COMMENTS AND RESPONSES

Comment on: Stefanovski et al. Estimating Hepatic Glucokinase Activity Using a Simple Model of Lactate Kinetics. Diabetes Care 2012;35: 1015–1020

Current understanding of the role of hepatic glucokinase activity in hepatic glucose disposal has emerged largely from studies on hepatocytes and animal models. The lack of availability of simple noninvasive methods for determining hepatic glucokinase flux in vivo has been a major hurdle for studying glucokinase in man. Thus the recent report of a noninvasive method for determining glucokinase flux from lactate kinetics after intravenous glucose loading is an exciting new development (1). In hepatocyte models, glucokinase activity is a major determinant of both glycogen synthesis and glycolysis (2,3). Glucokinase is regulated acutely by adaptive interaction with a glucokinase regulatory protein (GCKR), which sequesters glucokinase in the nucleus in the fasted state, allowing rapid translocation to the cytoplasm (activation) during postprandial hyperglycemia. Chronic regulation is through transcriptional control of glucokinase and GCKR by insulin and glucose (3). Key questions are whether lactate kinetics in response to hyperglycemia (1) provide an "absolute" or "relative" measure of liver glucokinase flux, and if the latter, then what are its limitations?

The method assumes that when blood glucose is elevated to ~17 mmol/L by intravenous glucose injection, the liver responds by increased glucokinase flux and elevation in glucose 6-phosphate, which is converted to lactate and released into the blood (1). It assumes that glycogen synthesis from glucose and mitochondrial pyruvate metabolism are negligible and that glucokinase flux and lactate production respond to hyperglycemia but not to dynamic endocrine changes. The estimate for glucokinase flux determined in nondiabetic subjects was 10 nmol/min per mL liver (1). This is 50% lower than hepatic glucose uptake (20 nmol/min per mL liver) determined from accumulation of [^{18}F]-2-fluoro-2-deoxyglucose in dynamic scans at euglycemia (4). Although differences in glucokinase activity between populations cannot be excluded, the 50% discrepancy is consistent with hepatocyte data, which show that rates of lactate formation and glycogen synthesis are 50% and 10%, respectively, of glucokinase flux (5). Lactate kinetics therefore likely provides a "relative" rather than "absolute" measure of glucokinase flux. An underestimation of 50% would not invalidate the method if the fractional conversion of glucose 6-phosphate to lactate were independent of the variables being assessed. Accordingly, in hepatocytes maintained in defined conditions, lactate production in response to small molecule glucokinase activators closely parallels glucokinase flux (5). However, the assumptions that elevation in glucokinase flux and lactate production respond only to hyperglycemia and not to hormones require scrutiny. Whereas glucokinase translocation and glucokinase flux are more responsive to hyperglycemia than to changes in the insulin-to-glucagon ratio, lactate formation from glucose 6-phosphate is more responsive to glucagon than is glucokinase flux (2,3). Indeed fructose 2,6-bisphosphate, the key regulator of glycolysis, was discovered through a search for the mechanism by which glucagon inhibits hepatic glycolysis (2). Thus the insulin and glucagon responses to hyperglycemia may influence the fractional conversion of glucose 6-phosphate to lactate and are potential confounding factors to lactate dynamics. Validation of the method in controlled endocrine conditions could address this issue. This method is potentially a very useful tool to advance the understanding of glucokinase flux in man.

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