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Letters and Comments

Interaction with PFK-/FBP-2 is essential to glucokinase molecular physiology

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The recent review by P. B. Iynedjian, *Molecular Physiology of Mammalian Glucokinase* (DOI 10.1007/s00018-008-8322-9), presented a critical perspective on issues of systemic human fuel metabolism and the molecular mechanisms that work in discrete tissues to influence homeostasis, glycemia, and energy balance. The review correctly points to the role of the human liver, yet in making the case for glucokinase (GCK), overlooked a number of related mechanisms that are directly relevant to the regulation of these processes. Led by recent results, we have come to understand that a more complete picture of metabolic regulation is provided by considering the interaction of GCK with 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (BIF) and fructose 2,6-bisphosphate (Fru-2,6-P_2). GCK and BIF/Fru-2,6-P_2 interact in many ways. Here we point to a few mechanisms that are directly relevant to the Review. Recent studies at the molecular [1], cellular [2, 3], and *in vivo* [4] levels all support a critical role for the interaction of GCK and BIF/Fru-2,6-P_2 in the coordinated up-regulation of hepatic glucose disposal in both the acute and chronic phases. These appropriately coordinate changes in hepatic carbohydrate metabolism with that of lipid in the liver and systemically.

A central element that provides sensitivity to the nutritional and hormonal state for the liver BIF/Fru-2,6-P_2 system is phosphorylation/dephosphorylation at Ser32. Phosphorylation of BIF (P-BIF) is promoted by glucagon and makes the enzyme a net consumer of Fru-2,6-P_2, while glucose and insulin promote dephosphorylation of BIF and support increased Fru-2,6-P_2. Prior to the reports that BIF influences GCK translocation from the nucleus [3], the relevance of the differential effects of insulin and glucose and glucagon in regard to BIF/Fru-2,6-P_2 was thought to be important only for the reciprocal changes in each of the activities of PFK-2/FBP-2 that result in rapid changes of Fru-2,6-P_2 content. However, we now understand that the same dephosphorylation of P-BIF also modulates the binding of PFK-2/FBP-2 to GCK in the liver, thereby facilitating the translocation of GCK from the nucleus [3]. Additionally, *in vitro* results suggest that the binding of GCK to the FBP-2 domain of BIF results in a 1:1 complex that has both increased GCK and PFK-2 activities, while FBP-2 is unchanged [1]. Thus, the binding of GCK to BIF coordinately up-regulates the phosphorylation of glucose (GCK) and the committing step to glycolysis (PFK-1) *via* increased Fru-2,6-P_2.

Hepatic GCK expression is unquestionably regulated by insulin yet is not strictly dependent on the presence of insulin. In fact, we have documented that increasing

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hepatic Fru-2,6-P_2 levels stimulates GCK expression in livers of streptozotocin (STZ)-treated mice, that is, in the absence of any detectable circulating insulin [4]. This observation strongly suggests that an insulin-independent signal transduction pathway can stimulate hepatic expression of GCK. The fact that increasing hepatic Fru-2,6-P_2 levels increased the amount and phosphorylation of PKB (Akt) points to the very important concept of a Fru-2,6-P_2-based signaling pathway. Additionally, decreased hepatic Fru-2,6-P_2 levels block insulin-stimulated Akt phosphorylation, underscoring the relevance of Fru-2,6-P_2 to hepatic GCK gene expression [4]. The critical point is that these gene expression effects demonstrate metabolic coordination, similar to that promoted by the binding of BIF and GCK, because the *in vivo* adenovirus overexpression studies produced a chronic elevation of hepatic Fru-2,6-P_2 content and this long-term stimulation of PFK-1 activity was matched by increasing the amount of GCK, thus boosting the phosphorylation of glucose to match the increased glycolysis (reviewed in [4]).

The subtleties of the coordination between GCK and BIF/Fru-2,6-P_2 were underscored by direct comparison of adenovirus-mediated overexpression of GCK with a mutant BIF that is constitutively in the high PFK-2 activity state in the livers of diabetic mice [5]. The treatments had identical positive effects on hepatic carbohydrate metabolism and glycemia, reducing circulating insulin to the same extent. Yet, while the mutant BIF-expressing animals presented with reduced serum lipid and normal livers, those expressing GCK presented with severe hepatic steatosis and elevated serum lipids. Thus, modulation of hepatic carbohydrate metabolism at subsequent steps, glucose phosphorylation (GCK) or proportioning of hexose phosphate to glycolysis (BIF/Fru-2,6-P_2), can produce significantly different downstream results with regard to the coordination of carbohydrate and lipid metabolism in the liver and systemically. Thus, the formation of the GCK_2BIF_2 complex channels serum glucose to hepatic glycolysis and anchors GCK in the cytosol, away from the inhibitory GCK regulatory protein in the nucleus. Increased hepatic BIF and Fru-2,6-P_2 also promote loss of adiposity and reduced food intake, demonstrating that the interactions of GCK with BIF/Fru-2,6-P_2 are clearly important in coordinating fuel metabolism.

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