Kinetic Model of Amyloid Beta Distribution and Allometric Scaling from Mouse to Monkey and Human

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INTRODUCTION

Amyloid Beta (Aβ) is important biomarker of Alzheimer disease, and it is hypothesized that it plays role in neurotoxicity. Decreasing Aβ levels in brain could be a potential therapy, while measuring its level in CSF and plasma can be used for diagnostic purposes. It is thus important to understand how Aβ distributes among different compartments. Here we present an updated model, describing Aβ kinetics in mouse and its allometric scaling to monkey and human.

METHODS

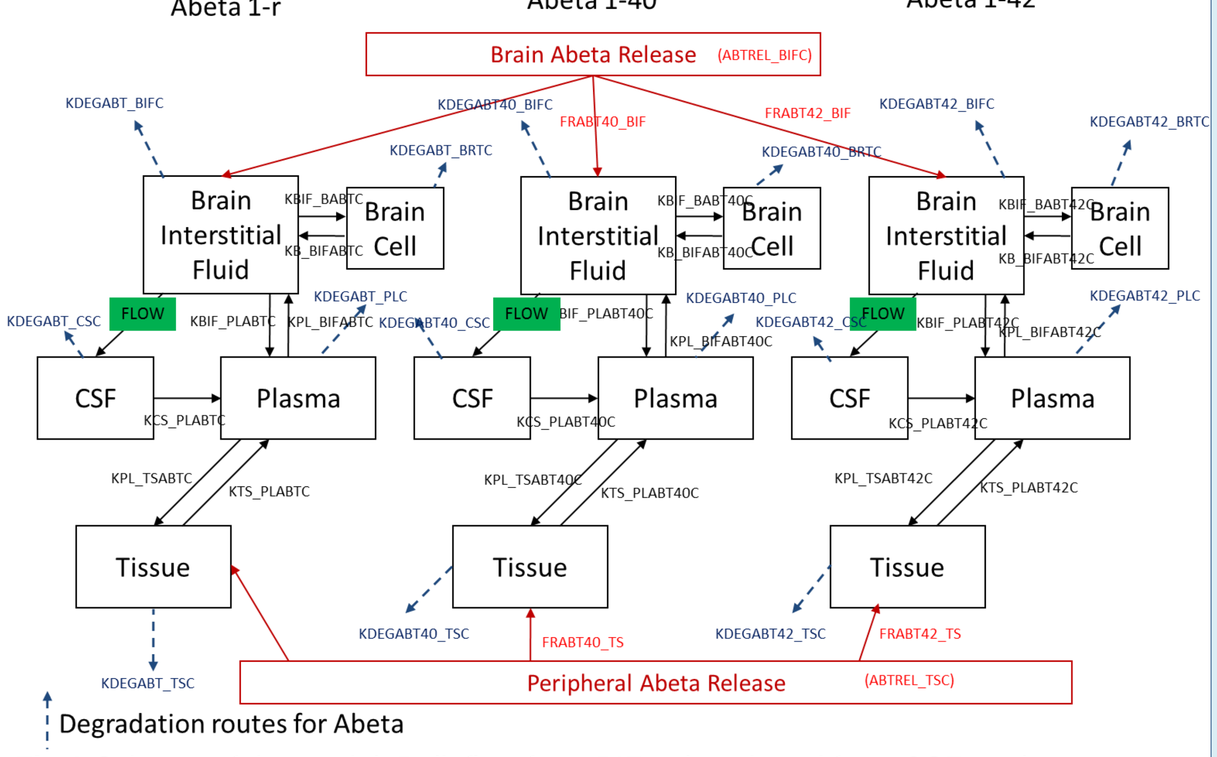

Fig.1 Scheme of the model. Bulk flow from BIF to lymph and from CSF to plasma have been also taken into account (not shown).

1. We suppose the flow from BIF to plasma is described by following law [1]

$$JBIF\_PL = KBIF\_PL \cdot Ab/(K_m + Ab) \quad (1)$$

2.We suppose the flow from plasma to tissue is described by following law

$$JPL\_TS = KPL\_TS \cdot Ab^{GAM1} \quad (2)$$

3.We used next laws for allometric scaling

$$K = Ko \cdot BW^{-0.15}$$ for processes in brain, [2]; (3)

$$K = Ko \cdot BW^{-1/4}$$ for all other processes. (4)

4. We performed local sensitivity analysis for BMS708163 PD data: small change (increasing) some parameter and look how will change some variable in each time point:

$S_{Xi,kj}(t)=d\ log\ Xi(t)/d\ log\ kj$, *Xi – variable, kj – parameter.* (5)

5. For model calibration we used published [3-9] and internal Pfizer data for mouse, monkey and human, most of them on the distribution of isotope labeled Aβ. Most of the kinetic data for model calibration have been obtained in wild-type mouse, so aggregation of Aβ was not considered. The mouse model was also tested against reported CSF and brain Aβ time courses after a dose of a γ-secretase inhibitor (GSI). For description of monkey and human data only releases of Aβ and fractions for different forms were fitted. Brain concentration was taken for fitting as

$$Ab\_BRN = (Ab\_BIF \cdot BIF + Ab\_BC \cdot BC)/(BIF + BC) \quad (6)$$

All the calculations and fitting were done in DBSolve Optimum software.

REFERENCES

1. Macheras, P. Carrier mediated transport of can obey fractal kinetics. *Pharm Res*, (1981) *32*(6), 709-717,
2. Karbowski, J. Global and regional brain metabolic scaling and its functional consequences. *BMC biology* (2007), *5*, 18.
3. Shibata M,et al. Clearance of Alzheimer's amyloid-β_{1-40} peptide from brain by LDL receptor-related protein-1 at the blood brain barrier. *J Clin Invest* (2000) 106(12):1489-1499.
4. Deane R, et al. apoE isoform-specific disruption of amyloid β peptide clearance from mouse brain. *The Journal of Clinical Investigation* (2008), 118(12).
5. Ghiso J, et al. Systemic catabolism of Alzheimer's Aβ40 and Aβ42. *J Biol Chem* (2004) 279(44): 45897-45908
6. Kandimalla KK, et al. Pharmacokinetic analysis of the blood-brain barrier transport of ^{125}I-Amyloid β protein 40 in wild-type and Alzheimer's disease transgenic mice (APP, PS1) and its implications for amyloid plaque formation. *J Pharmacol Exp Ther* (2005) 313(3):1370-1378.
7. Cook JJ, et al. Acute γ-secretase inhibition of nonhuman primate CNS shifts amyloid precursor protein (APP) metabolism from amyloid-β production to alternative APP fragments without amyloid-β rebound. *J Neurosci* (2010) 30(19): 6743-6750.
8. Bateman RJ, et al.. Human amyloid-β synthesis and clearance rates as measured in cerebrospinal fluid *in vivo*. *Nature Medicine* (2006) 12(7):856-861.
9. Bateman RJ et al. Fluctuations of CSF amyloid-β levels. *Neurology* (2007) 68:666-669

RESULTS

Model satisfactorily reproduced different published experimental data

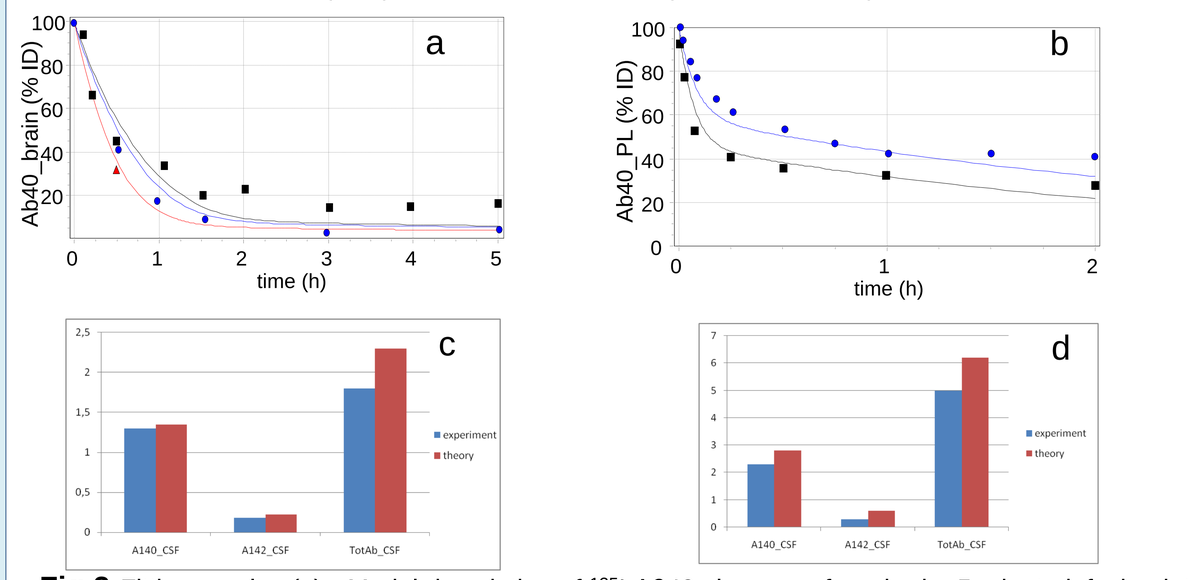

Fig.2 Fitting results. (a) - Model description of ^{125}I-Aβ40 clearance from brain, 5 minute infusion into C57BL/6 male mice brain ISF [3,4], three different doses); (b) clearance from plasma (iv bolus in B65JLF1/7 [5] or B6/SJL [6] mice, different doses). (c, d) –steady state values (in nM) for monkey and human, Pfizer data and [9].

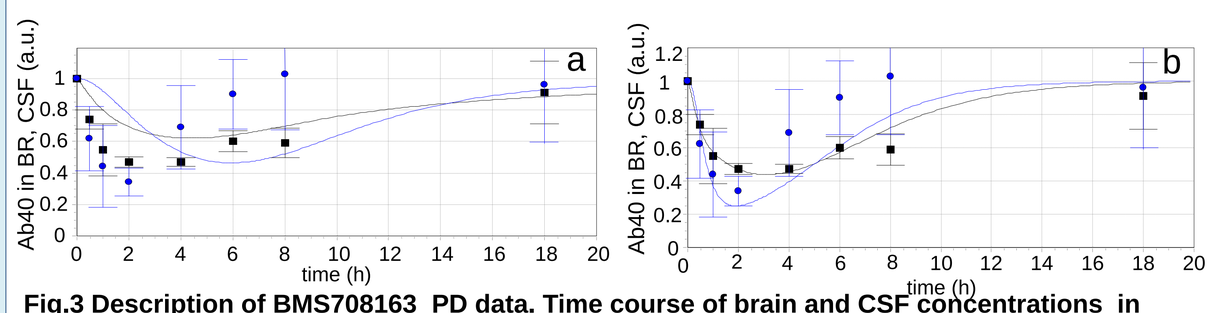

Fig.3 Description of BMS708163 PD data. Time course of brain and CSF concentrations in mice after single 30 mg/kg dose of GSI inhibitor. (a) description of data using the parameters fitted to multiple published data (b) – BMS708163 PD data fitted separately from other data. Black curve – brain concentration, blue curve – CSF concentration

As it can be seen from Fig.3, CSF and brain curves cannot be fitted even without taking into account other data. Thus explanation of problem by different experimental technics is not sufficient.

In our model CSF concentration is determined by the bulk flow from BIF, and thus it strongly depends on the BIF concentration, which, in turn, makes input into the brain concentration (see Eq.6). We have analyzed also influence of parameters on the time shift between two minimums:

$$Dt = TIME(CSFmin) - TIME(BRmin)$$

and found that most important parameter is KBIF_BABT. Increasing its value we may achieve negative values of Dt. It means that our understanding of the distribution between BC and BIF may be inconsistent.

Table 1. Values of parameters fitted to published mouse data

	AB_40	AB_42	AB_rest	Local sensitivity (max)	
				Ab_BRN	Ab_CSF
kFLOW1 (L/h/BW$^{0.85}$)	4E-4	4E-4	4E-4	-0.07	0
FLOWisf_csfC	0.12	0.12	0.12	0	1
GAM1	0.7	0.7	0.7		
KBIF_BABT (BW$^{0.15}$/h)	0.08	0.08	0.08	0.35	0.25
KB_BIFABT (BW$^{0.15}$/h)	0.05	0.05	0.05	-0.45	-0.06
KBIF_PLABT(BW$^{0.15}$/h)	0.07	0.01	0.07	-0.06	-0.28
KPL_BIFABT(BW$^{0.25}$/h)	0.05	0.05	0.05	-0.01	0.05
kFLOWCS_PLABT (L/h/BW$^{0.85}$)	3.4E-04	3.4E-04	3.4E-04	0	-1.2
KPL_TSABT (nM^{1-GAM1}.BW$^{0.25}$/h)	27	27	27		
KTS_PLABT (BW$^{0.25}$/h)	3.13	3.13	3.13		
KmB (nM)	0.05	0.05	0.05		
KDEGABT_BIF (BW$^{0.15}$/h)	0.35	0.1	0.35	-0.15	-1.1
KDEGABT_BRT (BW$^{0.15}$/h)	9.6E-02	0.02	9.6E-02	-0.02	-0.018
KDEGABT_PL (BW$^{0.25}$/h)	1.24E-06	1.24E-06	1.2E-06		
KDEGABT_CS (BW$^{0.25}$/h)	2.3E-08	2.3E-08	2.3E-08		
KDEGABT_TS (BW$^{0.25}$/h)	0.1843	0.1843	0.1843		

Table 2. Values of Aβ release parameters fitted to published data for different species

Parameter	Parameter Symbol	Parameter Value		
		Mouse	Monkey	Human
Release of Abeta (nmol/hr/BW$^{0.75}$)				
Brain Interstitial Fluid	ABTREL_BIFC	6e-3	0.03	0.1
Peripheral Tissue	ABTREL_TSC	0.01	0.015	1.65e-03
Fraction Abeta1-40 Produced				
Brain Interstitial Fluid	FRABT40_BIF	0.34	0.6	0.3
Peripheral Tissue	FRABT40_TS	0.5	0.4	0.6
Fraction Abeta1-42 Produced				
Brain Interstitial Fluid	FRABT42_BIF	0.04	0.06	0.02
Peripheral Tissue	FRABT42_TS	0.25	0.085	0.2

CONCLUSIONS

- ✓ Parameter values in the updated model provided better descriptions of existing data.
- ✓ Allometric scaling to other speciies can be achieved by fitting only the Aβ production with fraction of releases
- ✓ For better description of the GSI some additional data about dynamics of the Aβ distribution between BC and BIF would be helpful.

CONTACTS

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