Peroxisome proliferator-activated receptor agonists may treat alcohol dependence

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Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor proteins that regulate the expression of genes. Drugs that activate PPARs - PPAR agonists - are used to treat diabetes and elevated blood lipids. Given previous rodent research, this study examined the effects of different classes of PPAR agonists on chronic alcohol intake and preference in mice with a genetic predisposition for heavy drinking, and then examined genome-wide association data for polymorphisms in PPAR genes in alcohol-dependent (AD) humans. Findings indicate potential for repurposing FDA-approved PPARα or PPARγ agonists for the treatment of AD.

Results will be published in the January 2015 online-only issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"PPAR receptors are biochemical sensors found in many cells in the body," explained R. Adron Harris, director of the Waggoner Center for Alcohol and Addiction Research at The University of Texas as well as corresponding author for the study. "Their job is to monitor our levels of sugars, fats, and other sources of energy and adjust our body metabolism to keep the levels of these nutrients at correct levels. However, sometimes our bodies or our diets and lifestyles cause undesirably high levels of sugar, leading to diabetes, or fats leading to hyperlipidemia, which can often be corrected by activating PPAR receptors with drugs called PPAR agonists."

Harris added that although PPAR agonists were initially developed to control blood levels of sugar and fat, they were later found to also act on the brain, thought to possibly guard against neurodegeneration, and are currently being tested as a remedy for Alzheimer's Disease.

"Especially over the past five years, there has been an increasing awareness that the brain uses many of the same signaling molecules as those used by the immune system," added Robert Hitzemann, professor and chair of the department of behavioral neuroscience at Oregon Health and Science University. "In some cases the brain may be using these molecules for immune-related functions, [such as] response to inflammation caused by brain injury. However, in other cases the brain may simply have 'hijacked' the molecules to serve a different function, [such as] communication among normal cells, including between neurons and glia. Scientists have been asking what happens to these neuro-immune genes in response to excessive [drinking, finding that they] are significantly affected. Many of the pathways affected are those that would be susceptible to regulation by PPARs."

"Because of these brain effects, several research groups have asked if PPAR agonists might be useful in drug addiction," said Harris. "Several of these drugs are currently being tested for opiate addiction in humans. And, because these drugs are already approved by the FDA for humans, the drugs could be used 'off label' for treatment of alcoholism or other addictions. This is the first study to combine human genetic studies of alcoholism with animal models of alcohol consumption to show a connection between PPAR receptors and drugs acting on these receptors with alcohol abuse."

Harris and his colleagues used two different behavioral tests to measure intake of 15 percent alcohol in C57BL/6J male mice: 24-hour two-bottle choice, and three-hour/limited access two-bottle choice, drinking in the dark. They measured the effects of PPAR agonists - pioglitazone (10

and 30 mg/kg), fenofibrate (50 and 150 mg/kg), GW0742 (10 mg/kg), tesaglitazar (1.5 mg/kg) and bezafibrate (25 and 75 mg/kg) - on alcohol intake and preference. Fenofibric acid, the active metabolite of fenofibrate, was also quantified in mouse plasma, liver, and brain. The study authors also examined human data from the Collaborative Study on the Genetics of Alcoholism (COGA), analyzing the association of single nucleotide polymorphisms (SNPs or DNA sequence variations)) in different PPAR genes - PPARA, PPARD, PPARG, and PPARGC1A - with two phenotypes: DSM-IV AD, DSM-IV withdrawal.

"Alcohol abuse is one of the major health problems in the US and in much of the developed world, yet we have very few therapeutic approaches for these problems," said Harris. "There are few pharmacological treatments; only three FDA-approved drugs. It is extremely slow and expensive to develop and test a new drug, so progress in my lifetime is most likely if we use an existing, FDA-approved drug for a new purpose. In this case, we found that activation of two isoforms of PPARs, α and γ, reduced alcohol intake and preference in the two different consumption tests in mice. These findings, as well as the genetic association between AD or withdrawal in humans, indicate potential for repurposing FDA-approved PPARα or PPARγ agonists for the treatment of AD."

"[These results make] a convincing argument that it is the α receptor agonists, for example, fenofibrate, that will show the most promise for human studies," said Hitzeman. "However, these drugs are not without side-effects [such as] dysregulation of body temperature, hives, itching, muscle aches and pains, nausea and vomiting. Thus, one goal of any FDA-approved clinical trial will be to determine the minimum dose with the maximum effect on alcohol consumption. There also may be new drugs in the PPAR pipeline that should be considered for a clinical trial especially if they have a better side-effect profile. [That said,] for years researchers have focused on manipulating alcohol consumption [via]

drugs which act on neurotransmitter/neuromodulator receptors. The approach here is novel and even if drugs like fenofibrate do not appear to be clinically useful, the idea that such drugs could be useful in reframing the experimental and clinical approaches to treatment [is valuable.]"

Harris agreed. "There continue to be surprises in the neurobiology of alcoholism," he said, "and new genetic techniques and 'big data' approaches enable discovery of new changes in the brain and new opportunities to normalize those changes. The next steps are human laboratory studies using a limited number of alcoholics to ask if they reduce any effects of alcohol, such as craving."

"It is often said that research in animals, and especially mice, will have little benefit in attempting to treat the human condition," said Hitzeman. "However, animals, like humans, will consume excessive amounts of alcohol and other substances of abuse. Thus the homology is not so distant as it is in the case of other psychiatric disorders such as schizophrenia. Interestingly, [the study authors] were not only able to test in mice their working hypotheses but then were also able to provide genetic evidence for the role the PPARs in AD. This [is] a great example of the convergence of basic and clinical research."

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