Project title: Systems biology modeling of ethanol's effects on human retinoid metabolism

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Background: Consumption of alcohol promotes diseases such as fetal alcohol syndrome and cancers. The underlying cause for the link between alcohol and disease may be that alcohol causes changes in the use of vitamin A. One hypothesis is that alcohol blocks the enzyme alcohol dehydrogenase from properly metabolizing vitamin A. We used computer models and laboratory measurements to test this hypothesis. We built computer simulations of human enzyme function and purified recombinant enzymes from bacteria to carry out our investigations. Our approach is very powerful because it combines laboratory tests and computer modeling and allows us to study enzyme function under a variety of highly complex cellular conditions.

Advances: Our studies have shown that:

A) Under complex cellular conditions, both simulations and laboratory tests show that alcohol is able to substantially decrease the rate of vitamin A processing by alcohol dehydrogenase [1].
B) One of the metabolic products of alcohol (NADH) interferes with metabolism. Because other factors can change the level of this metabolite, this finding identifies novel factors that may vary within people and explain differences in individual responses to alcohol [1].
C) A carcinogenic breakdown product of alcohol (acetaldehyde) does not block alcohol dehydrogenase's ability to metabolize vitamin A. Thus, it does not have the same disease-causing mechanism of ethanol alone [2].

Thus, we have developed a validated computational model of this enzyme system [1-3] which can be used to assess the degree to which genetic makeup and alcohol alter the synthesis of retinoic acid and, thereby, promote human disease.

How NCRR Grant Enabled Advance: Funds from the NCRR have supported this project from its inception. The equipment necessary to purify human enzymes and the computers for modeling were purchased through this program. Most student salaries were funded for both academic year (3-4 students) and summer (3-4 full-time students). The PI was released from half of her teaching load to be able to pursue these studies and to mentor students. The preliminary data from the early studies was used to obtain two grants from the MJ Murdock Charitable trust, including one for mentoring a high school teacher into research. Finally, all modeling was accomplished based on mentoring relationships with the Metabolic Modeling group at Oxford-Brookes University (UK). INBRE-supported travel has allowed this ongoing mentoring relationship. Overall, this grant supported development of a strong research infrastructure in the state of Idaho which has provided the PI with needed collaborators and mentors at all the state universities.

Public Health Impact Statement: Changes in retinoic acid levels have been implicated in the development of alcohol-related cancers in chronic heavy drinkers and in fetal alcohol syndrome. *This project is significant because* it created a computational systems biology model of the effect of alcohol consumption on the enzymes which maintain proper vitamin A-derivative levels in human tissue. Also, it improves upon the available enzyme data to construct a valid model of ethanol and retinoid metabolism in human tissues. The computer model will allow testing of the effect of combinations of ethanol levels, retinol supply, and oxidative capacity (affecting NADH levels) and genetic variation in enzyme levels in a variety of simulated tissue types. Such analysis could never take place in living tissue but serves as a methodology for identifying novel hypotheses and interactions that *could* be tested in controlled human studies or identified in epidemiological analysis.

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1. Chase, J.R., M.G. Poolman, and D.F. Fell, *Contribution of NADH increases to ethanol's inhibition of retinol oxidation by human ADH isoforms.* Alcoholism: Clinical and Experimental Research, 2009. **33**(4): p. 571-580. PMCID 19183134
2. Chase, J.R. *Computational modeling of liver ADH oxidation of retinol: elevated acetaldehyde inhibits ethanol but not retinol oxidation.* in *Systems Biochemistry*. 2010. University of York, York, UK: Biochemical Society Conferences.
3. Chase, J.R., *Modeling of human retinoid metabolism: mechanisms of alcohol-related disease*, in *Metabolic pathway analysis 2011*2011, Biochemical Society Conferences: University of Chester, Chester, UK.