee, Faculty of Medicine of the University of Chile.

Fenofibrate treatment

After 60 days of continuous (24 h/day) free choice between 10% (v/v) ethanol solution and water, UChB rats were divided into 2 groups ($n = 6$ rats per group). One group was treated with fenofibrate (Fibronil, Royal Pharma, Chile) administered orally as an aqueous suspension (10 mL/kg) at a dose of 50 mg/kg/day for 14 consecutive days (from day 61 to day 75), whereas the control group was treated with vehicle (water, 10 mL/kg, p.o.) for 14 consecutive days. The dose of fenofibrate was chosen as an intermediate that has proven effective in reducing dyslipidemia in other studies (Chen et al., 2008). Fenofibrate or vehicle was administered by gavage before lights were turned off (at 19:00 h). Ethanol 10% (v/v), water, and food were accessible *ad libitum* continuously 24 h/day. Ethanol intake was recorded twice, 2 h after lights-off (at 21:00 h) and after 24 h on the following day (18:55 h), following fenofibrate or vehicle administration, whereas water intake was recorded 24 h after drug administration (18:55 h). The mean voluntary ethanol consumption for each rat was expressed as g/kg body weight/2 h and as g/kg body weight/24 h.

Arterial acetaldehyde determination

To determine arterial acetaldehyde levels, both the fenofibrate and the vehicle control groups were deprived of 10% alcohol for 24 h prior to sampling. Thereafter, ethanol was administered orally (as a 20% solution in saline, 5 mL/kg) at a dose of 1 g/kg, immediately after the last dose of fenofibrate (or vehicle). Blood samples for acetaldehyde measurement were drawn from the carotid artery of the anesthetized rats (ketamine hydrochloride 60 mg/kg plus acetopromazine 2 mg/kg) at 5, 10, 15, 30, and 60 min after ethanol administration. The blood samples (0.1 mL) were diluted 10-fold in cold distilled water, and acetaldehyde was measured by gas chromatography of headspace gas (Quintanilla, Tampier, Sapag, Gerdtzen, & Israel, 2007).

Reversal of fenofibrate effect

A separate experiment was conducted to determine whether the inhibition of ethanol intake induced by fenofibrate treatment (50 mg/kg) was reversible. UChB rats ($n = 10$) were allowed to voluntarily drink 10% v/v alcohol and water for 72 days on a 24-h basis. After the alcohol intake had stabilized, 50 mg/kg fenofibrate

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