Postprocessing and Cross Validation

Modeling and Quantification

Plasma Input and Reference Tissue Compartment Models

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Learning Objectives:

- Understanding of plasma input models
- Understanding of reference tissue models
- Understanding of the steps needed to select the most appropriate model

Molecular in vivo imaging techniques provide non-invasive measurements of regional tissue uptake and clearance of molecules of interest. The kinetic behavior of these molecules depends on several underlying physiological and/or biochemical processes. Tracer kinetic modeling is required to extract quantitative information on the specific molecular process under study. Although this will be illustrated for PET studies, the same principles apply to MRI and optical imaging. PET provides for accurate measurements of regional tissue concentrations of radioactivity, but appropriate tracer kinetic models are needed to translate these measurements of tissue tracer concentrations into quantitative values of tissue function or molecular process under study. Such a tracer model is a mathematical description of the fate of the tracer in the human body, in particular the organ under study. Although other types of models have been proposed, in practice, essentially all models used are compartment models. In these models the possible distribution of a tracer is divided into a limited number of discrete compartments. In practice, data from a single dynamic scan can only be fitted to a single or a two tissue compartment model. A single tissue compartment model would be appropriate for a blood flow (perfusion) tracer (no further interactions in tissue), but also needs to be used when kinetics between different tissue compartments are such that they cannot be identified individually. In a two tissue compartment model, a second compartment can be identified in which case the first compartment usually reflects non-displaceable tracer and the second metabolized or bound tracer. For a single tissue compartment model the outcome measure usually is the volume of distribution (V_T). For a two tissue compartment model it can also be V_T, but certainly for receptor studies non-displaceable binding potential (BP_{ND}) would be better, as it provides information on specific binding only, whilst V_T contains both specific and non-displaceable signals. Selection of both tracer kinetic model and outcome measure depends on the specific tracer being used (is a second compartment identifiable) and on accuracy and precision of the outcome measures. Both models mentioned above require a metabolite corrected arterial plasma input function. Measurement of such an input function is labor intensive (measurement of radiolabeled plasma metabolites) and rather invasive (arterial cannulation). For receptor studies, however, if a region devoid of these receptors exists, it is possible to use reference tissue models. In these models the reference region is used as an indirect input function for measuring BP_{ND} in the target region. In this contribution the mathematical background of single and two tissue compartments will be presented. In addition, the biological interpretation and validity of the various outcome measures will be discussed. Next, the mathematical background of reference tissue models will be presented, and attention will be paid to the underlying assumptions of those models. Finally, the various steps needed to select a model for a new tracer will be discussed.

Relevant Publications:

1. Gunn RN, Gunn SR, Cunningham VJ (2001) Positron emission tomography compartmental models. J Cereb Blood Flow Metab 21:635-652
2. Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE (2007) Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 27:1533-1539
3. Lammertsma AA, Bench CJ, Hume SP, Osman S, Gunn K, Brooks DJ, Frackowiak RSJ (1996) Comparison of methods for analysis of clinical [11C]raclopride studies. J Cereb Blood Flow Metab 16:42-52
4. Lammertsma AA, Hume SP (1996) Simplified reference tissue model for PET receptor studies. NeuroImage 4:153-158

Disclosure of author financial interest or relationships: A.A. Lammertsma, Philips, Grant/research support; Hoffmann-La Roche, Grant/research support.