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FACT SHEET

Assessment of Glucose Fluxes Using Stable-Isotope Methods

Background

The metabolic flux of glucose through the different pathways can be measured using stable isotope tracer methodologies and have shown to be sensitive to detect changes with treatment even before effects on glucose concentrations are identified.

Key Methods

Fasting Endogenous Glucose Production (EGP)

Isotope dilution technique:[1]

- Stable isotope labeled glucose (e.g. 6,6-$^{2}H_2$-glucose) is administered as a primed-continuous infusion for several hours.
- Plasma glucose enrichments are determined by Mass Spectrometry at steady state.
- EGP is calculated using steady-state equations.

Bolus injection method:[2]

- Stable isotope labeled glucose is administered as a bolus and frequent blood samples are collected for 1–3 h.
- The decay of plasma glucose enrichments is fit to a two- or three-exponential curve.
- EGP is calculated from the fit parameters.

Gluconeogenesis and Glycogenolysis:

The contribution of gluconeogenesis and glycogenolysis to fasting EGP can be measured simultaneously by the infusion of 2-$^{13}C_1$-glycerol and the use of Mass Isotopomer Distribution Analyses (MIDA).

Hepatic and Peripheral Insulin Sensitivity:[3]

Stable isotope tracer methodology (hot GINF method) combined with the hyperinsulinemic euglycemic clamp allows the simultaneous measurement of fasting EGP, insulin-mediated suppression of hepatic glucose production (hepatic insulin sensitivity, Figure 1), and tissue glucose disposal (peripheral insulin sensitivity) independent of the effects of hyperglycemia per se.[4]

Postprandial Glucose Fluxes:

The dual glucose tracer method can be used to assess glucose fluxes during a mixed meal tolerance test.[5,6]

- This method utilizes two distinct glucose tracers that can be differentiated analytically (e.g., U-$^{13}C_6$-glucose and 6,6-$^{2}H_2$-glucose). One is infused and the other is given orally.
- Glucose fluxes such as EGP suppression, intestinal glucose absorption and whole-body glucose disposal during the meal are calculated using mathematical models.

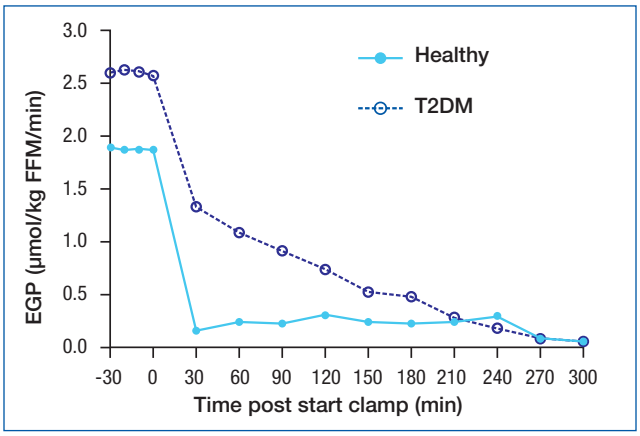

Figure 1. EGP measured after an overnight fast (from -30 to 0 min) and during a hyperinsulinemic euglycemic clamp (from 0 to 300 min) in a healthy subject and a person with type 2 diabetes. Insulin was infused at 40 mU/m^2/min.

Utility for Clinical Drug Development

Quantitative measurements of glucose metabolic pathways provide critical information regarding the mechanism of action of glucose-lowering drugs. With a wide range of stable isotope tracers and methods available, small studies can be designed to provide comprehensive assessment of multiple pathways.[7]

References:
[1] Steele R et al. Am J Physiol. 1956;187(1):15-24; [2] H ovorka R et al. Am J Physiol. 1997;273(1 Pt 1):E192-201; [3] Hellerstein MK et al. J Clin Invest. 1997;100(5):1305-19; [4] Steele R et al. Am J Physiol. 1965;208:301-6; [5] Steel R et al. Diabetes. 1968;17(7):415-21; [6] Haidar et al. Am J Physiol Endocrinol Metab. 2010;302(12):E1493-501; [7] Beysen C et al. Diabetologia. 2012;55(2):432-42.

For Further Reading:
Beysen C et al. Isotopic Tracers for the Measurement of Metabolic Flux Rates. In: Krentz AJ, Weyer C, Hompesch M (Eds). Translational Research Methods in Diabetes, Obesity, and Nonalcoholic Fatty Liver Disease: A Focus on Early Phase Clinical Drug Development. Springer 2019.

ProSciento, Inc.
Headquartered in San Diego, CA, USA
(P) +1 (619) 427-1300
bd@prosciento.com
www.prosciento.com