Modelling of [11C]PE2I

This document reviews the publications on the analysis of [11C]PE2I PET studies and SPECT studies with PE2I labelled with other tracers.

Specificity

Unlike many other DAT ligands, [11C]PE2I is a highly selective ligand for DAT, and does not accumulate in regions rich in the serotonin or noradrenaline transporter. The extrastriatal PE2I binding is very low (Hall et al. 1999). *In vitro* binding of [125I]PE2I in substantia nigra was about 50% of binding in caudate and putamen, and 15% in thalamus (Hall et al. 1999). In displacement and pre-treatment measurements the cerebellum-to-blood ratio did not change (Poyot et al. 2001; Halldin et al. 2003), supporting the use of cerebellum as a reference region.

[11C]PE2I shows relatively high non-specific binding to white matter of both cerebrum and cerebellum: it is evident in most published *in vitro* binding assays and PET images (Hall et al. 1999; Poyot et al. 2001); *in vitro* accumulation of [125I]PE2I corresponds to 30-35% of the specific binding in caudate and putamen (Hall et al. 1999). This is probably due to its relatively high lipophilicity (Hall et al. 1999).

Compartment model analysis

Pinborg et al. (2002, 2005) have fitted traditional one- and two-tissue compartment models to human [123I]PE2I-SPECT data. They found that for all ROIs, AIC indicated a significantly better fit using the two-tissue compartment model compared with the one-tissue compartment model, and that this was most evident in the receptor poor cortical regions. They assumed that the second tissue compartment may be explained by parallel compartment (heterogeneity) instead of serial compartment (non-specific binding), which might in turn explain cause the non-physiological rate constants and compartment distribution volumes (Pinborg et al. 2002). Because of the poor resolution of SPECT and PET scanners, one can expect that the relatively high accumulation in white matter may form most of the "parallel compartment". Another explanation, presence of a radioactive metabolite passing the blood-brain barrier, is unlikely, because the two main metabolites of [11C]PE2I are polar compounds (Halldin et al. 2003).

Pinborg et al. (2002) estimated that the first-pass extraction fraction of [123I]PE2I was about 0.72 in striatum and about 0.34-0.42 in cortical regions. With [11C]PE2I the first-pass extraction fraction might be even higher. This suggests, that when vascular radioactivity concentration is concerned, arterial blood concentration represents only the arterial fraction of it, and venous volume fraction can possibly be neglected.

The full reference tissue model and the simplified reference tissue model performed equally well with [123I]PE2I SPECT data based on Akaike information criterion

values, and the BP estimates were similar than with Logan analysis when study length was 90 min or longer (Pinborg et al., 2005).

Multi-injection method

Poyot et al (2001) validated the use of multi-injection protocol with arterial input in primates for estimation of B'max. In putamen and caudate, B'max correlated strictly with [^{125}I]PE2I determined *in vitro*, although the values were different.

Non-compartment analysis (Logan plot)

SPECT studies in healthy volunteers, Parkinson's disease (PD) patients, and nonhuman primates with [^{123}I]PE2I have validated the use of this tracer and Logan graphical method with occipital cortex input for studying the binding of PE2I and the clinical features of PD (Pinborg et al. 2002 and 2005; Prunier et al. 2003a; Prunier et al. 2003b). In SPECT studies, occipital cortex is used as reference region instead of cerebellum because occipital cortex is readily visible and well defined in SPECT images.

Pinborg et al. (2002) applied Logan plot to the [^{123}I]PE2I SPECT studies with metabolite corrected plasma input, and reference tissue input with and without reference tissue k_2 correction ($k'_2=0.013\pm0.006$ min^{-1} from six subjects, determined from the intercept of the plasma input Logan plot of the occipital cortex). Their Logan plot linearity is not reached before 120 min in all cases, neither with plasma or occipital cortex input. Surprisingly, applying k'_2 correction did not decrease the time to reach linearity, but even increased it in some cases. Pinborg et al. (2002) recommend using Logan plot with occipital cortex input without k'_2 correction.

Peak equilibrium (ratio) analysis

Peak equilibrium analysis, (striatum-occipital cortex)/occipital cortex ratio at the peak of (striatum-occipital cortex) curve, provided similar BP estimates and SEM than simplified reference tissue model for [^{123}I]PE2I (Pinborg et al., 2005). However, the ratio was highly variable from 0 to 70-80 min after injection, making identification of the correct scan period important and thus in practice requiring dynamic acquisition. Therefore, Pinborg et al. (2005) suggest using bolus/infusion protocol even in clinical studies, because then a certain scan time (after 120 min of constant infusion) can be applied for all subjects.

Simplified reference tissue model (SRTM)

Jucaite et al. (2005) and Leroy et al. (2007) used simplified reference tissue model with cerebellum as reference region to estimate regional BP values. Jucaite et al. (2006) compared SRTM and plasma input models, and suggest that SRTM can be used in clinical studies when arterial sampling need to be avoided.

References

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