[^{11}C]NNC 756: validation of analysis method

Introduction

The D_1 receptor radiotracer [^{11}C]NNC 756 has been developed and validated in Karolinska Institutet [Halldin et al., 1991]. This tracer provides a high binding ratio but has also significant affinity for 5-HT$_2$ receptors [Karlsson et al., 1993]. Metabolites of this tracer seem to be conjugated and thus they should not pass the blood-brain barrier [Karlsson et al., 1993; Abi-Dargham et al., 1999]. Based on the published information [Karlsson et al., 1993; Abi-Dargham et al., 1999] and personal communications, blood sampling was considered unnecessary. Without metabolite corrected plasma data a complete validation or comparison of analysis methods is impossible. The choice of analysis methods is limited to those utilizing receptor-free area in the brain as a reference region. The usage of cerebellum as reference region has been validated [Karlsson et al., 1993]. Methods based on calculation of simple ratios are not reliable with this tracer because it does not reach equilibrium during the imaging time [Karlsson et al., 1993; Laihinen et al., 1994]. The reference input methods are validated here with simulations that are based on the baboon data presented by Abi-Dargham et al. (1999).

Methods

Plasma data and metabolite corrected plasma data were retrieved from Fig. 2 in the article by Abi-Dargham et al. (1999). Tissue curves were simulated with rate constants averaged from striatum and frontal cortex values from the same article: K_1=0.473, k_2=0.068, k_4=0.0535. The k_3/k_4 was given values between 1.0 and 10. The reference region (cerebellum) was simulated with rate constants K_1=0.432, k_2=0.097, k_5=0.017 and k_6=0.029 (k_5/k_6=0.586). A blood volume of 4 % was assumed for all simulated regions. A 90-min PET study was simulated with frames 2x30 s, 2x1 min, 1x2 min, 5x5 min and 6x10 min. Simulated curves were analyzed with graphical method for reversible binding [Logan et al., 1996] with and without setting k_2^{ref}=0.097, assuming that plot is linear between 30-90 min from injection. This method estimates distribution volume ratio (DVR) as the slope, and binding potential (BP) can be calculated as BP=DVR-1. Additionally, data were analysed with simplified reference tissue model (SRTM) [Lammertsma and Hume, 1996], using data between 0-90 min. SRTM produces BP values directly.

Results and discussion

The reference input Logan plots of simulated curves are shown in Fig. 1. The plots are linear during the time (30-90 min) that was used in the linear fit.

Simulated tissue curves and curves fitted with SRTM are shown in Fig. 2. Although in physiological ranges the fits are good, with high binding potentials the fits tend to be worse.
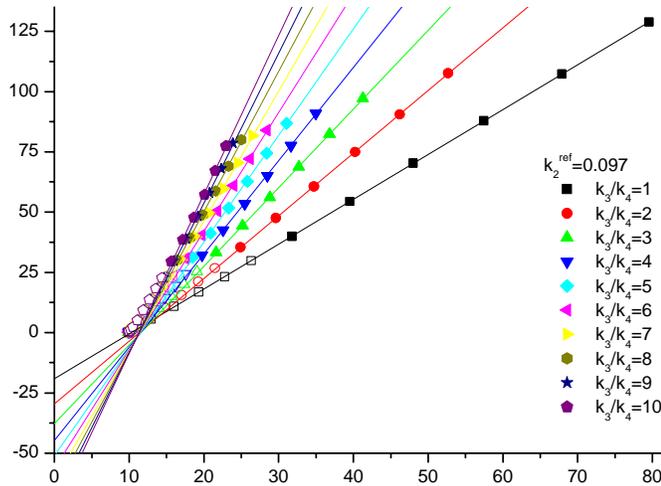

Fig. 1. Graphical analysis (Logan plot) of simulated data, correcting for reference region k_2.

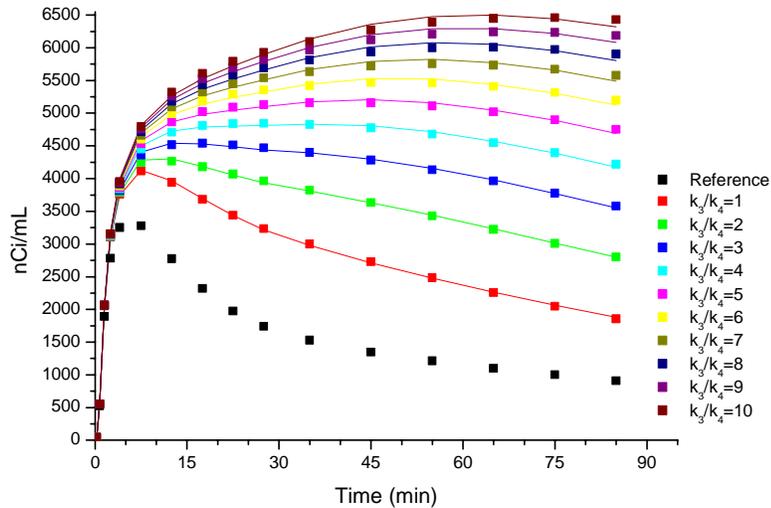**Fig. 2.** Simulated data fitted using simplified reference tissue model.

Fig. 3. shows the correlations between the actual k_3/k_4 ratios and the binding potentials estimated with Logan plot and SRTM. Correlations seem to be less linear with high binding potentials. If Logan plot is corrected for reference tissue k_2, it provides binding potentials that are similar to the ones produced by SRTM. Also Logan plot without correcting for k_2^{ref} produced BP values that correlate with k_3/k_4, although the underestimation is higher. Until recently, this method has been applied in Turku PET Centre [Kemppainen et al., 2000; Rinne et al., 2002; Hagelberg et al., 2003]. Because population average of k_2 of cerebellum is not known for human studies, and it cannot be measured without blood sampling and plasma metabolite analysis, the SRTM is recommended as an analysis method for [^{11}C]NNC 756 studies.
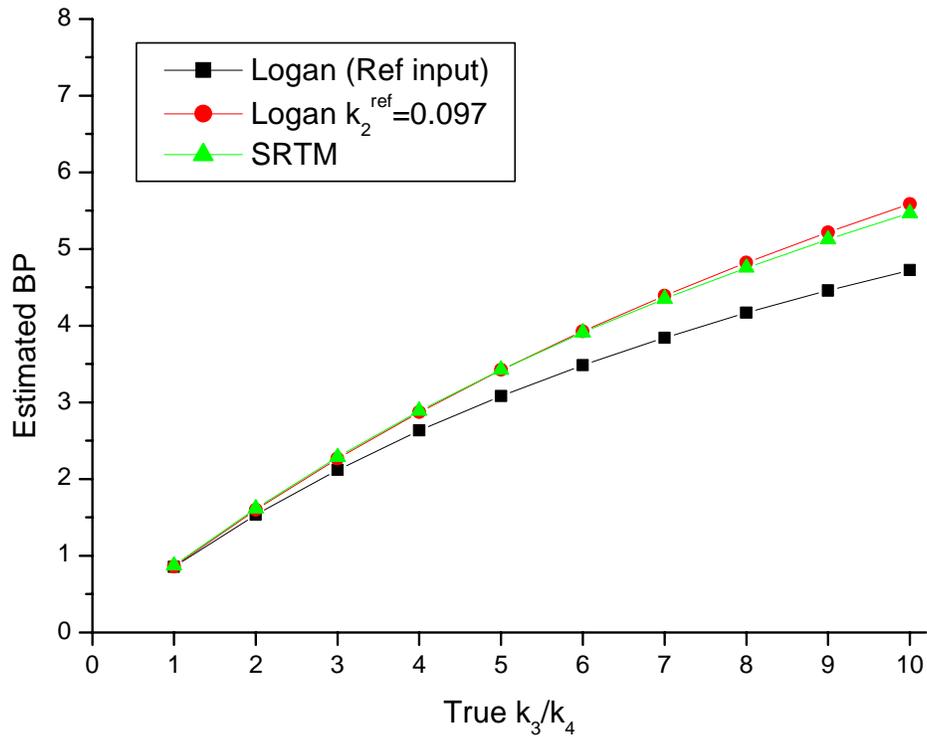
Fig. 3. Correlation between binding potential estimated from the simulated data and the k_3/k_4 ratio that was actually used to simulate the data.

Conclusion

The binding potentials calculated without plasma input with the Logan plot and simplified reference tissue compartment model correlate with true k_3/k_4 values in [^{11}C]NNC 756 studies. Although both can give comparable results, simplified reference tissue model is recommended.

References

1. Abi-Dargham A, Simpson N, Kegeles L, Parsey R, Hwang DR, Anjivel S, Zea-Ponce Y, Lombardo I, van Heertum R, Mann JJ, Foged C, Halldin C, Laruelle M. PET studies of binding competition between endogenous dopamine and the D_1 radiotracer [^{11}C]NNC 756. *Synapse* 1999;32:93-109.
2. Hagelberg N, Forssell H, Rinne JO, Scheinin H, Taiminen T, Aalto S, Luutonen S, Någren K, Jääskelainen S. Striatal dopamine D1 and D2 receptors in burning mouth syndrome. *Pain* 2003;101:149-154.

3. Halldin C, Hansen K, Foged C, Grønvald FC, Farde L. Preparation of [^{11}C]NNC 756, a new selective dopamine D1 receptor ligand for PET. *J Nucl Med* 1991;32:934-935.

4. Karlsson P, Farde L, Halldin C, Swahn CG, Sedvall G, Foged C, Hansen KT, Skrumsager B. PET examination of [^{11}C]NNC 687 and [^{11}C]NNC 756 as new radioligands for the D_1-dopamine receptor. *Psychopharmacology* 1993;113:149-156.

5. Kemppainen N, Ruottinen H, Någren K, Rinne JO. PET shows that striatal dopamine D1 and D2 receptors are differentially affected in AD. *Neurology* 2000;55:205-209.

6. Laihinen AO, Rinne JO, Ruottinen HM, Någren KÅ, Lehikoinen PK, Oikonen VJ, Ruotsalainen UH, Rinne UK. PET studies on dopamine D_1 receptors in the human brain with carbon-11-SCH 39166 and carbon-11-NNC 756. *J Nucl Med* 1994;35:1916-1920.

7. Lammertsma AA, Hume SP. Simplified reference tissue model for PET receptor studies. *Neuroimage* 1996;4:153-158.

8. Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL. Distribution volume ratios without blood sampling from graphical analysis of PET data. *J Cereb Blood Flow Metab* 1996;16:834-840.

9. Rinne JO, Ruottinen HM, Någren K, Åberg LE, Santavuori P. Positron emission tomography shows reduced striatal dopamine D_1 but not D_2 receptors in juvenile neuronal ceroid lipofuscinosis. *Neuropediatrics* 2002;33:138-141.