

## Letter to the Editor

**PPAR $\alpha$  Agonists Reduce Alcohol Drinking: Do They Act in the Brain or in the Liver?**Eduardo Karahanian<sup>1,\*</sup>, Mario Rivera-Meza<sup>2</sup>, María Elena Quintanilla<sup>2</sup>, Daniel Muñoz<sup>1</sup>, Katia Fernández<sup>3</sup>, and Yedy Israel<sup>2</sup><sup>1</sup>Center for Biomedical Research, Faculty of Health Sciences, Universidad Autónoma de Chile, Santiago, Chile, <sup>2</sup>Program of Molecular and Clinical Pharmacology, Institute of Biomedical Sciences, Faculty of Medicine, Universidad de Chile, Santiago, Chile, and <sup>3</sup>Faculty of Health and Dentistry, Universidad Diego Portales, Santiago, Chile

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There are good news for the alcohol field. In the past few years, peroxisome proliferator-activator drugs were reported to reduce voluntary alcohol intake in animal models. Barson *et al.* (2009) showed that gemfibrozil reduced alcohol drinking in rats. Recently, similar results were obtained with fenofibrate in high-alcohol-drinker UChB rats (Karahanian *et al.*, 2014) and mice (Blednov *et al.*, 2015). Moreover, a phase 2 clinical trial led by Barbara Mason (The Scripps Research Institute) was started to test the hypothesis that alcohol-dependent subjects treated with fenofibrate will report decreased craving for alcohol following cue-exposure and will report less drinking post treatment (clinicaltrials.gov/ct2/show/NCT02158273).

The peroxisome proliferator-activated receptors (PPARs) are transcription factors (nuclear receptors) that play essential roles in the regulation of cellular differentiation, development and metabolism. Three types of PPARs have been identified: alpha, gamma and beta/delta. PPAR $\alpha$  is the most abundant isoform in the liver; PPAR $\beta/\delta$  is expressed ubiquitously in all tissues; and PPAR $\gamma$  is expressed mainly in adipose tissue. PPAR $\alpha$  is activated by natural ligands (some types of fatty acids) and by synthetic agonists such as fibrate drugs (clofibrate, gemfibrozil, ciprofibrate, bezafibrate and fenofibrate). Fibrates are widely used in the clinic for the treatment of high blood-triglyceride levels.

The mechanisms by which PPAR $\alpha$  agonists are effective in reducing alcohol consumption are not fully understood. Currently, there are two views: (a) fibrates would act in the brain, changing the expression of genes related to cue-craving and executive function and also modulating the neuroimmune system through anti-inflammatory actions and (b) their effect would be attained in the liver, where PPAR $\alpha$  activation leads to peroxisomal proliferation, thus increasing hepatic catalase levels and hydrogen peroxide that readily convert ethanol into acetaldehyde; the rise of acetaldehyde in blood ultimately would lead to alcohol aversion. Could both effects play a role in reducing ethanol intake?

**EFFECT AT THE CNS LEVEL**

In recent papers by A. Harris and associates (Ferguson *et al.*, 2014; Blednov *et al.*, 2015) fenofibrate (PPAR $\alpha$  agonist), pioglitazone

(PPAR $\gamma$  agonist) and tesaglitazar (dual PPAR $\alpha$  and  $\gamma$  agonist) significantly reduced ethanol intake in mice; tesaglitazar was more effective than fenofibrate or pioglitazone in a continuous access paradigm (75% for tesaglitazar vs. 50% reduction for fenofibrate or pioglitazone), suggesting that the activation of both PPAR $\alpha$  and  $\gamma$  receptors is involved in the reduction in alcohol intake. Pioglitazone was effective only for 6 h after daily administration of the drug, unlike fenofibrate and tesaglitazar that showed a long lasting effect. Further, pioglitazone was totally ineffective in a binge model of limited access to ethanol (Blednov *et al.*, 2015). The authors hypothesized that changes in brain gene expression following drug treatment lead to reduced ethanol drinking. Accordingly, they found up-regulation of several neuropeptide-coding genes in GABAergic neurons located in the amygdala (area involved in memory consolidation and conditioning) and the prefrontal cortex (involved in executive decision). Interestingly, they also found up-regulation of genes involved in dopaminergic transmission and down-regulation of genes involved in the glutamate signaling pathway (Ferguson *et al.*, 2014).

On the other hand, knockout studies of genes important for immune and inflammatory responses showed that the neuroimmune system is involved in a yet unknown mechanism of alcohol intake behavior (Blednov *et al.*, 2011). Although the neuroimmune system is implicated, this does not necessarily indicate that the agonist drugs or knockouts exert their action in the CNS. Systemic injection of PPAR agonists induced changes in the expression of immune-related genes in the liver but did not produce prominent changes in neuroimmune pathways in the brain (Ferguson *et al.*, 2014). One possibility is that the immunomodulation occurs peripherally, and later this has effects on alcohol consumption at central level.

There are two areas of concern about the ‘CNS hypothesis’: (a) the ability of PPAR $\alpha$  agonists to reach the brain and (b) the level of expression of PPAR $\alpha$  in different brain regions. Blednov *et al.* (2015) reported that in mice treated for 8 days with a high dose of 150 mg/kg/day given orally, fenofibrate levels in the brain were only 0.7% of those determined in the liver ( $\mu\text{g/g}$  tissue). This is in close agreement with early studies by Weil *et al.* (1988) (0.4% in brain relative to liver).

However, it is always possible that these very low levels of fenofibrate might be enough to achieve an effect in the brain. In general, the expression of PPAR $\alpha$  in the brain is very low in comparison to other organs (Kainu *et al.*, 1994; Cullingford *et al.*, 1998; Moreno *et al.*, 2004). This receptor was detected in the granular cells of the cerebellar cortex, glia and in the dentate gyrus of the hippocampus.

## EFFECT IN THE LIVER

The main action of PPAR $\alpha$  activation in the liver is the stimulation of fatty acid oxidation in the peroxisomes. To achieve it, activated PPAR $\alpha$  enhances the expression of enzymes involved in the catabolism of fatty acids including the H<sub>2</sub>O<sub>2</sub>-generating peroxisomal fatty acyl-CoA oxidase, and (though not proved in humans) the proliferation of liver peroxisomes. This constitutes the putative basis of the therapeutic efficacy of fibrates in reducing blood triglyceride levels. The activation of PPAR $\alpha$  also increases the levels of catalase in the liver (Henninger *et al.*, 1987; Clouet *et al.*, 1990; Arnaiz *et al.*, 1995). Besides alcohol dehydrogenase and CYP2E1, catalase activity is also relevant in the metabolism of ethanol into acetaldehyde (Handler and Thurman, 1988).

Karahanian *et al.* (2014) proposed the ‘catalase blood-acetaldehyde hypothesis’ to explain the effectiveness of fibrates to reduce alcohol intake: namely peroxisome proliferation in the liver would lead to increases in hepatic catalase and elevations of systemic acetaldehyde. These investigators administered fenofibrate orally (50 mg/kg/day) for 14 days to UChB rats that had ingested alcohol for 2 months (Karahanian *et al.*, 2014). A reduction of ethanol intake of 70% was observed when alcohol consumption was recorded every 24 h. When ethanol consumption was determined within the first 2 h of access (reaching an intake of 1–1.2 g ethanol/kg), the reduction induced by fenofibrate was 90%. The oral administration of 1 g ethanol/kg produced a marked increase in blood acetaldehyde in fenofibrate-treated animals (70 vs. 7  $\mu$ M in controls). Liver catalase activity following fenofibrate treatment was increased 3-fold. Other hepatic enzymes responsible for the metabolism of ethanol were not altered (Karahanian *et al.*, 2014).

## CONCLUDING REMARKS

Both peroxisome proliferator-activating drugs, acting at PPAR $\alpha$  and PPAR $\gamma$ , appear to be involved in reducing ethanol intake in animals, and a potentiation effect may occur when both are activated. PPAR $\gamma$  agonists *per se* reduced ethanol drinking in alcohol-preferring rats (Stopponi *et al.*, 2011), while these effects were prevented by injection of a selective PPAR $\gamma$  antagonist into a lateral cerebral ventricle, showing the importance of central PPAR $\gamma$  in mediating a reduced alcohol intake. Given the present data, it seems likely that a reduction of

ethanol intake by PPAR agonists is due to the activation of PPAR $\gamma$  in the brain and the activation of PPAR $\alpha$  in the liver.

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