Fenofibrate administration reduces alcohol and saccharin intake in rats: Possible effects at peripheral and central levels

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We have previously shown that the administration of fenofibrate to high-drinker UChB rats markedly reduces voluntary ethanol intake. Fenofibrate is a peroxisome proliferator-activated receptor alpha (PPAR?) agonist, which induces the proliferation of peroxisomes in the liver, leading to increases in catalase levels that result in acetaldehyde accumulation at aversive levels in the blood when animals consume ethanol. In these new studies, we aimed to investigate if the effect of fenofibrate on ethanol intake is produced exclusively in the liver (increasing catalase and systemic levels of acetaldehyde) or there might be additional effects at central level. High drinker rats (UChB) were allowed to voluntary drink 10% ethanol for 2 months. Afterward, a daily dose of fenofibrate (25, 50 or 100 mg/kg/day) or vehicle (as control) was administered orally for 14 days. Voluntary ethanol intake was recorded daily. After that time, animals were deprived of ethanol access for 24 h and administered with an oral dose of ethanol (1 g/kg) for acetaldehyde determination in blood. Fenofibrate reduced ethanol voluntary intake by 60%, in chronically drinking rats, at the three doses tested. Acetaldehyde in the blood rose up to between 80 μM and 100 μM. Considering the reduction of ethanol consumption, blood acetaldehyde levels and body weight evolution, the better results were obtained at a dose of 50 mg fenofibrate/kg/day. This dose of fenofibrate also reduced the voluntary intake of 0.2% saccharin by 35% and increased catalase levels 2.5-fold in the liver but showed no effects on catalase levels in the brain. To further study if fenofibrate administration

changes the motivational properties of ethanol, a conditioned-place preference experiment was carried out. Animals treated with fenofibrate (50 mg/kg/day) did not develop ethanol-conditioned place preference (CPP).In an additional experiment, chronically ethanol-drinking rats underwent two cycles of ethanol deprivation/re-access, and fenofibrate (50 mg/kg/day) was given only in deprivation periods; under this paradigm, fenofibrate was also able to generate a prolonged (30 days) decreasing of ethanol consumption, suggesting some effect beyond the acetaldehyde-generated aversion. In summary, reduction of ethanol intake by fenofibrate appears to be a consequence of a combination of catalase induction in the liver and central pharmacological effects.

Alcoholism

Catalase

Fibrates

Peroxisome proliferator-activated receptor alpha

Treatment