Imaging the 18-kDa Translocator Protein in Alcohol Use Disorders

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Chronic alcohol use is thought to disturb brain homeostasis by influencing microglial function. Positron emission tomography (PET) imaging of the 18-kDa translocator protein (TSPO), an imaging marker influenced by microglia number, was measured with the radioligand [^{11}C]PBR28. TSPO levels were measured in 15 healthy controls and 15 alcohol-dependent subjects after 1-4 days (*n*=14) or 24 days (*n*=1) of alcohol abstinence. TSPO was quantified by estimating total distribution volumes (*V*T) using multilinear analysis with arterial blood sampling to measure the parent [11C]PBR28 input function. Alcohol dependent subjects exhibited significantly lower [11C]PBR28 levels than healthy controls (p=0.034). On average, TSPO levels were 10% lower in alcohol dependent subjects. Exploratory analyses suggested a negative relationship of TSPO levels in hippocampus and striatum with alcohol dependence severity (p<0.035). In a subset of subjects, peripheral immune responsivity was assessed by culturing monocytes extracted from venous blood samples both with and without lipopolysaccharide (LPS). Monocyte response was quantified by measuring the fold-change of cytokine levels in LPS-stimulated cultures relative to saline cultures. Peripheral monocyte response to immune stimulus was lower in alcohol dependent subjects for the pro-inflammatory cytokines interleukin-6 and interleukin-8. The imaging data indicate lower TSPO levels throughout the brain and a smaller peripheral pro-inflammatory response in alcohol dependent subjects compared to healthy controls. These findings could be attributed to lower numbers of microglia in alcohol use disorder. Importantly, [11C]PBR28 *V*T is significantly reduced in a preclinical model of microglial depletion, demonstrating that [11C]PBR28 is sensitive to settings of reduced microglia number. To bridge the gap between acute alcohol exposure, which triggers an immune response, and reduction in microglia number after chronic (~years) of alcohol exposure, we are developing a new imaging paradigm to measure the immune response to acute alcohol in people. Our preliminary data (n=2) demonstrate that oral alcohol (0.08 BAL) acutely increases [11C]PBR28 *V*T by ~20% throughout the brain. Follow-up whole body scans reveal that alcohol elevates radioactivity concentrations in gastrointestinal areas. These exciting preliminary data encourage future research investigating the role of neuroimmune signaling in progression of alcohol use disorder and tolerance to alcohol. Moreover, the innovative whole body imaging approach holds promise for study of brain-gut immune interactions in alcohol use disorders. Taken together, this work suggests altered microglia homeostasis in alcohol dependence, implying a potential role for pharmaceuticals tuning the neuroimmune system as therapeutics for alcohol dependence.

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