Editorial: Ebb and Tide of Glucokinase

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This journal’s editors have asked me to comment on the paper in this issue by Jetton et al. entitled “Substrate induced nuclear export and peripheral compartmentalization of hepatic glucokinase correlates with glycogen deposition.” The investigations of these authors exemplify the remarkable recent trend in studies of intermediary metabolism paying careful attention to the precise intracellular location of biochemical processes including also those that are conventionally assumed to occur in the aqueous cytoplasmic compartment. The investigative history of the glucokinase enzyme—the topic of the paper editorialized here—strikingly illustrates the slow pace of evolution in studies of this particular aspect of intermediary metabolism, starting perhaps with the pioneering concepts of Paul Srere in the sixties [1].

Glucokinase was long considered a typical soluble cytosolic enzyme. Sidney Weinhouse and Alberto Sols discovered the enzyme in the high speed supernatant of liver extracts with negligible residue in the particulate fraction [2,3]. This distribution contrasted with that of glucose-6-phosphatase which was associated with the microsomes. A striking intraacinar gradient of glucokinase exhibiting significantly higher activities in the pericentral as compared to the peripheral zones was discovered in the late seventies [4]. It is of interest that glucose-6-phosphatase has an intraacinar gradient opposite to that of glucokinase. The kinetic characteristics of the enzyme, its S0.5 of about 8.0 mM, ATP Km of about 0.3 mM and Hill coefficient of about 1.7 explained its optimal operation in the aqueous cytosolic compartment of hepatocytes where physiological glucose levels of 5 to 8 mM approximate those of plasma and ATP, the second substrate, is about 2.5 mM [5]. Consequently, a soluble glucokinase could operate close to its inflection point of about 4.0 mM where it is most responsive to changes of glucose levels. Since the enzyme is not directly controlled by glucose-6-phosphate as feedback inhibitor—more about this later—regulation of its activity was initially thought to be primarily due to alteration of protein synthesis stimulated by insulin. After glucokinase was discovered in pancreatic islets the conceptualization of the enzyme as cytoplasmic beta-cell glucose sensor followed the general outline of its biochemistry in hepatocytes except that its expression was considered to be controlled directly by glucose rather than by insulin [5].
The “classic picture,” as briefly outlined above, has been replaced step by step by a dynamic “modern view” in which subcellular compartmentation and allosteric regulation add a higher level of complexity and the possibility of control on a time scale of seconds to minutes. This development is greeted with a sense of excitement in this sector of metabolic regulation research. The present report by Jetton et al. has to be read with such a mind set.

A few historical and prospective comments about these recent discoveries may aid in the understanding of this important topic. The seminal discovery of the glucokinase regulatory protein (GKRP) in the late 1980s by van Schaftingen got the ball rolling. GKRP is a 68.5 KD protein that inhibits glucokinase competitively with glucose [6]. Its efficacy is increased by fructose-6-phosphate (F6P) and diminished by fructose-1-phosphate (F1P) explaining the physiologically and potentially therapeutic relevant activation of glucose metabolism by fructose. It is noteworthy that GKRP regulation of glucokinase does not seem to be a factor in pancreatic beta-cell glucose metabolism. The work of Agius, Miwa, Mookhtiar and Toyoda opened an entirely new dimension by demonstrating the nuclear localization of GKRP and its role in glucokinase redistribution between nuclear and cytosolic compartments, the nutrient regulated intracellular “ebb and tide” of glucokinase [7,8]. The newest extension of this dynamic view is seen in the present and related publications demonstrating quite convincingly that glucokinase associates reversibly with the glycogen synthesis apparatus as it initiates the postprandial process of glucose polymerization at sites close to the cell membrane of the hepatocyte.

Recent observations suggesting an association of glu-
The ligand induced slow transition (LIST) of glucokinase regulation (Figure 1). Central to this model are minimal working model of this particular aspect of enzyme and entices the writer of this editorial to sketch a sketch drawn here are mitigated somewhat by the outcome of studies with GKRP knockout mice [13]. Surprisingly, these animals are phenotypically normal. Most importantly, there seems to be no gross defect of glucose homeostasis, even though nuclear GK sequestration is abrogated and total GK content of hepatocytes is reduced by ca 50%. It will be illuminating to use these knockout mice in studies similar to those presented here by Jetton et al. to study intracellular GK redistribution during fructose and glucose loads in the absence of GKRP. Does the movement of GK to the cell membrane depend on nuclear GKRP? The model predicts that it would not. One should not forget however that, viewed in isolation, studies with gene knockout animals might be misleading.

This simple model could explain the currently published liver data. It implies that activated GK\(^1\) has new binding sites exposed allowing the attachment of the enzyme to cellular matrix components. It also implies the possibility of point mutations of GK that might specifically interfere with this process and might be a cause of MODY-2 or even permanent neonatal diabetes mellitus (PNDM) [14]. It is noteworthy in this context that the diabetogenic effect of certain GK mutations in MODY-2 remains unexplained. The model raises the possibility of impaired or enhanced intracellular GK redistribution which might be caused by pathological changes of the components that participate in this process but would not be GK linked, i.e. are possible candidates for MODY-X. The full characterization of GK missense mutations causing PHHI, MODY-2 and PNDM will therefore require the assessment of sequences that must be postulated to govern enzyme compartmentation. Incidentally, much of what has been discussed here may also pertain to the pancreatic beta-cell, with modifications, of course, because GKRP is probably absent.

Certain spontaneous and man made mutants of GK may represent the fully activated state depicted here as GK\(^2\) [11]. They have a kcat of as much as 1.5 times normal, a glucose So.5 of 1.0 to 2.5 mM instead of 8.5 mM and lower Hill coefficients (a measure of the cooperativity with glucose). It is conceivable that mutant induced changes of the enzyme influence its subcellular distribution that occurs physiologically. It seems plausible to predict that certain activated GK forms would enhance translocation to the cell membrane. Individuals with such...
mutations (i.e. V455M) maintain significant glycogen stores in the face of low bloodsugar of about 2.5 mM as shown by the results of glucagon challenges. GK activated by allosteric mutants offers a unique opportunity for studying the biochemistry of intracellular movements of enzyme.

These are just a few of the implications of the modernized view of GK biochemistry as exemplified by the paper of Jetton et al. It can be expected that the continued pursuit of research focusing on the dynamics of intracellular hepatic (or beta-cell) GK distribution as influenced by nutritional, pharmacological and genetic factors will greatly expand our understanding of glucose homeostasis in health and will assist in the therapeutic management of diabetes mellitus and related disorders.

References
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