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Adipose Tissue, Appetite, & Obesity

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Quantifying Liver and Brain Levels of 11β-hydroxysteroid Dehydrogenase Type 1 in Obesity Using Positron Emission Tomography Imaging

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Objectives: Cortisol is known to promote adipocyte differentiation and maturation, and prolonged exposure to excess cortisol contributes to the development of obesity and metabolic dysregulation. The intracellular 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) enzyme catalyzes the conversion of inactive cortisone to active cortisol. Recently, we demonstrated reduced brain 11β-HSD1 levels in vivo with increasing body mass index (BMI), using positron emission tomography (PET) radioligands [^{11}C]- and [^{18}F]AS2471907(1). PET imaging can simultaneously quantify uptake in multiple organs (e.g., liver/brain). [^{18}F] AS2471907 has high uptake and specific binding in the brain and liver(2). Liver and brain 11β-HSD1 measured by PET imaging may help elucidate the roles of cortisol activation in the setting of metabolic dysregulation. Thus, we performed PET imaging studies to examine 11β-HSD1 levels in the liver and brain.

Methods: Nine individuals (5F/4M) with a range of BMIs (22.6-34.4 kg/m^2) underwent a 90 min PET/CT acquisition with arterial plasma sampling after injection of [^{18}F] AS2471907. Regions-of-interest (ROI) for the liver were manually drawn on a summed PET image (60-90 min). Seventeen brain ROIs were selected from the anatomical automatic labeling (AAL) template and applied to the dynamic PET images to generate time-activity-curves (TACs). Brain volume of distribution (VT, mL/cm^3), the target tissue to plasma ratio of radioligand at equilibrium, was estimated for each ROI using the multilinear analysis-1 method with plasma input function. Mean whole-brain VT values were calculated by averaging all ROIs. Given the appearance of irreversible kinetics in the liver, Ki (min-1), the rate of irreversible tracer uptake, was calculated using the Patlak method.

Results: Qualitative brain and liver uptake was assessed by examining a summed PET image (SUV 60-

90min). The parent fraction in plasma was 88±1% at 90 min, indicating negligible plasma radiolabeled-metabolites contributing the measured signal in the liver. Kinetic modeling estimates demonstrated decreasing whole brain VT with increasing BMI (R^2=0.53), similar to our previously published study examining only brain in a larger cohort(1). Patlak methods provided good estimates of Ki. In an opposite manner from the brain, correlations seen in the liver using Ki were positively correlated with BMI (R^2=0.57).

Conclusions: These preliminary studies suggest obesity is associated with increased 11β-HSD1 levels in the liver but decreased 11β-HSD1 levels in the brain. Clinically, liver specific 11β-HSD1 inhibitors may prove beneficial in treating metabolic sequalae of obesity such non-alcoholic fatty liver disease (NAFLD) by inhibiting activity of higher 11β-HSD1 levels. Further studies in NAFLD and obesity are necessary to determine appropriate populations that would benefit from 11β-HSD1 inhibitors and longitudinal in vivo PET imaging to help inform development of future therapeutics.

References: [1] Bini, et al, Molecular Imaging and Biology, 2020. [2] Bini, et al, IEEE Trans on Radiation and Plasma Medical Sciences, 2021

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