Fenofibrate-a ppar? agonist-increases alcohol dehydrogenase levels in the liver: Implications for its possible use as an ethanol-aversive drug [Fenofibrato-un agonista de ppar?-incrementa los niveles de la alcohol deshidrogenasa hepática: Implicaciones para su posible uso como una droga aversiva al etanol]

Muñoz D.

Rivera-Meza M.

Flores-Bastías O.

Quintanilla M.E.

Karahanian E.

After ethanol consumption, disulfiram increases blood-acetaldehyde levels, generating an aversive reaction that deters alcohol drinking. Given the major secondary effects of disulfiram, finding other effective drugs to reduce alcohol consumption in individuals with alcohol-use-disorder is highly desirable. It has been reported that administering fenofibrate to high-drinking rats increases hepatic catalase levels and blood acetaldehyde after administering ethanol and a 60-70% inhibition of voluntary alcohol intake. This work evaluated whether fenofibrate has an additional effect on the activity of other ethanol-metabolizing enzymes, which could contribute to the high acetaldehyde levels generated upon administering ethanol. Male high-drinker rats were allowed to voluntary drink 10% ethanol or water for 2 months. Subsequently, fenofibrate (100 mg/kg/day) or vehicle was administered orally for 14 days. Then, alcohol dehydrogenase (ADH1) and aldehyde dehydrogenase (ALDH2) protein levels and enzymatic activities in the livers were quantified. Fenofibrate treatment produced a marked increase in ADH1 protein levels (396% ± 18%, $p < 0.001$) and enzymatic activity (425% ± 25%, $p < 0.001$). Fenofibrate did not result in differences in ALDH2 activity or in ALDH2 protein levels. The studies show that treatment with fenofibrate not only increased the activity of catalase in the liver of alcohol-drinking rats, as reported earlier, but also increased the levels and enzymatic activity of ADH1, while ALDH2 remained unchanged. The increases in ADH1 contribute to explaining the remarkable effect of fenofibrate in raising blood

levels of acetaldehyde in ethanol-consuming animals, in which a marked reduction of alcohol intake is recorded.

Alcohol dehydrogenase

Alcohol use disorder treatment

Fibrate

Peroxisome proliferator-activated receptor

PPAR