Quantitation of Cerebral Glucose Utilization using the Arterial Input Function or the Standardized Uptake Value (SUV)

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A. Introduction

Contemporary image analysis of cerebral glucose metabolism has its origin from the work of Kety and Schmidt in the 1940s for the determination of global cerebral blood flow (CBF) by the adaptation of the Fick Principle (Kety and Schmidt, 1941). They understood that CBF could be determined with the use of a freely diffusible and inert gas such as nitrous oxide as it would be taken up by the brain on a per unit time basis and that uptake is equal to the amount of gas delivered (arterial input function) minus the amount leaving the brain (venous output function).

Historically, Sokoloff et al (1977) described the C-14 deoxyglucose autoradiographic method for the determination of the regional cerebral glucose utilization (metabolic rate of glucose; MRGlc) in serial slices of the rat brain. The method is essentially a block diagram of the input of the radiotracer into the brain and the output to the venous system. This is described in Figure 1:

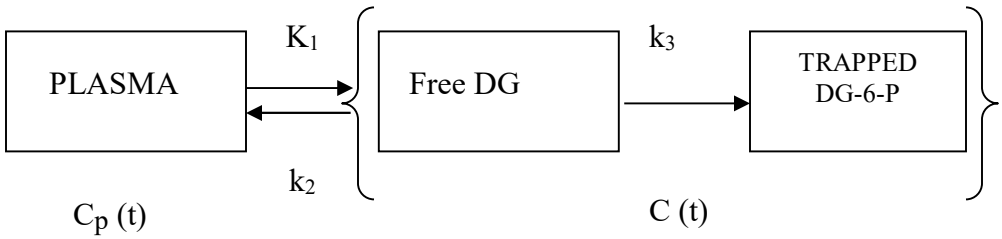

Fig. 1. The model of DG entrapment in cerebral tissues where the deoxy-form of glucose is entrapped, phosphorylated and then is unable to be further metabolized by hexokinase causing the radiolabeled species to remain "stable" in a localized region for sufficient duration to allow imaging. The rate constants of K1, k2 and k3 are, respectively, the forward and reverse transport into tissue and the rate of phosphorylation of DG-6-P (note: a small dephosphorylation in the brain, k4, is often ignored as phosphatase activity in the brain is negligible; it should also be noted, however, that dephosphorylation in background tissues such as the liver are not negligible and will contribute to radioactivity in the blood over time).

B. The Mathematics of Deoxyglucose Physiology

The Sokoloff equation of the metabolic rate of glucose utilization (MRGlc) can be written simply as:

$$MRGlc = \{ [Glucose_{arterial}]/ (Lump\ constant)^{*} \} * \{K_1 (k_3/k_2+k_3)\} = \{[Glc_a]/LC\} * Ki$$

$$\text{Where, } K_i = \{K_1*(k_3/k_2+k_3))$$

The "Lumped constant", or LC, is simply a constant that accounts for the differences in transporter and phosphorylation of DG versus glucose (Reivich, 1979; Huang, 2000).

The Ki can be measured in a variety of ways but is typically expressed as follows:

$$Ki = \left\{ \frac{[\text{ total radioactivity concentration region "x" at time T}] - [\text{free DG in region "x"}]}{/\ [\text{integral to time T of the available DG for uptake}]} \right\}$$

The invasive technique in the rat involving arterial sampling and then histologic tomography was quickly translated to a non-invasive method for in-vivo analysis similar to the Kety-Schmidt CBF approach with the advent of both PET systems and PET radiotracers in the late 70's (Phelps, et al, 1979). The fluorinated form of DG was shown to exhibit very similar kinetics to DG and thus rapid radiochemistry synthetic methods using the 2 hour physical half-life F-18 isotope were developed to label DG (now FDG). Along with the radiochemistry advances, positron cameras with the necessary computational capacity to create "high resolution" tomographic images of regional brain anatomy were also developed.

The standard imaging method for a quantitative Sokoloff-based determination of FDG uptake in neurological studies involves the following:

- A qualified PET system with appropriate QA testing prior to the patient scan,
- A sufficient dose of F-18 FDG per the statistical requirements of the PET camera (typically 220-260 MBq),
- An arterial line for collection of blood (input function determination), (NOTE: an arterialized-venous line, i.e. a heated (~39ºC water bath) hand with a sample port introduced in a retro-directional manner to the venous flow from the fingers, has been used with moderate success; a venous line alone provides a reduced FDG concentration value relative to the arterial concentration at the same time[1],
- Capture of a fasting (>~6 hrs) glucose blood sample prior to F-18 FDG,
- An attenuation map (topographic statistics are sufficient) of the head (or tissues of interest) collected just prior to dosing and with positional constraint sufficient to hold the patient head position during the PET scan,
- Sampling of the arterial input function in a manner sufficient to collect the slope of the influx, the Cmax and slope of the washout of the F-18 FDG upon injection and there should be minimal delay in the collection line so the blood represents that in circulation captured as "events" in the region at the moment of capture,
- A PET system with sufficient resolution for the target of interest,
- Capture of sufficient counts/statistics to reconstruct the tomographic plane of interest,
- Capture of these counts in the tomographic slices of interest sufficiently after the decline in the plasma input function (40-45 min post-injection typically)
- Reconstruction of the PET coincidence events in a manner (algorithm and filters chosen) that minimize influences of noise, scatter and resolution.

[1] The work of Takagi et al, has shown the heated hand approach at 40 minutes after injection provides a CMRGlc (cerebral metabolic rate) value of 1.3 ± 5.4% lower than the actual values. Non-heated venous sampling further underestimates the CMRGlc.

The major assumptions one makes for a PET scan include 1) the time after injection, T, is sufficiently large, i.e. 40 - 45 minutes after injection so the residual F-18 FDG in the blood is small (negligible input to the brain), 2) patient has "normal" renal function (creatinine clearance > 60-70 mL/min; or, a serum creatinine level of less than 1.2 mg/dL) so blood levels can reach sufficiently low levels by 40-45 min post injection, 3) background tissue dephosphorylation is not large or delayed, further diminishing the input function (K_1) to zero. These assumptions simplify the equation further to:

$$\text{MRGlc} = \{[\text{Glc}]/\text{LC}\} * \{\{\text{C(t)} - \text{free FDG in tissue at T}\} / \{\text{integral of FDG in plasma over time} - \text{lag time}\}$$

Assuming the free FDG is negligible and there is no lag time for the FDG in plasma (ie a sampling line that had no dead volume), then the equation is further simplified as:

$$\text{MRGlc} = \{\text{C(T)} / \text{integral of FDG in plasma to T}\}$$

The integral in the denominator is proportional to the injected dose divided by body weight as

$$[\text{integral of the plasma time-activity curve}] = b * \{ \text{dose/body weight} \},$$

where the term "b" is a proportionality constant not dependent on the patients. Thus the equation becomes even simpler as,

$$\text{MRGlc} = \{[\text{Glc}]/100\} * \{ \text{C(T)}/[\text{dose/BW}] \} / [\text{LC} * b/100]$$

where, the quantity within the braces is called the "SUV", or "**Standardized Uptake Value**". With the "LC" as a constant and also the value of "b" a constant, the terms then provide a proportionality constant for MRGlc as

$$\text{MRGlc} \propto \textbf{Standardized Uptake Value} \text{ (SUV)};$$

NOTE: SUV is a dimentionless tissue Q value divided by a normalizing Q (Thie, 2004)

C. The Application of the SUV in Oncology and Neuroscience

The assumptions of the SUV method include:

- Negligible free FDG in tissue at the time of the PET scan;
- Equilibrium was reached between the plasma and brain tissue;
- The integrated plasma time-activity curve is proportional to dose and inversely proportional to body weight; and,
- All tissues are similarly affected by changes in endogenous glucose.

A formal review of the SUV including a full description of the mathematics and the relationship between glucose utilization rate and the SUV can be found in the article written by SC Huang (Huang, 2000).

The SUV assumptions work well for brain tumor PET scans, as discussed above, at a time greater than 40-45 minutes after injection (scan times can be different for tissues

other than the brain as, for example, lung cancer, and the metastases, is an exception due to dephosphorylation outside the brain). The assumption of the plasma FDG being proportional to body weight is true except in low kidney function, high body fat or some other metabolic disorders and thus there is an advocacy for the use of the lean body mass or body surface area in the calculation rather than simple gravimetric values. Tissue uptake should behave similarly to changes in free glucose (or deoxyglucose), however, most tumors, the brain and the small bowel (including ovaries) exhibit uptake inversely proportional to the plasma glucose while MRGlc remains approximately constant. The skeletal muscle and kidneys behave proportionately during hypoglycemia so fasting is the normal condition for a PET scan.

The magnitude of the errors for these assumptions ranges from unknown to >30%. The assumption of negligible free FDG after 40-45 minutes has an approximate error of <10% (except in lung cancer). The assumption of reaching equilibrium between plasma FDG and free FDG in tissues ia also < 10% error. The assumption of the integrated plasma FDG curve is proportional to the dose and inversely proportional the patient's body weight can have an error greater than 30%. Attenuation and scatter likely account for about a 10% error. Local tissue resolution, i.e. brain nucleus size or tumor size, ROI edge detection and FDG concentration has a 20-30% error especially if <1 cm in diameter and is also system resolution dependant. The assumption that all tissues are similarly affected by changes in the endogenous glucose levels cannot be estimated.

Conclusion

The Standardized Uptake Value (SUV) is a semi-quantitative analysis that is widely adopted in oncology for the distinction of malignant and benign lesions (Thie, 2004) but its application in strictly controlled neuroscience studies is not as well adopted at this time. The institutional choices for establishing the appropriateness of a SUV value as an acceptable diagnostic evaluation for a neuroscience question, i.e. the ROC operating points, selection of patient populations and specific pathologies, to define the SUV evaluations is widely divergent and no compelling standards such as those for tumor pathologies has, to date, been adopted in the literature and thus the application of SUV to neuroscience studies is still not formally adopted.

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