How Should Lumped Constant Be Estimated for Hepatic ^{18}F-FDG Glucose in Humans?

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Hepatic glucose metabolism plays a key role in human metabolic homeostasis. In the current issue of *The Journal of Nuclear Medicine,* Trägårdh et al. (*1*) examine the challenges of using dynamic ^{18}F-FDG PET of the liver for measuring hepatic glucose uptake in humans. This method may be of great use in research and for treatment of patients with liver disease. However, structural differences between glucose and its analog tracer ^{18}F-FDG, with the hydroxy group (OH) in the 2-position of glucose being replaced by the positron-emitting radionuclide fluorine-^{18}F in ^{18}F-FDG, may lead to a different hepatic metabolic rate of ^{18}F-FDG than of glucose. This may be accounted for by multiplication of a proportionality factor, the so-called lumped constant (LC), which in general takes into account the difference in uptake by plasma-membrane transporters and metabolism by intracellular enzymes between tracer and tracee in a steady state. Clearly, the value of the LC is critical in calculating the hepatic glucose metabolic rate when ^{18}F-FDG is used as the tracer. Trägårdh et al. wanted to determine an in vivo operational LC for hepatic ^{18}F-FDG glucose in healthy humans to allow for quantitative PET assessment of hepatic glucose metabolism by dynamic ^{18}F-FDG PET scanning.

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In brief, this well-designed study in healthy human subjects combines coadministration of the glucose analog tracer ^{18}F-FDG and the true glucose tracer ^{3}H-glucose by intravenous bolus injection or constant intravenous infusion with 60-min dynamic ^{18}F-FDG PET of the liver and measurements of 180-min time courses of ^{18}F-FDG and ^{3}H-glucose concentrations in arterial and hepatic venous blood samples. Hepatic blood flow was measured by indocyanine infusion.

Metabolism of ^{3}H-glucose and ^{18}F-FDG in the intact liver takes place in hepatocytes lining blood-perfused sinusoids where both tracers undergo phosphorylation by glucokinase to ^{3}H-glucose-6-phosphate and ^{18}F-FDG-6-phosphate, respectively. The liver sinusoids are lined by highly fenestrated endothelial cells with no basal membrane, in contrast to other capillaries. Substances such as glucose and ^{18}F-FDG pass unrestricted through an extended plasma volume directly to the hepatocyte plasma membrane. This membrane is characterized by a very high capacity for transport of hexoses (*2*) and does not hinder passage of the 2 carbohydrates from plasma into hepatocyte cytosol. Thus, the hepatic LC for ^{18}F-FDG glucose does not depend on differences in membrane transport but only on enzyme kinetics for glucokinase (*3,4*):

$$LC = \frac{V^*_{max}/K^*_m}{V_{max}/K_m}. \quad \text{Eq. 1}$$

Asterisks indicate ^{18}F-FDG, and no asterisks indicate ^{3}H-glucose. V^*_{max} and V_{max} are the in vivo maximal hepatic removal capacities of ^{18}F-FDG and ^{3}H-glucose, and K^*_m and K_m the corresponding Michaelis constants. V^*_{max}/K^*_m and V_{max}/K_m are the respective flow-independent first-order intrinsic clearances (*5*).

For the in vivo liver, parallel sinusoids are perfused by blood flowing from the portal vein–hepatic artery flow-weighted mixed inlet (*6,7*) to the common outlet in the hepatic vein. In a steady state, the sinusoidal blood concentration of substrates, here ^{18}F-FDG and ^{3}H-glucose, decreases continuously along the sinusoid, and hepatic extraction fractions are calculated as

$$E^* = \frac{C^*_{in} - C^*_{out}}{C^*_{in}} \text{ and } E = \frac{C_{in} - C_{out}}{C_{in}}, \quad \text{Eq. 2}$$

where C_{in} is the inlet concentration and C_{out} the outlet concentration, with asterisks indicating ^{18}F-FDG and no asterisks ^{3}H-glucose. From $V^*_{max}/K^*_m = -F^*\ln(1-E^*)$ and $V_{max}/K_m = -F\ln(1-E)$ (*4,5,8*) and $F^* = F$,

$$LC = \frac{\ln(1-E^*)}{\ln(1-E)}. \quad \text{Eq. 3}$$

This is the physiologically correct LC for hepatic uptake of tracer from blood in vivo.

The practical estimation of LC in vivo is subject to fascinating challenges. It is not possible to estimate directly the kinetic parameters in Equation 1 for ^{18}F-FDG and ^{3}H-glucose since this would cause unacceptably high radioactivity exposure to research participants and staffs. Use of unlabeled glucose is not an issue because any attempt to experimentally change plasma glucose is immediately followed by counterregulatory neurohumoral responses keeping plasma glucose unchanged. The use of tracers,

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however, enables the application of simple in vivo first-order kinetics, at the prevailing plasma glucose levels.

C^*_{in} and C_{in} are flow-weighted mixed inlet concentrations from the portal vein (~75% of total blood flow) and hepatic artery (~25%). It has been observed that after bolus tracer administration of ^{18}F-FDG to 40-kg pigs, the portal vein time–activity curve was delayed and dispersed compared with the hepatic artery time–activity curve, but after a few minutes the portal vein and hepatic artery time–activity curves were similar (*9*). Because the portal vein is inaccessible for blood sampling in healthy humans, it seems reasonable to use late arterial blood concentrations, approximating steady state, for calculating hepatic extraction fractions by Equation 2 and LC from Equation 3 as in Trägårdh et al. (*1*). During constant intravenous infusion of both tracers, the extraction fractions were positive in all cases, and LC was not significantly different from 1.0.

In passing, we should point out that the use of E^*/E as a measure of LC in some studies (*10*) is valid only for the in vivo situation with perfused sinusoids or capillaries when E^* and E are very small relative to unity, because then E^* and E approximate $\ln(1 - E^*)$ and $\ln(1 - E)$, respectively, in practice, at near-saturated removal (*4*). Moreover, the use of negative extraction fractions in the calculation of LC (*10*) is incorrect, partly because the whole idea of LC is that it describes net removal of the tracer from blood and partly because E^* and E in Equation 3 must be positive.

The study by Trägårdh et al. raises interesting questions about how tracer distribution in the prehepatic splanchnic area may affect the calculated extraction fractions. After an intravenous bolus of both tracers, the initial increase in blood concentration gave rise to short-lasting initial positive splanchnic extraction fractions, which were followed by a decrease and negative extraction fractions. During constant infusion of the tracers, initialized by a small priming bolus, the extraction fraction remained positive. These findings are in agreement with an initial rapid hepatic uptake from the rising blood tracer concentration during passage of the tracer bolus through the blood vessels followed by backflux to blood during the subsequent decreasing blood concentration (*11*). This is a well-known phenomenon in capillary physiology but it is especially pronounced here because of the large volume of distribution of the combined prehepatic splanchnic and hepatic distribution volumes. This phenomenon cannot be investigated meticulously for ^{18}F-FDG and the human liver because of the requirements of invasive blood sampling from the portal vein, but this could be done in pigs.

The PET data in Trägårdh et al. showed that ^{18}F-FDG had a net uptake in the liver and was trapped in liver tissue, which could be quantified in every experiment as the net unidirectional hepatic metabolic clearance by K^*_{PET}, the Gjedde–Patlak analysis. Using these findings, a steady-state hepatic extraction fraction of ^{18}F-FDG was calculated as $E^*_{PET} = K^*_{PET}/Q$, with Q being the blood flow rate F, corrected for liver volume. E^*_{PET} was positive in every experiment; it ranged from 0.002 to 0.008, with no significant difference between bolus and infusion administrations, and interestingly, it was of the same order of magnitude as E^* from the constant infusion experiments. ^{3}H-glucose is not a PET tracer, and thus it is not possible to noninvasively estimate any LC for regional liver tissue. Nevertheless, if we, in view of the similarity of E^*_{PET} and E^*, assume liver tissue LC for ^{18}F-FDG glucose in the present normal livers to be about 1.0, the question is raised of what it would be in liver cirrhosis, and what the intrahepatic regional variation would be.

In this context, the hexose galactose is interesting because it has a negligible blood concentration under fasting conditions and, unlike glucose, can be manipulated experimentally without any signs of metabolic counterregulation. Consequently, we successfully estimated in vivo V_{max} and K_m for unlabeled galactose, using a wide range of steady-state concentrations of galactose in pigs (*12*) and humans (*13,14*). When combined with tracer studies using the galactose analog 2-^{18}F-fluoro-2-deoxy-D-galactose (^{18}F-FDGal) and calculation of values of $-F \ln(1 - E^*_{18F - FDGal})$ from blood measurements, LC values for hepatic ^{18}F-FDGal–galactose were estimated; in normal pigs they were on average 0.14 (*12*), in healthy human subjects 0.13 (*13*), and in patients with cirrhosis 0.24 (*14*). Moreover, mean net hepatic metabolic clearance K^*_{PET} for ^{18}F-FDGal was lower in cirrhosis and with larger intrahepatic heterogeneity than in normal livers (*15*). This raises the question of whether LC for ^{18}F-FDG glucose in cirrhosis is different from that in normal liver, and with larger intrahepatic heterogeneity. And finally, how does possible changed splanchnic hemodynamics in patients with liver disease affect LC for ^{18}F-FDG glucose?

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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