

Evaluation of 14(R,S)-[18-F] Fluoro-6-Thia-Heptadecanoic Acid (FTHA) as a Positron Emission Tomography Fatty Acid Tracer of Beta-Oxidation in the Heart

Robert A. Pooley

A new radiolabeled long-chain fatty acid analog, 14(R,S)-[18-F]fluoro-6-Thia-heptadecanoic acid (FTHA), was designed to undergo metabolic trapping subsequent to its commitment to the Beta-oxidation pathway. FTHA was evaluated with respect to its ability to accurately determine rates of Beta-oxidation under various conditions in two animal models for heart research: isolated perfused working rat heart and open-chest extracorporeally perfused swine heart. FTHA was infused into working rat hearts and radioactivity accumulation measured by external coincidence detection. The slope of linear radioactivity accumulation was scaled to determine an estimate for the rate of Beta-oxidation. This was compared to the rate determined from the standard tracer, 3H-palmitate (3H-PA). Experiments were conducted under conditions of low and high workload, various palmitate ([PA]) and glucose perfusate concentrations, fed and fasted states, and suppression of Beta-oxidation by inhibition of fatty acid transport using etomoxir. Swine LAD artery and vein were cannulated. LAD artery was perfused from the femoral artery through a perfusion pump. FTHA and 3H-PA were simultaneously infused over a 45-minute period divided into three 15 minute segments of control or intervention: period 1 -- hyperemia using adenosine to maintain pressure, period 2 -- control, period 3 -- Beta-oxidation suppressing using lactate. Arterial and venous blood samples were collected and assayed for 3H₂O and 18F concentrations. Isolated rat heart experiments determined that FTHA uptake was sensitive to changes in energy demand. Calculated rates of Beta-oxidation from FTHA and 3H-PA were not significantly different at 0.5 mM and 0.65 mM [PA]. The calculated rate of Beta-oxidation was significantly lower than that determined from 3H-PA at 0.8 mM [PA], indicating a decreased sensitivity to Beta-oxidation rates under high substrate supply conditions. Inhibition of Beta-oxidation with etomoxir reduced rates from FTHA and 3H-PA by comparable factors (90% at 30 mg/kg etomoxir). Swine experiments demonstrated the independence of FTHA uptake from flow. Suppression of Beta-oxidation with lactate resulted in significant decreases in FTHA and 3H₂O fractions. The results demonstrate the sensitivity of FTHA to Beta-oxidation rates at normal fatty acid concentrations and indicate the potential of FTHA to be a true fatty acid tracer of Beta-oxidation.