Biomathematical Modeling Approach to Predict Clinical SUVRs for Amyloid PET Imaging

VII. 5. Biomathematical Modeling Approach to Predict Clinical SUVRs for Amyloid PET Imaging

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Introduction

The aggregation of amyloid β peptide is one of the pathological observations in the brains of individuals with Alzheimer's disease (AD). Amyloid imaging using positron emission tomography (PET) has been recognized as having an important role in the diagnosis of AD[1)]. In the last decade, many PET radioligands for amyloid imaging have been developed; some of them have successfully been applied in human PET studies.

In general, the discovery and development of radioligands for clinical application requires complicated and sometimes empirical procedures in terms of chemical (e.g., stability of labeling and lipophilicity) or biological (e.g., affinity, metabolites and density of the target) factors[2,3)]. Even though these factors have been well-investigated in the case of candidate radioligands, several factors obtained in *in vitro* or *in vivo* animal studies may not be applicable to human studies; it is not easy to develop successful radioligands and satisfy clinical demands[4)]. We need to know not only the micro parameters of the candidate radioligands but also overall macroscopic performance.

Recently, there has been growing interest concerning more efficient development of successful radioligands in clinical studies using systematic evaluation of their overall performance (e.g., outcome measures)[3)]. It is obvious that the use of *in vivo* PET scans in experimental animals or humans is the fastest and easiest approach for the evaluation of the overall performance of the candidate radioligand. However, the development of a labelling protocol for positron emitter isotopes and the synthesis of a radioligand for PET studies are

labor intensive and also take considerable time. Therefore, in order to contribute on the radioligand development, we proposed a new method to predict standardized uptake value (*SUVR*) of amyloid PET radioligands using biomathematical modeling and *in silico* parameters (Fig. 1)[5]. The methodology includes empirical formula of lipophilosity (logP), free fraction of radioligand in blood (f_p) and free fraction of radioligand in tissue (f_{ND}). In this study, we investigated the influence of empirical formulae based on 3 datasets of f_p and f_{ND} reported by Guo et al.[3], Summerfield et al.[6], and Wan&Mauer[7,8] on the outcome, predicted SUVRs, of [^{11}C]PiB, [^{11}C]BF-227, [^{11}C]AZD2184, [^{11}C]SB-13, [^{18}F]FACT, [^{18}F]florbetapir, [^{18}F]florbetaben, [^{18}F]flutemetamol, [^{18}F]FDDNP and [^{18}F]AZD4694.

Material and Methods

We assumed that the radioligand for amyloid imaging obeyed the simplified one-tissue compartment model (1TCM) (Fig. 1). The kinetic parameters (K_1, k_2 and BP_{ND}) for each radioligand in the human brain were mathematically modelled, where K_1, k_2 and BP_{ND} are the influx and efflux rate constants between arterial plasma and brain tissue, and the binding potential, respectively. The time–activity curves (TACs), with or without specific binding of the radioligand in brain tissue, were calculated as follows:

$$\begin{aligned} C_{target}(t) &= K_1 \cdot C_p(t) \otimes \exp\left[-\left(\frac{k_2}{1+BP_{ND}}\right)t\right] \\ C_{reference}(t) &= K_1 \cdot C_p(t) \otimes \exp(-k_2 t) \end{aligned} \quad (1)$$

where C_{target} is the TAC of the target region, where the radioligand specifically binds to the target protein. $C_{reference}$ is the TAC of the reference region without the target protein. C_p is the arterial plasma input function. The influx rate constant from plasma to brain tissue, K_1 [mL/cm^3/min] was formulated using the Renkin–Crone model as follows:

$$K_1 = f \cdot \left[1 - e^{(-PS/f)}\right] \quad (2)$$

where P, f and S are capillary permeability [cm/min], perfusion [mL/cm^3/min] and capillary surface area [cm^2/cm^3 of brain], respectively. f and S were set to 0.6 [mL/cm^3/min] and 150 [cm^2/cm^3 of brain], respectively. Permeability P in **Eq. (2)** was empirically formulated as follows [3]:

$$P = 10^{\left\{-0.121(c\log D - 2.298)^2 - 2.544\log\left(V_x^{1/3}\right) - 2.525\right\}} \quad (3)$$

where *clogD* and V_x are lipophilicity and the McGowan volume [cm^3/mol/100], respectively. The efflux rate constant from brain tissue to plasma, k_2 [1/min], was expressed using the following equation, assuming equilibrium in the radioligand

concentrations between plasma and brain tissue.

$$k_2 = \frac{V_{aq\_P} \cdot K_1}{V_{aq\_T}} \cdot \frac{f_{ND}}{f_P} \tag{4}$$

where V_{aq_p} and V_{aq_T} are the apparent aqueous volume in plasma, the apparent aqueous volume in tissue and these were set to 0.98 [solvent/mL of plasma] and 0.9 [solvent/mL of tissue], respectively[3]. Both f_P and f_{ND} were estimated from empirical formulae, which were established from f_P and f_{ND} measured from *in vitro* binding experiments using mouse brain and plasma, and *in silico* lipophilicity. Here in this study, we tested 3 data sets of f_P and f_{ND} reported by Guo et al.[3], Summerfield et al.[6], and Wan&Mauer[7,8]. The radioligand binding capacity at the target site, BP_{ND}, was modelled[5] as follows:

$$BP_{ND} = f_{ND}\left\{\frac{B_{avail-42}}{K_{D-42}} + \frac{B_{avail-40}}{K_{D-40}}\right\} = f_{ND}\left\{\frac{a}{K_{D-42}} + \frac{(1-a)}{K_{D-40}}\right\}B_{avail} \tag{5}$$
$$B_{avail} = B_{avail-42} + B_{avail-40}$$

where a, $K_{D\text{-}42}$ and $K_{D\text{-}40}$ are the fractions of $A\beta_{1\text{-}42}$, the dissociation constant for $A\beta_{1\text{-}42}$ and $A\beta_{1\text{-}40}$, respectively. $B_{avail\text{-}42}$, $B_{avail\text{-}40}$ and B_{avail} were available binding sites of $A\beta_{1\text{-}42}$ and $A\beta_{1\text{-}40}$, ($A\beta_{1\text{-}42}$ + $A\beta_{1\text{-}40}$), respectively. a was assumed to have a value of 0.7, which is biochemically derived from fractions of extra-cellular insoluble $A\beta_{1\text{-}42}$ in both AD and HC brains [9]. The TACs of the target and reference regions were calculated using K_1, k_2 and BP_{ND} and fixed arterial input function C_p using Eq. (1). The parameter of interest, *SUVR*, was then estimated from the predicted TACs. Finally, for each data sets of f_p and f_{ND}, the predicted *SUVR* were compared with their clinical counterparts, *SUVR*[5].

Results and discussion

Figure 2A shows the relationships between *in silico* lipophilicity and *in vitro* $f_{ND,}$ and Fig. 2B shows the relationships between *in vitro* f_{ND} and f_P using the datasets of Guo's, Summerfield's and Wan&Maurer's, respectively. For each dataset, correlations between lipophilicity and f_{ND} and between f_{ND} and f_P were observed. Figure 3 shows the relationship between predicted SUVR and clinically observed SUVRs, these results were obtained by applying empirical formulae in Fig. 2 into the prediction scheme of SUVR of the 10 amyloid radioligands. In this study, we calculated Moriguchi logP as the lipophilicity[5]. Even though there was inconsistent use of lipophilicity between the 3 datasets (clogD and clogP by different softwares) and ours (*MlogP*) for the estimation of f_p and f_{ND}, positive

correlations between predicted and clinically observed SUVRs were observed (Fig. 3). These results supported the fact that our approach (*MlogP*) without the use of *in vitro* experiments for f_p and f_{ND} estimation can be applied to other amyloid radioligands, even though the data-sets selected for estimation of f_p and f_{ND} resulted in different values of the predicted SUVRs.

Conclusion

For all 3 data sets of f_p and f_{ND}, predicted *SUVR* showed good correlation with clinically observed *SUVR* for the 10 clinically applied amyloid tracers, however, the values of predicted SUVR were different from each datasets. These results will be contributed on the future improvement of the methodology.

References

1) Okamura N, Harada R, et al. *Ageing Res Rev*. (2016) 107-13.
2) Innis RB, Cunningham VJ, et al. *J Cereb Blood Flow Metab*. **27** (2007) 1533-9.
3) Guo Q, Brady M, et al. *J Nucl Med*. **50** (2009) 1715-23.
4) Laruelle M, Slifstein M, et al. *Mol Imaging Biol*. **5** (2003) 363-75.
5) Arakawa Y, Nai Y, et al. *J Nucl Med*. **58** (2017) 1285-92.
6) Summerfield SG, Read K, et al. *J Pharmacol Exp Ther*. **322** (2007) 205-13.
7) Maurer TS, Debartolo DB, et al. *Drug metabolism and disposition: the biological fate of chemicals*. **33** (2005) 175-81.
8) Wan H, Rehngren M, et al. *J Med Chem*. **50** (2007) 4606-15.
9) Steinerman JR, Irizarry M, et al. *Arch Neurol*. **65** (2008) 906-12.

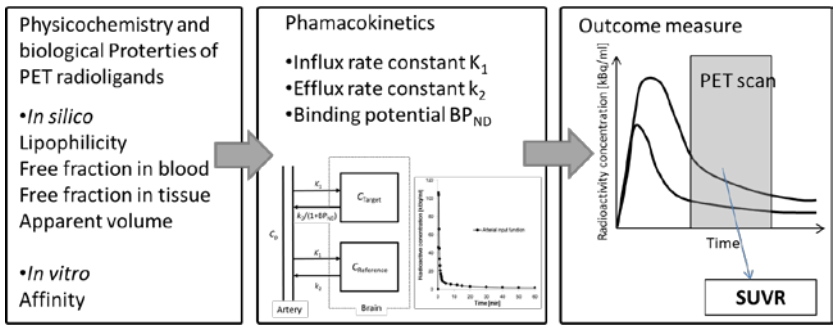

Figure 1. Overview of our biomathematical model: From physicochemical/biological properties of PET radioligand, pharmacokinetic parameters (K_1, k_2 and BP_{ND}) are estimated, then outcome measure (SUVR) is predicted through time activity curves of simplified 1 tissue model for both target and reference regions.

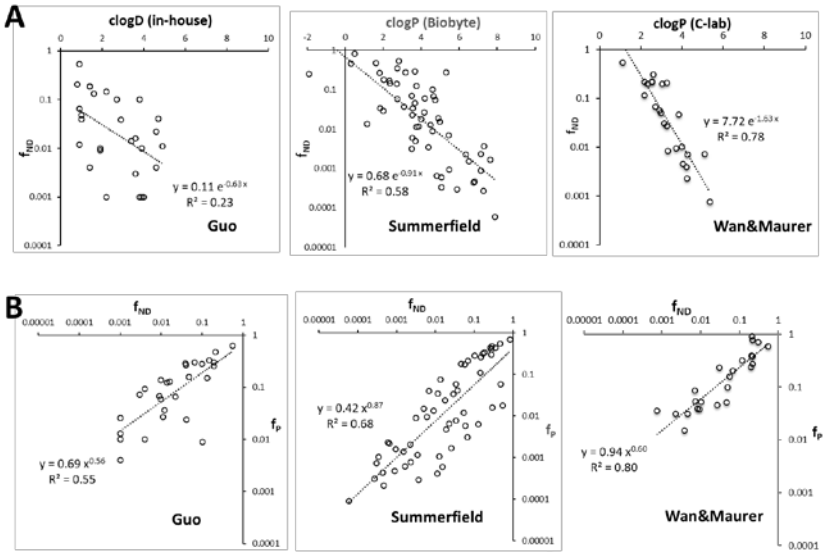

Figure 2 Relationship between in silico lippophilisity and f_p (A) and between f_p and f_{ND} (B) for 3 databases of Guo's, Summerfield's and Wan&Maurer's.

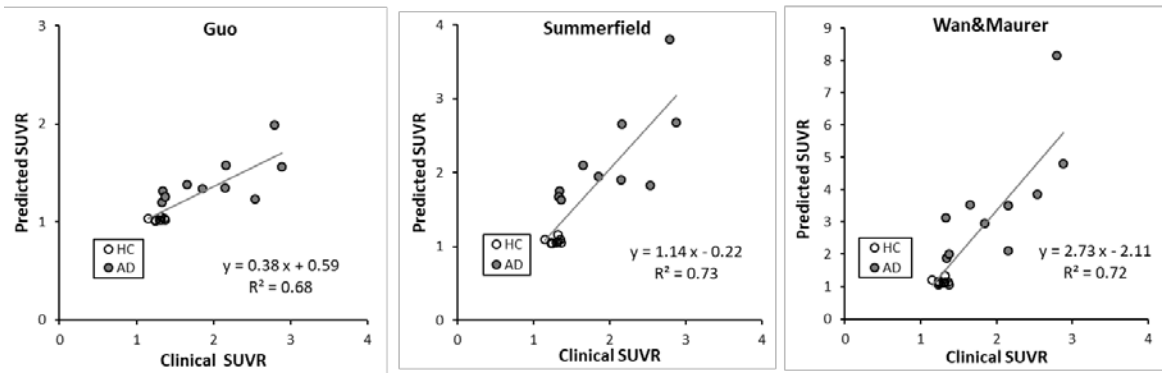

Figure 3 Relationship between clinically observed SUVR and predicted SUVR by our model based on 3 databases, Guo's (A), Summerfield's (B) and Wan&Maurer's (C).