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 UCCh 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-activator 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. PPARα is the most abundant isoform in the liver; PPARβ/δ is expressed ubiquitously in all tissues; and PPARγ is expressed mainly in adipose tissue. PPARα 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 PPARα 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 PPARα 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 (PPARα agonist), pioglitazone (PPARγ agonist) and tesaglitazar (dual PPARα and γ 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 PPARα and γ 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 PPARα agonists to reach the brain and (b) the level of expression of PPARα 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 (μg/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 PPARα 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 PPARα activation in the liver is the stimulation of fatty acid oxidation in the peroxisomes. To achieve it, activated PPARα enhances the expression of enzymes involved in the catabolism of fatty acids including the H2O2-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 PPARα 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 2 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 µM 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 PPARα and PPARγ, appear to be involved in reducing ethanol intake in animals, and a potentiation effect may occur when both are activated. PPARγ agonists per se reduced ethanol drinking in alcohol-preferring rats (Stopponi et al., 2011), while these effects were prevented by injection of a selective PPARγ antagonist into a lateral cerebral ventricle, showing the importance of central PPARγ 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 PPARγ in the brain and the activation of PPARα in the liver.

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