E-cigarette nicotine exposure increases hepatic fat content reducing liver-derived fuel for the brain

Terry D. Hinds, Jr.¹ Xiaoming Fan², Jiang Tian², and Youssef Sari³

¹Center for Hypertension and Personalized Medicine, Department of Physiology & Pharmacology, ²Department of Medicine, ³Department of Pharmacology and Experimental Therapeutics, University of Toledo College of Medicine

It is well known that nicotine in cigarette smoking and electronic cigarettes (E-cigs) is a significant cause for their addiction. Today, there are approximately 10.8 million people in the U.S. using E-cigs, and in 2016 more than 2 million E-cigs users were middle and high school students, which has grown to an epidemic proportion. Drugs of abuse cause an enormous use of glucose in the major reward areas of the brain, including the nucleus accumbens (NAc). Typically, glucose is used for energy metabolism in the brain, supplying adenosine triphosphate (ATP) for synaptic plasticity and epigenetic signaling via phosphorylation of histones. Energy can be resupplied to the brain via the liver by β-oxidation of fatty acids, predominantly β-hydroxybutyrate (βOHB), which mainly occurs under genetic control by the nuclear receptor peroxisome proliferator-activated receptor alpha (PPARα). We have found that E-cig nicotine exposure in mice causes a significant (p<0.05) increase in hepatic fat content, which most likely transpired due to the reduction in PPARα expression, which was decreased 47% in males and 59% in females. PPARα levels were unchanged in the brain. However, after nicotine exposure, βOHB plasma levels and βOHB dehydrogenase (BDH1) in the prefrontal cortex were significantly (p<0.05) lower. BDH1 assist in the conversion of βOHB to ATP, which is used for epigenetic signaling via phosphorylation of histones or directly inhibits HDACs. Our work hypothesizes that E-cig nicotine reduces hepatic PPARα level preventing the production of βOHB, diminishing energy supply to the brain, remodeling epigenetic signaling that increases drug dependence.