Investigation of the fluorine-18-2FDG/glucose lumped constant behavior in isolated working rat hearts

Chin Kau Ng

The behavior of the $\sp{18}$F-2FDG/Glucose lumped constant (LC) in heart was investigated using an improved isolated perfused working rat heart model, quantitative external counting of total tissue radioactivity by fast coincidence detection of positron-emitting radionuclides, and digital compartmental modeling of tracer kinetics.

The ability of the 2FDG compartmental model to predict the time courses of the fractions of the total radioactivity attributable to 2FDG-6-phosphate was biochemically validated for six perfusion conditions by directly assaying the 2FDG-6-phosphate fractions from acid extractions of freeze-clamped myocardial tissue. In $\sp{14}$C 2FDG recirculation experiments, chromatographic analyses indicated that the only two significant species in the myocardium were $\sp{14}$C 2FDG and $\sp{14}$C 2FDG-6-phosphate. The use of 2- ($\sp3$H) glucose for measuring glucose phosphorylation rates was also validated by correlating steady-state tritiated water production with enzymatic assay of glucose disappearance.

From constant infusion experiments, the values of the LC were determined to be 0.942 $\pm$ 0.062, 0.770 $\pm$ 0.166, 1.191 $\pm$ 0.054, 0.685 $\pm$ 0.093, and 0.334 $\pm$ 0.026, for hearts perfused with 5 and 30 mM glucose without insulin, and 2, 3.5, and 5 mM glucose with insulin respectively. The monotonic decrease of the LC as glucose concentration is increased in the presence of insulin can be explained by the shift in control strength for glucose uptake between membrane transport and the phosphorylation reaction. Bolus injection experiments analyzed with compartmental models indicated the occurrence of the following sequence: limited glucose supply relative to metabolic demand; decreased cellular glucose content; increased importance of the transport process in the limitation of hexose uptake; increased value for the LC.

Although the ratio $k\sbsp {3}{*}/k\sbsp {2}{*}$ of the fitted model rate constants for phosphorylation and for backflux across the cell membrane demonstrated a clear trend as a predictor of the changes in the LC, it may be impractical in a clinical setting. The ratio of slope over intercept from the ramp-like accumulation of total radioactivity during constant infusion of 2FDG was shown to be a better indicator. This index is very stable experimentally and does not require compartmental modeling to compute. Thus the kinetics of 2FDG measured in clinical studies of myocardial disease may provide information about local changes in the LC, and thus truly accurate values for rates of glucose metabolism.